14 November 2024
EMA/CHMP/554847/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yervoy	Ipilimumab
OPDIVO	Nivolumab

Procedure No. EMEA/H/C/xxxx/WS/2672

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
1L	First-line
2L	Second-line
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
BICR	Blinded independent central review
BOR	Best overall response
Cavg	Average concentration
Cavgss	Average concentration at steady state
CDx	Companion Diagnostics
chemo	Chemotherapy
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
Cmaxss	Maximum concentration at steady state
Cmin	Minimum concentration
Cminss	Minimum concentration at steady state
CoC	Contribution of components
CR	Complete response
CRC	Colorectal cancer
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical Trial Assays
CTA -	CTA negative
CTA +	CTA positive
DBL	Database lock
DCR	Disease control rate
DMC	Data monitoring committee
dMMR	Deficient mismatch repair
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
E-R	Exposure - response
ESMO	European Society for Medical Oncology
EU-27	European Union (27 countries as of 1-Feb-2020 [Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, Sweden])
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
GCP	Good Clinical Practice
HLGT	High level group term
HR	Hazard ratio

Term	Definition
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMAE	Immune-mediated adverse event
Ipi	Ipilimumab
IRB	Institutional Review Board
IV	Intravenous
KM	Kaplan Meier
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally important difference
MMR	Mismatch repair (of DNA)
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
Nab	Neutralizing antibodies
NB	Notified body
NCCN	National Comprehensive Cancer Network
Nivo	Nivolumab
NPA	Negative Percent Agreement
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
pCR	Pathologic complete response
PCR	Polymerase chain reaction
PD	Progressive disease
PD-L1	Programmed cell death ligand-1
PEP	Performance Evaluation Plan
PFS	Progression-free survival
PFS2	Progression-free survival on next line of treatment (time to second progression)
PL	Package leaflet
pMR	Pathologic major response
popPK	Population pharmacokinetics
PPA	Positive Percent Agreement
pPR	Pathologic partial response
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	Quality of life
QXW	Once every X weeks
RECIST	Response evaluation criteria in solid tumours
RFS	Recurrence free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology

Term	Definition
SCS	Summary of Clinical Safety
SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standard medical query
SOC	System organ class; standard of care
TMB	Tumour mutational burden
TTR	Time to response
UI	Utility index
US	United States of America
USPI	United States Prescribing Information
VAS	Visual analogue scale

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 10 April 2024 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

A Worksharing application for OPDIVO and YERVOY, as follows:

Extension of indication to include OPDIVO in combination with ipilimumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 37.0 of the RMP has also been submitted.

Extension of indication to include YERVOY in combination with nivolumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.0 of the RMP has also been submitted.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The design of the phase 3b randomized study CA2098HW was briefly discussed as part of the SA advice (EMEA/H/SA/3330/4/2019/II) for the second line setting (EMEA/H/C/xxxx/WS/1840).

1.1. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure: Peter Mol

Timetable	Actual dates
Submission date	10 April 2024
Start of procedure:	27 April 2024
CHMP Rapporteur Assessment Report	18 June 2024
PRAC Rapporteur Assessment Report	25 June 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	21 October 2024
CHMP members comments	4 November 2024
Updated CHMP Rapporteur Assessment Report	7 November 2024
Opinion	14 November 2024

2. Scientific discussion

2.1. Introduction

This is an extension of indication to include nivolumab in combination with ipilimumab (hereafter referred to as nivo+ipi) for the first-line treatment of adults with unresectable or metastatic mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer based on the pivotal randomized, open-label, 3-arm phase 3 study CA2098HW investigating nivo+ipi vs nivolumab monotherapy or standard of care (SOC).

2.1.1. Problem statement

Disease or condition

The MAH applied for the following indication:

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or metastatic mismatch repair deficient or microsatellite instability-high colorectal cancer.

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable or metastatic mismatch repair deficient or microsatellite instability-high colorectal cancer.

Epidemiology and risk factors, screening tools/prevention

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease.[1] Worldwide, CRC is the third most common form of cancer, with 1.93 million new cases diagnosed worldwide in 2020, constituting 10% of all new cancers. In 2020, in EU-27 countries, it is estimated that CRC accounted for 12.7% of all new cancer diagnoses (341,419 new CRC cases) and 12.4% of all deaths due to cancer (156,105 deaths due to CRC).[2] The risk of developing CRC is influenced by both environmental and genetic factors.[3]

MSI-H/dMMR colorectal tumours are identified in approximately 15% of CRC patients. Among patients with metastatic CRC (mCRC), those with MSI H/dMMR tumours comprise approximately 4-7%.[4,5]

Biologic features, aetiology and pathogenesis

Mismatch repair proteins (MMR) repair insertions or deletions in microsatellites, which are repetitive DNA units. MLH1, MSH2, MSH6 and PMS2 are known MMR gene products. Dysfunction of this system is known as deficient mismatch repair (dMMR), which leads to the insertion or deletion of the repeating nucleotides microsatellites during DNA replication and accumulation of mutations due to failure to correct errors in nucleotide repeat. This form of genomic instability is called microsatellite instability (MSI). 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. There are two forms of MSI colorectal cancer: (1) the hereditary type, caused by the deficiency of MMR system resulting from a germline mutation in MMR genes predisposing to Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer, which is the most common hereditary colon cancer syndrome, inherited in an autosomal dominant pattern; (2) the sporadic form, which is related to the somatic inactivation of the same pathway, most commonly through hypermethylation (epigenetic inactivation) of the MLH1 gene, or mutations in mismatch repair genes MLH1, MSH2, MSH6, or PMS2 leading to sporadic MSI/dMMR CRC.

Recent studies highlighted genetic diversity and distinct patterns in CRC with MSI, suggesting substantial heterogeneity, also based on MSI aetiology.[6] Methylation of the MLH1 promoter region in the sporadic form is strongly associated with the BRAF V600E gene mutation. The presence of the BRAF V600E mutation in CRC essentially excludes Lynch syndrome, except for rare cases associated with PMS2 germ-line mutation. While BRAF V600E mutation has a negative prognostic impact in proficient MMR CRC, data on the role of BRAF in relation to MMR status are scarce and the impact of BRAFV600E mutation on MSI CRCs remains controversial.[7] By contrast, KRAS mutations (in codons 12 or 13) are inversely correlated with MSI-H status.[8]

[1] National Cancer Institute: Surveillance, Epidemiology, and End Results Program: Cancer stat facts: Colon and rectum cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed 16-Jul-2020
[2] European Commission. ECIS - European Cancer Information System. Colorectal cancer burden in EU-27 cancer factsheet. https://ecis.jrc.ec.europa.eu/factsheets.php. Accessed on 5-Oct-2023.
[3] Xi Y, Xu Pengfei. Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology. 2021, 14 (2021): 101174.
[4] Battaglin F, Naseem M, Lenz HJ et al. Microsatellite Instability in Colorectal Cancer: Overview of Its Clinical Significance and Novel Perspectives. Clin Adv Hematol Oncol. 2018 Nov;16(11):735-745.
[5] Gutierrez C, Ogino S, Meyerhardt J, et al. The Prevalence and Prognosis of Microsatellite Instability-High/Mismatch Repair-Deficient Colorectal Adenocarcinomas in the United States. JCO Precision Oncology. 2023 Jan;7:e2200179.
[6] Battaglin F et al. Microsatellite Instability in Colorectal Cancer: Overview of Its Clinical Significance and Novel Perspectives. Clin Adv Hematol Oncol 2018;16(11):735-747.
[7] Cohen R et al. Clinical and molecular characterisation of hereditary and sporadic metastatic colorectal cancers harbouring microsatellite instability/DNA mismatch repair deficiency. Eur J Cancer 2017; 86:266e274.
[8] Gelsomino F et al. The evolving role of microsatellite instability in colorectal cancer:A review. Canc Treat Rev 2016;51:19-26.

Clinical presentation, diagnosis and stage/prognosis

MSI-H CRCs are usually diagnosed at younger age and at an earlier stage than microsatellite stable (MSS) CRC, with a predominance in the right colon. The sporadic form is however characterized by older age at diagnosis than the hereditary one and it's more often associated with female sex and cigarette smoking.[9] Regardless whether hereditary or sporadic, MSI-H CRCs are histologically characterized by great production of mucin with extracellular accumulation, signet ring and medullary types, often admixed, with increased numbers of tumour-infiltrating lymphocytes and prominent Crohn's-like lymphoid reaction.[10] Patients with Lynch syndrome have an increased risk of synchronous or metachronous tumours, as well as higher risk for the development of extracolonic cancer, in particular endometrial carcinoma, and also cancers of the small bowel, stomach, genitourinary and biliary tract.

With regard to the molecular diagnosis, MMR or MSI status can be determined by examining either: (1) protein expression by IHC staining for 4 MMR proteins (MLH1/MSH2/MSH6/PMS2) on tumour samples to identify negative or loss of staining (i.e. loss of protein expression) that characterize dMMR as a surrogate for MSI; or (2) molecular DNA testing PCR-based microsatellite instability analysis evaluating a specific panels of microsatellite markers to identify instability in selected loci. In general, tumours are classified as MSI-H (including MMR deficient) when expression of at least 1 of 4 MMR proteins is not detectable by IHC, or when 30% or more of the loci show instability. Both methods are sensitive and specific for MSI detection and have a high concordance rate. Although both IHC- and PCR-based approaches are currently considered the standard for MSI detection, several studies have proposed other methods such as NGS.[10,11] These tests are performed directly on tumour samples.

International guidelines (ESMO, NCCN, ASCO) recommend MMR/MSI testing with either an MMR protein IHC-based assay or PCR-based MSI loci for all patients with CRC in clinical decision making. A recent report on immunotherapy in mCRC has shown that an unacceptable percentage of patients (almost 10%) had been enrolled in immunotherapy trials and experienced failure due to false positive dMMR or MSI-PCR results assessed by local laboratories.[11] The consensus panel recommends the use of both MMR-IHC and MSI-PCR to assess the eligibility to treatment with immune checkpoint inhibitors of mCRC and other cancers of the Lynch syndrome spectrum.[12]

While MSI-H/dMMR cancer can be associated with a favourable prognosis in early-stage disease, in the metastatic setting this is associated with a worse prognosis (or unclear association with prognosis). Findings from a pooled analysis of four phase 3 studies in participants with mCRC treated with first-line SOC therapies, showed that the median PFS and OS were significantly worse for participants with MSI-H/dMMR CRC compared with participants whose tumours were microsatellite stable (PFS: HR=1.33; 95% CI:1.12–1.57; OS: HR=1.35;95% CI:1.13–1.61).[13]

The underlying hypothesis for studies with anti PD-1/PD-L1 antibodies in MSI-H/dMMR cancer is that MSI-H/dMMR cancers are characterized by a high burden of somatic mutation and tumour-specific neoantigen load mediated by MSI and common defects in MMR, which can be recognized by the patient's immune system.[10] In this subset of MSI-H/dMMR cancer patients a large number of activated CD8 positive cytotoxic T cells and a cytokine-rich environment have been observed, associated with upregulated

[9] Jonathan A Nowak JA et al. Detection of Mismatch Repair Deficiency and Microsatellite Instability in Colorectal Adenocarcinoma by Targeted Next-Generation Sequencing. J Mol Diagn. 2017 Jan;19(1):84-91.
[10] Gatalica Z et al. High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine. Fam Cancer. 2016; 15: 405–412.
[11] Cohen, Romain, et al. Association of primary resistance to immune checkpoint inhibitors in metastatic colorectal cancer with misdiagnosis of microsatellite instability or mismatch repair deficiency status. JAMA oncology 201; 5(4): 551-555.
[12] Luchini C., Bibeau F., et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol 2019; 30(8); 1232-1243
[13] 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.

expression of PD-1 and PD-L1 and others checkpoints (e.g. CTLA-4). As a result, the MSI-H/dMMR phenotype represents a unique immunobiology that implicates the role of lymphocyte infiltration, high mutational load, and responsiveness to immune checkpoint blockade that can be addressed by anti-PD-1 therapy. Not all patients with MSI-H tumours, however, respond to immunotherapy, suggesting that a deeper understanding of immune-related mechanisms in MSI-H CRC is required.[14]

Clinical significance MSI-H/dMMR

The MMR pathway is used by normal proliferating cells to repair mutations that may occur during DNA replication. Loss of function of any of the following four MMR proteins, MLH1, PMS2, MSH2 MSH6, results in MMR deficiency and leads to an increased mutation rate and appearance of neoantigens. MMR deficient tumours may be more responsive to immunotherapies than tumours with functioning MMR pathways due to the increased presence of neoantigens and immune cell recruitment.

Microsatellites are short, tandem repeated DNA sequences 1–6 base pairs in length. These repeats are distributed throughout the genome and often vary in length from one individual to another due to differences in the number of tandem repeats at each locus. Microsatellite markers can be used to detect a form of genomic instability called MSI. MSI is a change in length of a microsatellite allele due to insertion or deletion of repeat units during DNA replication and failure of the DNA mismatch repair system to correct these errors. Microsatellite instability (MSI) is a clinically important molecular phenotype used in evaluation of tumours which provides prognostic, therapeutic and familial cancer risk assessment information. Although MSI is classically associated with hereditary form of CRC, it is also present in other cancer types. Patients with a high MSI status show a better prognosis than MSS patients, and should consequently receive a different treatment. For example, tumour cells with MSI-H and impaired mismatch repair are associated with a greater likelihood of successful treatment with immuno-oncology drugs such as the PD-1 checkpoint inhibitors. There are currently several approved checkpoint blockade drugs (e.g. Keytruda and Opdivo) for patients with unresectable or metastatic solid tumours with MSI-H or mismatch repair deficiency (dMMR). Therefore, MSI/MMR testing is now included in several guidelines for all colorectal cancers.

Management

The outcome of patients with mCRC has clearly improved during recent years with median survival now reaching 30 months in clinical trials. The treatment of mCRC patients should be seen as a continuum of care in which the determination of the goals of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life.[16]

Combination chemotherapy of FOLFOX (oxaliplatin, 5-FU, and leucovorin/folinic acid) or FOLFIRI (irinotecan, 5-FU, and leucovorin/folinic acid) are established first-line SOC chemotherapy options for mCRC. As chemotherapy alone, the two regimens have similar activity and are both partners for biologicals, but have a different toxicity profile, and may be used depending on the physician's recommendation and regional preference. Capecitabine per os can be used instead of IV 5-FU in combination with oxaliplatin. Monoclonal antibodies against vascular endothelial growth factor VEGF (bevacizumab, EMEA/H/C/000582/II/0014, 25/01/2008) and against the epidermal growth factor receptor EGFR (cetuximab, EMEA/H/C/000558, 29/06/2004, and panitumumab, EMEA/H/C/000741, 03/12/2007) are approved for use in combination with chemotherapy as first-line treatment in CRC, since they improve the outcome of mCRC.

Following recent approval of pembrolizumab in the EU for the first-line treatment of metastatic MSI-H or dMMR CRC in adults (EMEA/H/C/003820/II/0091, 21/01/2021), the ESMO guidelines have been updated

[14] Olivera AF et al. Review of PD-1/PD-L1 Inhibitors in Metastatic dMMR/MSI-H Colorectal Cancer. Front Oncol 2019;9:396.

to recommend pembrolizumab as 1L therapy for metastatic MSI-H/dMMR CRC.[15] The KEYNOTE-177 study demonstrated improved PFS with an anti-PD1 single agent vs chemo in MSI-H mCRC patients, supporting approval of pembrolizumab in the 1L setting. Median PFS was 16.5 months (95% CI: 5.4, 32.4) with pembrolizumab versus 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).

A summary of approved treatments for first-line treatment of mCRC is presented in table below.

Although the KEYNOTE-177 study demonstrated improved PFS with pembrolizumab vs chemo in MSI-H mCRC patients there is still an unmet medical need, as more than half of the patients do not respond to pembrolizumab and 52% progress or die within 2 years. Factors such as presence of RAS-mutations, high tumour burden, or liver/lung metastases were associated with a lesser PFS benefit with IO monotherapy across multiple studies.[16,17] In addition, in the KEYNOTE-177 study, high rates of primary disease progression with pembrolizumab compared with chemo manifested as early detriment on PFS and OS curves, highlighting the remaining unmet need.

Table 1 Approved treatments relevant for 1L unresectable or metastatic MSI-H or dMMR CRC

Product Name	Dosing/ Administration	Efficacy Information	Reference
FOLFOX +/- bevacizumab	Oxaliplatin 85mg/m^2 IV D1 Leucovorin 200mg/m^2 5FU 400mg/m^2 bolus on D1, followed by 1200 mg/m^2/d x 2D Bevacizumab 5mg/kg, Q2-3W	The addition of bevacizumab to FOLFOX has shown improvements in PFS and OS compared to FOLFOX alone. FOLFOX: mPFS: 8.7m mOS: 19.5m ORR: 45% FOLFOX + bevacizumab: mPFS: 11.3m mOS: 25.9m	Goldberg RM, Sargent D, Morton R, et al. Gastrointestinal Cancer. 2016; 22(1), 23-30. Cutsem VE, Rivera F, Berry S, et al. Elsevier. 2009; 20(11), 1842-7.
FOLFOX +/- cetuximab	Folinic Acid 200-400 mg/m^2, IV Fluorouracil bolus dose 400-500 mg/m^2, followed by a continuous infusion of 2,400-3,000 mg/m^2 over 46 to 48 hours. Oxaliplatin:85 mg/m² IV infusion over two hours on the first day of the cycle. Cetuximab: initial dose 400 mg/m^2, maintenance dose 250 mg/m^2	Improved outcomes of ORR, PFS in the FOLFOX + cetuximab group compared to the FOLFOX alone group in KRAS WT population. FOLFOX + cetuximab vs FOLFOX in ITT: ORR: 46% vs 36% mPFS: 7.2m vs 7.2m FOLFOX + cetuximab vs FOLFOX in KRAS WT: ORR: 61% vs 37% mPFS: 7.7m vs 7.2m	Bokemeyer C, Bondarenko I, Makhson A, et al. Colorectal Cancer. Journal of Clinical Oncology. 2008; 27(5), 663-71.

[15] Cervantes A., Adam R., et al. Metastatic colorectal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:10-32
[16] Andre TA, Shiu KK, Kim TW, et. al. Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. N Engl J Med 2020; 383:2207-18.
[17] Saberzadeh-Ardestani B, Jones JC, McWilliams RR, et al. Metastatic site and clinical outcome of patients with deficient mismatch repair metastatic colorectal cancer treated with an immune checkpoint inhibitor in the first-line setting. Eur J Cancer. 2024;196:113433.

Product Name	Dosing/ Administration	Efficacy Information	Reference
FOLFIRI +/- bevacizumab	Irinotecan: 180 mg/m^2 IV, C1D1, Leucovorin: 400 mg/m^2 IV, C1D1, Fluorouracil: 400 mg/m^2, C1 D1-2, 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: mPFS: 7.6m mOS: 23.1m ORR: 47.2% FOLFIRI + bevacizumab: mPFS: 11.6m mOS 23.7m	Fuchs CS, Marshal J, Mitchell E, et al. J Clin Oncol. 2007; 25(30), 4779-86. Cutsem VE, Rivera F, Berry S, et al. Elsevier. 2009; 20(11), 1842-7.
FOLFIRI + cetuximab	Irinotecan: 180 mg/m^2, IV, C1D1, Leucovorin: 200 mg/m^2, IV, C1D1, Fluorouracil: bolus dose 400-500 mg/m², followed by a continuous infusion of 2,400-3,000 mg/m^2 over 46-48 hours. Cetuximab: 400 mg/m^2, IV, maintenance doses 250 mg/m², IV	Improved ORR, PFS and OS with FOLFIRI + cetuximab compared to FOLFIRI alone. FOLFIRI: mPFS: 8.0m mOS: 18.6m ORR: 38.7% FOLFIRI + cetuximab: mPFS: 8.9m mOS: 19.9m ORR: 46.9%	Cutsem EV, Kohne CH, Erika H, et al. The New England Journal of Medicine. 2009; 360, 1408-17.
Keytruda (pembrolizumab)	200 mg Q3W or 400 mg Q6W	At median follow-up 32.4m (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 44m of median follow-up. mPFS: 16.5 vs 8.2m; HR 0.60; P=0.0002 ORR: 44% vs 33% Final OS analysis: mOS: NR vs 36.7m; HR 0.74, 95% CI: 0.53-1.03	Diaz LA Jr, Shiu KK, Kim TW, et al. Lancet Oncol. 2022; 23:659-70.

Note: Data for all SOC chemotherapy 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.

2.1.2. About the product

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2.

Ipilimumab is a human monoclonal antibody that targets CTLA-4. CTLA-4 inhibition can induce de novo T-cell responses and recruit novel/additional T cells to the tumour.

Nivolumab and ipilimumab each have distinct, but complementary, mechanisms of action, which may enhance responsiveness to the combination.[18]

Nivolumab as monotherapy or in combination is approved in the EU for the treatment of a wide variety of solid tumours and haematological malignancies. Nivolumab in combination with ipilimumab is approved in the EU for the treatment of melanoma, RCC, NSCLC, MPM, and OSCC. In addition, nivolumab in

[18] Nikoo M, Rabiee F, et al. Nivolumab plus ipilimumab combination therapy in cancer: Current evidence to data. Int Immunopharmacology 2023; 117: 109881.

combination with ipilimumab is indicated for the treatment of adult patients with dMMR/MSI-H mCRC after prior fluoropyrimidine-based combination chemotherapy (EMEA/H/C/xxxx/WS/1840, 24 Jun 2021).

The proposed dosing regimen consists of nivo 240 mg + ipi 1 mg/kg Q3W for up to 4 doses, followed by nivo 480 mg Q4W for a maximum of two years.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Two clinical studies (CA2098HW and CA209142) investigate the potential role of nivo monotherapy or combination therapy as a treatment option in MSI-H/dMMR mCRC. The current application for the 1L treatment with nivo+ipi in patients with histologically confirmed MSI-H/dMMR unresectable or mCRC is based primarily on data from pivotal study CA2098HW. It is also supported by data from study CA209142 providing evidence on contribution of the components and long-term outcomes in MSI-H/dMMR mCRC patients treated with nivo+ipi.

The design of the phase 3b randomized study CA2098HW was briefly discussed as part of the scientific advice (SA) (EMEA/H/SA/3330/4/2019/II) for the second line setting (EMEA/H/C/xxxx/WS/1840). The question was whether the data from study CA2098HW together with the results from the non-randomized phase 2 study CA209142 could facilitate an assessment of the benefit-risk of nivo+ipi in 1L patients. The design of study CA2098HW was in general considered acceptable. Issues raised related mainly to the pooling of results across lines of treatment. In addition, besides the initially planned primary endpoint being only PFS arm A (nivo monotherapy) vs PFS Arm B (nivo+ipi), comparisons of arms A with C (SOC) and B with C were needed. The lack of a ipilimumab monotherapy arm was agreed since adequate efficacy would not be anticipated. Further, in 1L and 2L setting the planned optional cross-over will confound OS, however this was acceptable from a pragmatic view given that nivolumab and ipilimumab were available for 'wild' cross-over.

The MAH clarified that they intended to strengthen the evidence in the 1L setting and dual primary endpoints would be PFS arm B vs arm A for all patients and PFS arm B vs C in 1L patients. No comparison of nivolumab monotherapy vs SOC was planned.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of nivolumab or ipilimumab.

Considering the above data, nivolumab or ipilimumab are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

Studies included in this application were conducted in accordance with the principles of GCP as defined by the ICH and were conducted to meet the ethical requirement of European Directive 2001/20/EC.

- Tabular overview of clinical studies

Study #/ Study Design	Study Population	Treatment	Number of Subjects	Key Efficacy Endpoint	Data Cutoff/ Database Lock
CA2098HW 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[a]	1L randomized; Arm B (N = 202) and Arm C (N = 101)	PFS per BICR in subjects with centrally confirmed MSI-H/dMMR mCRC	12-Oct-2023/ 15-Nov-2023
CA209142 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

[a] 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.

2.3.2. Clinical pharmacology

No clinical pharmacology package is submitted in the current application because the pharmacology of nivolumab monotherapy and in combination with ipilimumab is well established.

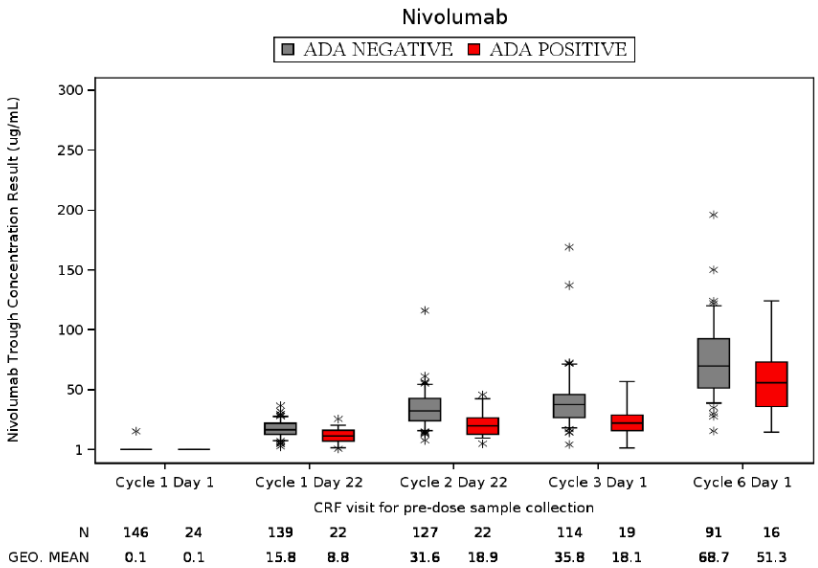
Nevertheless, immunogenicity was evaluated in the pivotal study, CA2098HW. Of the 177 nivo ADA-evaluable patients in the nivo+ipi arm, 12 (6.8%) patients were nivo ADA-positive at baseline, and 25 (14.1%) patients were treatment-emergent nivo ADA-positive. No patients were persistent positive, and no patients were neutralizing ADA-positive. Nivo ADA titers were low, ranging from 1 to 32.

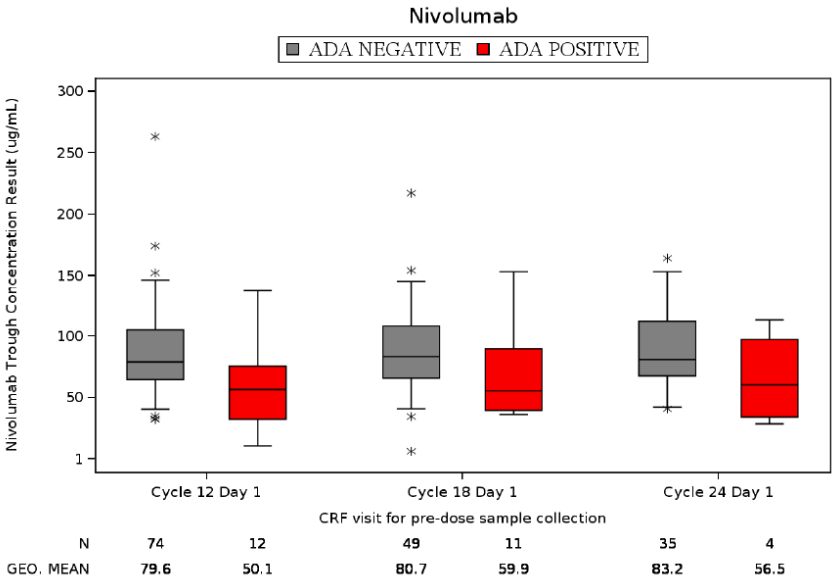
Of the 173 ipi ADA-evaluable patients in the nivo+ipi arm, 4 (2.3%) patients were ipi ADA-positive at baseline and 14 (8.1%) patients were treatment-emergent ipi ADA-positive. 1 (0.6%) patient was persistent positive for ipi ADA only. 1 (0.6%) patient was neutralizing ADA-positive for ipi ADA only (only

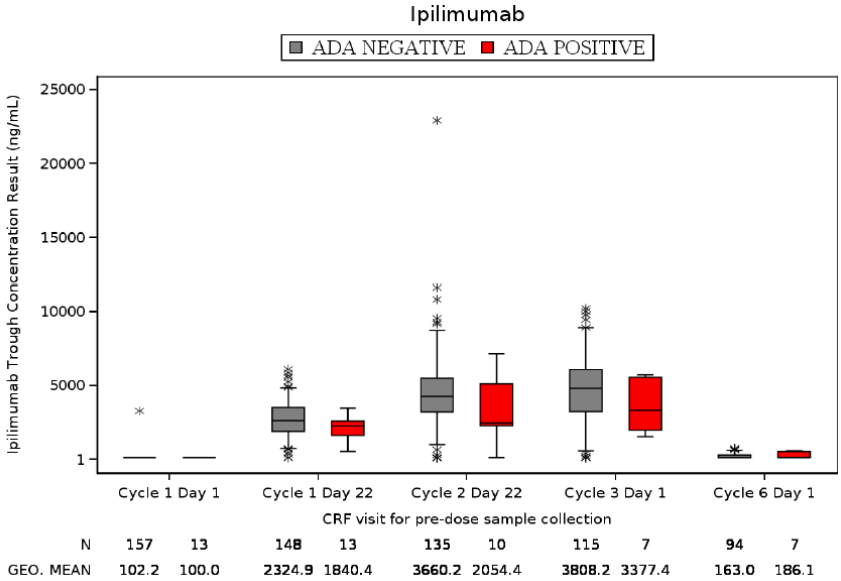
1 sample for this patient tested positive for ipi ADA and neutralizing ADA; all subsequent samples were ADA-negative).

The observed trough concentrations in patients with positive ADA (for either nivo or ipi) were within the concentration range observed in patients with negative ADA (for either nivo or ipi), although the distribution of observed trough concentrations in patients with positive ADA appeared to be slightly lower compared to that in patients with negative ADA at several assessment timepoints (Figure 1).

Figure 1 Distribution of trough concentrations at each assessment over time by ADA status - all subjects who are ADA Positive/Negative for both Nivo and Ipi







2.3.3. Discussion and conclusions on clinical pharmacology

Data on immunogenicity and the lower, but overlapping, geometric mean Ctrough values of nivolumab and ipilimumab in ADA positive patients were consistent with previous observations for this combination. The presence of nivo or ipi ADA did not appear to impact efficacy (data not shown) or safety (see Section 2.5.).

No further clinical pharmacology data is submitted in the current application which is acceptable as the pharmacology of nivolumab monotherapy and in combination with ipilimumab is well established.

2.4. Clinical efficacy

The efficacy data supporting this extension of indication are based on a single pivotal study, CA2098HW, which is an ongoing phase 3, randomized, 3-arm, open-label study of nivo (Arm A), nivo+ipi (Arm B) or investigator's choice chemo (Arm C) in patients with histologically confirmed recurrent or mCRC with known tumour MSI-H or dMMR status. In addition, data from Cohorts 1, 2, and 3 of a Phase 2 Study CA209142 with long-term follow-up provide supportive evidence on contribution of the components and long-term benefit of nivo+ipi in MSI-H/dMMR mCRC patients (see Table 2).

Table 2 Overview of Nivolumab clinical studies in MSI-H/dMMR mCRC

Study # Study Design	**Study Population**	**Treatment**	**Number of Subjects**	**Key Efficacy Endpoint**	**Study Status/ Data Cutoff/ DBL[a]**
Pivotal Study					
CA2098HW Phase 3, randomized, 3-arm open-label study of nivo, nivo+ipi or investigator's choice chemo[b]	Subjects with mCRC with known tumor MSI-H/ dMMR status per local standard of practice testing	**Arm A**: nivo 240 mg Q2W x 6, then nivo 480 mg Q4W **Arm B**: nivo 240 mg + ipi 1 mg/kg Q3W x 4, then nivo 480 mg Q4W **Arm C**: investigator's choice chemo*	1L Randomized; **Arm B** (N = 202) and **Arm C** (N = 101)	PFS per BICR in subjects with centrally confirmed MSI-H/dMMR mCRC	Ongoing 12-Oct-2023 15-Nov-2023
Supportive Study					

Study # Study Design	Study Population	Treatment	Number of Subjects	Key Efficacy Endpoint	Study Status/ Data Cutoff/ DBL[a]
CA209142 Phase 2, multicohort, open-label, nonrandomized 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	Ongoing 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, then nivo 3 mg/kg Q2W	N = 119 treated	ORR per BICR, PFS per BICR, and OS	Ongoing 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	Ongoing 25-Sep-2020 22-Oct-2020

[a] Data cutoff/DBL dates used for the analyses presented in this report

[b] Investigator's choice chemo: mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab

2.4.1. Dose response studies

No dose-response studies were submitted as part of this application.

2.4.2. Main study

Study CA2098HW

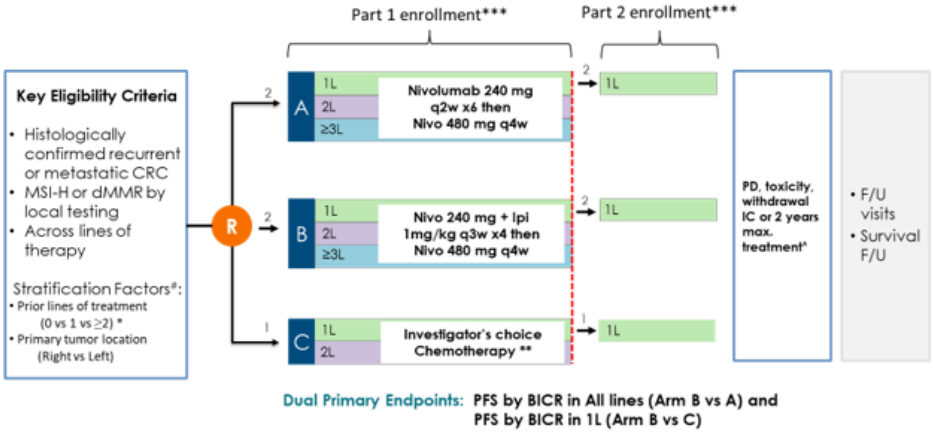
A phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (DMMR) metastatic colorectal cancer.

Study 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) in patients with histologically confirmed recurrent or mCRC with known tumour MSI-H or dMMR status. All patients were to have measurable disease by CT or MRI per RECIST 1.1 criteria and an ECOG PS ≤ 1. The study enrolment includes 2 sequential parts. Part 1 enrolment was open to patients across all lines of therapy, and Part 2 enrolment was open only to patients who had not received prior therapy for metastatic disease (1L patients). Enrolment in Part 2 started immediately after completion of Part 1 enrolment. Eligible 1L and 2L patients were randomized to Arm A (nivo), Arm B (nivo+ipi), or Arm C (chemo) in a 2:2:1 ratio and ≥ 3L patients were randomized to Arm A (nivo) and Arm B (nivo+ipi) in a 1:1 ratio. Patient's randomization was stratified by tumour location (right vs left) and by the number of prior treatments for metastatic disease (none, 1, ≥ 2, for Part 1 only). Patients in the chemo arm who experienced documented progression of disease per RECIST 1.1 by BICR had an option to crossover to receive nivo+ipi therapy (Crossover Cohort).

The dual primary endpoints were 1) PFS per RECIST 1.1 by BICR in all lines patients with centrally confirmed MSI-H/dMMR mCRC and 2) PFS per RECIST 1.1 by BICR 1L patients with centrally confirmed MSI-H/dMMR mCRC.

The clinical data cutoff for this CSR was 12 Oct 2023. In 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC in the nivo+ipi and chemo arms, minimum follow-up was 6.1 months and the median follow-up was 31.57 months.

Figure 2 Study schematic CA2098HW



1L, 2L, ≥ 3L: subgroups of subjects within each study arm for whom study treatment is 1L (0 prior lines of systemic therapy), 2L (1 prior line of systemic therapy) or 3L and beyond (2 or more prior lines of systemic therapy), respectively.

Line of therapy is not a stratification factor during Part 2 enrollment.

* Subjects with ≥ 2 prior lines were randomized only to Arm A or B during Part 1 enrollment; only subjects with 0 prior lines were randomized during Part 2 enrollment.

** Optional crossover for Arm C with nivo 240 mg Q2W x 6, then nivo 480 mg Q4W + ipi 1 mg/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 status who had not received prior therapy for metastatic disease (1L).

^ max treatment duration is not applicable for subjects in Arm C.

Rationale for selection of the dosing regimens is provided in Section 5.5 of the protocol.

Dual primary endpoints: 1) PFS per BICR in all lines subjects with centrally confirmed MSI-H/dMMR mCRC and 2) PFS per BICR in 1L subjects with centrally confirmed MSI-H/dMMR mCRC.

Methods

Study participants

Main inclusion criteria:

- Male or female ≥18 years of age
- Histologically confirmed recurrent or mCRC irrespective of prior treatment history with chemotherapy and/or targeted agents not amenable to surgery. This inclusion criterion is applicable only during Part 1* enrolment of the study.
- Histologically confirmed recurrent or mCRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery. Participants treated with adjuvant chemotherapy are eligible if disease progression occurred later than 6 months (≥ 6 months) after completion of chemotherapy. This inclusion criterion is applicable during Part 2* enrolment of the study.
- Known tumour MSI-H or dMMR status per local standard of practice.
- All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria.
- Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately.

- Adequate tumour tissue available. Tumour tissue specimens, either a FFPE tissue block (preferred) or unstained tumour tissue sections (minimum of 30 positively charged slides) from primary or metastatic site, must be submitted to the central laboratory. Central laboratory must provide IRT with confirmation of receipt of evaluable tumour tissue prior to randomization. Tumour tissue specimen must meet either of the criteria below:

    - Obtained within 3 months of enrolment with no intervening systemic anti-cancer treatment between time of acquisition and randomization AND this must be the same tissue sample as was used for local MMR/MSI testing;

    OR

    - If above is not available, archival tissue can be accepted if the same tissue was used for MMR/MSI testing.

    Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone samples are also unacceptable for submission.
- ECOG Performance Status ≤1
- Female participants of childbearing potential must have had a negative serum or urine pregnancy test within 24 hours prior to receiving the first dose of study medication
- Female participants of childbearing potential must have been willing to use an adequate method of contraception
- Female participants must not be breastfeeding
- Male participants of childbearing potential who are assigned to receive chemotherapy must have agreed to use an adequate method of contraception

Main key exclusion criteria:

- Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. (CT scan is acceptable if there is a contraindication for MRI). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 14 days prior to study drug administration.
- Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.
- History of interstitial lung disease or pneumonitis.
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured (for example squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast).

- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
- Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Clinically significant cardiovascular disease
- Clinically significant bleeding diathesis or coagulopathy.
- Non-healing wound, ulcer, or bone fracture.
- History of gastrointestinal perforation or abscess within 6 month prior to enrolment.
- Persistence of toxicities related to first-line chemotherapy grade > 1 (CTCAE v5.0) (except alopecia, fatigue or peripheral sensory neuropathy which can be Grade 2)
- 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-tumour vaccines or other immuno-stimulatory antitumor agents.
- Prior systemic anti-cancer treatment must have been completed at least 14 days prior to randomization.
- Participants who have received a live/attenuated vaccine within 30 days of randomization (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]). If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrolment must be delayed until the biologic impact of the vaccine or investigational product is stabilized.
- Current treatment with a non-topical medications known to be a strong inducers or inhibitors of CYP3A4, or strong inhibitors of UGT1A1. However, patients who either discontinue this treatment or switch to another medication at least 7 days prior to starting study treatment are eligible.

Treatments

Nivolumab monotherapy (Arm A)

Nivolumab at a dose of 240 mg as a 30 minute infusion on Day 1, and every 2 weeks (± 3 days) thereafter during Cycles 1 and 2 for a total of 6 doses (Q2W × 6 doses). Starting from Cycle 3 Day 1 participants should receive nivolumab as a 30 minutes infusion at a dose of 480 mg every 4 weeks (Q4W).

Nivolumab plus ipilimumab (Arm B)

Nivolumab at a dose of 240 mg as a 30 minute IV infusion followed by ipilimumab at a dose of 1 mg/kg administered IV over 30 minutes on Day 1 of Cycle 1 and every 3 weeks (± 3 days) thereafter during Cycles 1 and 2 for a total of 4 doses (Q3W × 4 doses). Starting from Cycle 3 Day 1 participants should receive nivolumab as a 30 minutes infusion at a dose of 480 mg every 4 weeks (Q4W).

Table 3 Selection and timing of dose for Nivolumab plus Ipilimumab combination therapy

	Cycle 1 (cycle = 6 weeks)		Cycle 2 (cycle = 6 weeks)		Cycle 3 and Beyond (cycle = 4 weeks)
	Day 1	Day 22	Day 1	Day 22	Day 1 of every 4 weeks
Nivolumab, 240 mg flat dose	X	X	X	X	--
Ipilimumab, 1 mg/kg	X	X	X	X	--
Nivolumab, 480 mg flat dose	--	--	--	--	X

Investigator's choice chemotherapy (Arm C)

Participants randomized to the chemotherapy arm may receive one of 6 SOC regimens.

mFOLFOX6: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 bolus followed by fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 during Cycles 1 and 2. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.

mFOLFOX6 + bevacizumab: Bevacizumab 5 mg/kg by iv infusion, followed by mFOLFOX6.

mFOLFOX6 + cetuximab: Cetuximab 500 mg/m^2 by iv infusion, followed by mFOLFOX6.

FOLFIRI: irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 and fluorouracil 2400 mg/m^2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.

FOLFIRI + bevacizumab: Bevacizumab 5 mg/kg by iv infusion, followed by FOLFIRI.

FOLFIRI + cetuximab: Cetuximab 500 mg/m^2 by iv infusion, followed by FOLFIRI.

Treatment duration:

Treatment should be continued until disease progression, toxicity, discontinuation for other reasons, or the maximum treatment duration was reached (2 years for nivo and nivo+ipi). In participants with late response (during second year of treatment nivo or nivo+ipi) study treatment could continue for up to an additional 12 months after onset of response. 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. The maximum treatment duration includes treatment beyond progression.

Patients in the chemo arm who experienced documented progression of disease per response evaluation criteria in solid tumours (RECIST) 1.1 by BICR had an option to crossover to receive nivo+ipi therapy (see Table 4) if they had completed at least Follow Up Visit 1 and met all other crossover criteria outlined in the protocol (Crossover Cohort).

Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue nivolumab as a single agent.

Table 4 Selection and timing of dose for Crossover Cohort

	Cycle 1 (cycle = 6 weeks)			Cycle 2 (cycle = 6 weeks)			Cycle 3 and Beyond (cycle = 4 weeks)	
	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15
Nivolumab, 240 mg flat dose	X	X	X	X	X	X	--	--
Ipilimumab, 1 mg/kg	X	--	--	X	--	--	X C3D1 and D1 of every 3 cycles	X C4D15 and D15 of every 3 cycles
Nivolumab, 480 mg flat dose	--	--	--	--	--	--	X	--

Tumour assessment is based on CT of the chest and CT/MRI of the abdomen, pelvis, and other known/suspected sites of disease. Tumour assessment should occur every 6 weeks from randomization for the first 24 weeks, and every 8 weeks thereafter up till week 96 (2 years). Thereafter, tumour assessment should occur every 16 weeks during year 3 and every 24 weeks from year 4 and beyond.

Objectives

Besides the primary aims, the following key secondary comparisons are part of the formal testing procedure: BICR-ORR (NIVO+IPI vs. NIVO in all lines); OS (NIVO+IPI vs. NIVO in all lines); BICR-PFS (NIVO+IPI vs. NIVO in 1L); BICR-ORR (NIVO+IPI vs. CHEMO in 1L); BICR-ORR (NIVO+IPI vs. NIVO in 1L); OS (NIVO+IPI vs. NIVO in 1L); OS (NIVO+IPI vs. CHEMO in 1L). As in the comparisons for the primary objective, these analyses only include patients with centrally confirmed dMMR/MSI-H mCRC.

Of all primary and secondary objectives included in the hierarchical testing procedure, this assessment report only includes the comparison of PFS of nivo+ipi vs chemotherapy in 1L, because the number of events required for the interim analysis of the other primary endpoint is not yet reached.

Primary objective

- To compare progression-free survival (PFS) per BICR of participants with centrally confirmed dMMR/MSI-H mCRC

Secondary objectives

- To estimate the PFS per BICR of participants with locally confirmed dMMR/MSI-H mCRC
- To estimate the PFS per investigator (centrally confirmed dMMR/MSI-H mCRC)
- To estimate the PFS per BICR by each central test

Exploratory objectives

- To explore potential biomarkers associated with clinical efficacy (centrally confirmed dMMR/MSI-H mCRC)
- To estimate PFS2 per investigator (centrally confirmed dMMR/MSI-H mCRC)
- To evaluate recurrence-free survival (RFS) per investigator after curative surgery (centrally confirmed dMMR/MSI-H mCRC)
- To further define safety and tolerability (central and local testing)
- To characterize immunogenicity of nivo+ipi (central and local testing)
- To evaluate patient reported outcome (PRO) using EORTC QLQ-C30 and EORTC QLQ-CR29 scale/item scores and score changes (central and local testing)
- To evaluate PRO using EuroQoL EQ-5D-3L visual analogue scale (VAS) and utility index (UI) scores and score changes (central and local testing)
- To characterize efficacy (PFS per BICR) for patients in the Crossover cohort (centrally confirmed dMMR/MSI-H mCRC)
- To characterize the safety for patients in the Crossover cohort (central and local testing)

Outcomes/endpoints

Primary endpoint:

- PFS per BICR centrally confirmed dMMR/MSI-H mCRC: PFS is defined as the time from randomization date to date of first objectively documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first.

Secondary endpoints:

- PFS per BICR locally confirmed dMMR/MSI-H mCRC: PFS is defined as the time from randomization date to date of first objectively documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first.
- PFS per investigator centrally confirmed dMMR/MSI-H mCRC: time from randomization date to date of investigator defined documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first.
- PFS per BICR centrally confirmed dMMR/MSI-H mCRC per central test: PFS is defined as the time from randomization date to date of first objectively documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first.

Exploratory endpoints:

- PFS2: 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.
- RFS: time from date of on study curative surgery to disease recurrence per investigator per RECIST 1.1 or death due to any cause, whichever occurred first.

  Pathological response in patients undergoing surgery on study is defined as:
  - Pathologic complete response: no residual viable tumour cells
  - Major pathologic response: < 10% of residual viable tumour cells (≥ 90% reduction of the tumour cells); includes patients with pathologic complete response
  - Pathologic partial response: < 50% but ≥ 10% of residual viable tumour cells (≥ 50% reduction of tumour cells)
  - Pathologic non-response: ≥ 50% residual viable tumour cells (< 50% reduction of tumour cells)
- Patient reported outcomes:
  - Mean score change from baseline for EORTC QLQ-C30 global health status/subscales. For EORTC QLQ-C30 scales, a meaningful difference in the change from baseline was ≥ 10 points
  - Mean score change in EORTC QLQ-CR29 symptom scores

Mean score change in For EQ-5D-3L VAS and UI. A meaningful change (MID) from baseline was 7 points for EQ-5D-3L VAS scores. A meaningful change from baseline (MID) was 0.08 for EQ-5D-3L UI scores.

Sample size

The sample size of the study is driven by the comparison of the two primary endpoints and the secondary endpoint of PFS comparison between 1L participants randomized to arm B (nivo+ipi) and arm A (nivo).

With respect to the primary endpoint of PFS per BICR for nivo+ipi vs chemo in 1L patients with centrally confirmed MSI-H/dMMR mCRC, it was assumed that the distribution of PFS in arm C in 1L follows exponential distribution with median PFS of 9 months. For PFS in arm B, however, a piecewise exponential distribution was assumed due to an expected plateau in the PFS curve, with a median PFS of approximately 56 months. 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 patients with centrally confirmed MSI-H/dMMR mCRC to the nivo+ipi and chemo arms during Part 1 and Part 2 enrolment at a 2:1 ratio.

An interim analysis was planned to be conducted when 85% of the total number of events were observed (approximately 106 events) and after the last patient was randomized in Part 2. At the time of the interim analysis, the information fraction was 80.0% (100/125). The final analysis is projected to be approximately 47 months, from the date of first participant being randomized to Part 1.

Randomisation

Eligible 1L and 2L patients were randomized to Arm A (nivo), Arm B (nivo+ipi), or Arm C (chemo) in a 2:2:1 ratio and ≥ 3L patients were randomized to Arm A (nivo) and Arm B (nivo+ipi) in a 1:1 ratio. The choice of chemotherapy regimen should be declared prior to randomization and this information be documented in the patients' medical records. Patients were randomized through Interactive Response Technology (IRT). Randomization was stratified by tumour location (right vs left) and by the number of prior treatments for metastatic disease (none, 1, ≥ 2, for Part 1 only).

Blinding (masking)

This is an open-label study.

Assessment of primary end point (PFS per BICR) will be done by BICR who will remained blinded to patient treatment assignment.

Statistical methods

Definition of primary endpoint

PFS is defined as the time from randomization date to the date of first objectively documented disease progression per RECIST 1.1 (i.e., radiologic) or death due to any cause, whichever occurs first. The following censoring rules are applied: Participants who receive subsequent anti-cancer therapy (including all systemic therapies, non-palliative radiotherapy or any radiotherapy administered on target lesions, and all surgeries) or switch to crossover will be censored at the date of the last evaluable tumour assessment conducted on or prior to the initiation of the subsequent anti-cancer therapy/crossover, participants who did not progress or die are censored on the date of their last evaluable tumour assessment, and participants who did not have any on study tumour assessments and did not die will be censored on their date of randomization.

Statistical analyses

Primary efficacy endpoint

The primary analysis comparing PFS (arm B vs. arm C in 1L) consists of a stratified log-rank test with stratification factor tumour sidedness (left vs right) per IRT ('as randomized') among all randomized patients with centrally confirmed dMMR/MSI-H mCRC. In addition, the following information is presented: the estimated HR (with 95% and adjusted CIs), obtained via a stratified Cox proportional hazards model; KM curves; estimates of the median PFS (with 95% CIs); and PFS rates (with 95% CIs) at fixed time points.

Supportive analyses

In total, 11 supportive analyses are specified. In summary, supportive analysis 1 and 2 concern the assessment of model/analysis assumptions: evaluation of the proportional hazard assumption, and the stratified log-rank test assumption of the treatment effect being equal among strata. If proportionality is considered unlikely, a max-combo test will be performed. Also, the hazard ratio will be estimated in two periods separately, with a cut-off point determined via a grid search. The third supportive analysis consists of a multivariate Cox regression model, adjusting for known or potential prognostic factors (age, sex, ECOG performance status, disease stage at initial diagnosis, liver metastasis per BICR, and PD-L1 status; the factors used in the randomization will be included in the model as stratification factors). Fourth, the distribution of baseline characteristics (demographics, disease characteristics and the stratification factors) between the two treatment arms will be inspected for potential imbalance in the subgroup of participants with centrally confirmed dMMR/MSI-H, with the option to perform additional adjusted analyses if a pronounced imbalance exist. Supportive analysis 5-7 are performed to assess the impact of stratification, and concern an analysis of PFS using stratification factors as obtained from the baseline CRF pages instead of from the IRT (performed only if at least one stratification variable/factor at randomization (as per IRT) and baseline are not concordant for at least 10% of the centrally confirmed dMMR/MSI-H randomized participants for the treatment arms and line of therapy of the comparison), an analysis of PFS using an un-stratified log-rank test, and a PFS analysis using an unstratified Cox proportional hazards model, adjusted for the stratification factors used in the randomization. Supportive analysis 8 uses a definition of PFS where events (progression or death) and disease assessments that occurred on or after subsequent anti-cancer therapy will be considered (no time point truncation), referred to as the 'EMA definition'. Supportive analysis 9 will evaluate the concordance between BICR vs. investigator assessment of PFS. In supportive analysis 10, patients with two or more consecutively missing disease assessments prior to a PFS event will be censored at the last disease assessment date prior the PFS event. Lastly, in analysis 11 (only performed if at least 10% of the progression-free participants are lost to follow-up), progression-free participants who are lost to follow-up for any cause will be considered as having an event at the time of the last tumour assessment date prior to loss to follow-up.

Subgroup analyses are prespecified for a range of baseline characteristics (see results section ancillary analyses 2.4.2.).

Analyses of secondary endpoints included in the current interim report

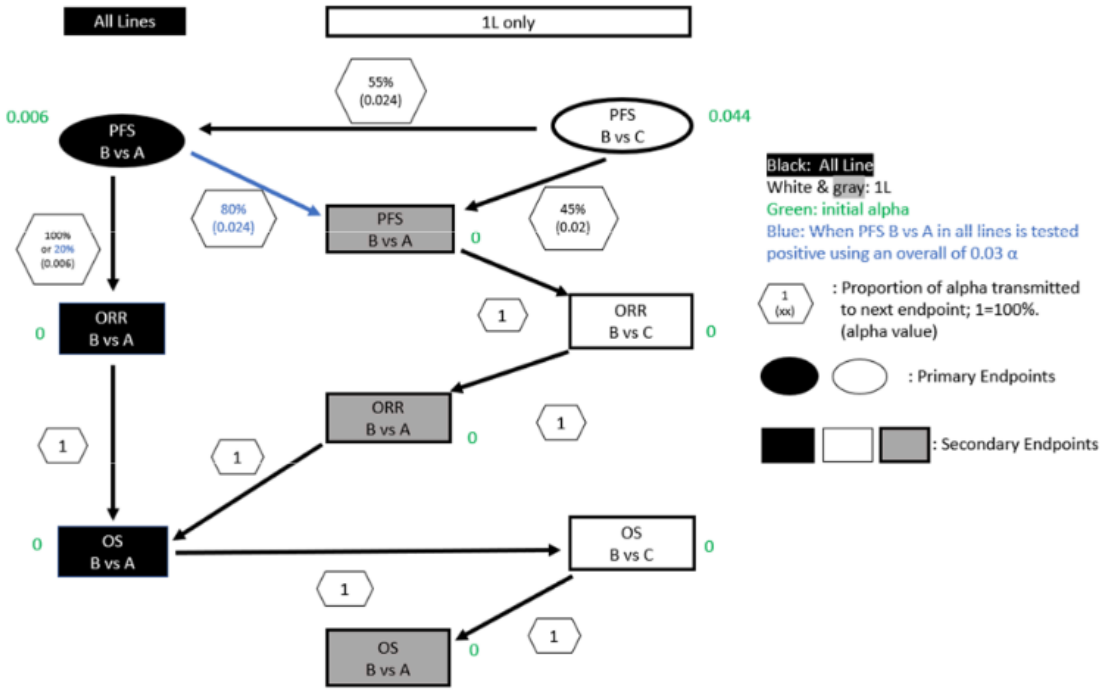
The analyses of secondary endpoints included in the current interim report (PFS by investigator nivo+ipi vs chemo in 1L randomized patients with centrally confirmed MSI-H/dMMR, PFS per BICR in all 1L randomized patients, and PFS by BICR by each central test of MSI/MMR) are similar to the analysis of the primary endpoint. Note that these secondary outcomes are not part of the formal testing procedure.

Protection of type I error across primary and secondary endpoints

On the study level, a hierarchical testing strategy is defined for all primary and key secondary comparisons (see figure below). This procedure is based on an initial split (0.006 and 0.044) of the overall alpha between the two primary comparisons. The first analysis to be performed is the analysis of BICR-PFS (NIVO+IPI vs. CHEMO, 1L) with alpha = 0.044. If significant, the alpha is propagated in part to the other primary comparison, and in part to the secondary comparison of BICR-PFS (NIVO+IPI vs. NIVO, 1L). The second primary comparison BICR-PFS (NIVO+IPI vs. NIVO, all lines) is performed with either alpha = 0.006 or 0.03, depending on the result of BICR-PFS (NIVO+IPI vs. CHEMO, 1L). If this second primary comparison is significant, the alpha is either propagated in full to the secondary comparison BICR-ORR (NIVO+IPI vs. NIVO in all lines), if BICR-PFS (NIVO+IPI vs. CHEMO, 1L) failed to reach significance, or, otherwise, split between BICR-ORR (NIVO+IPI vs. NIVO in all lines) (20%) and BICR-PFS (NIVO+IPI vs. NIVO, 1L) (80%). Subsequent analyses of secondary outcome variables are performed sequentially (continuing only when results are significant), but with an additional possibility of performing

the comparison OS (NIVO+IPI vs. NIVO, all lines), which can be tested when either the analysis for BICR-ORR (NIVO+IPI vs. NIVO, all lines) or BICR-ORR (NIVO+IPI vs. NIVO, 1L) reaches statistical significance. The order and timing of each of the tests is prespecified in the SAP, also in relation to the study-wise interim and final analyses, is pre-specified and prescribes that, in the current interim analysis, the comparison of PFS in arm B vs. C in 1L is the only comparison included in the hierarchical testing strategy that is to be performed.

Figure 3. Hierarchical testing strategy in Study CA2098HW



A: nivolumab monotherapy; B: nivo+ipi, C; chemotherapy

Interim analyses

For both primary comparisons, as well as for the secondary comparison of PFS (B vs A in 1L), an interim analysis is planned, using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

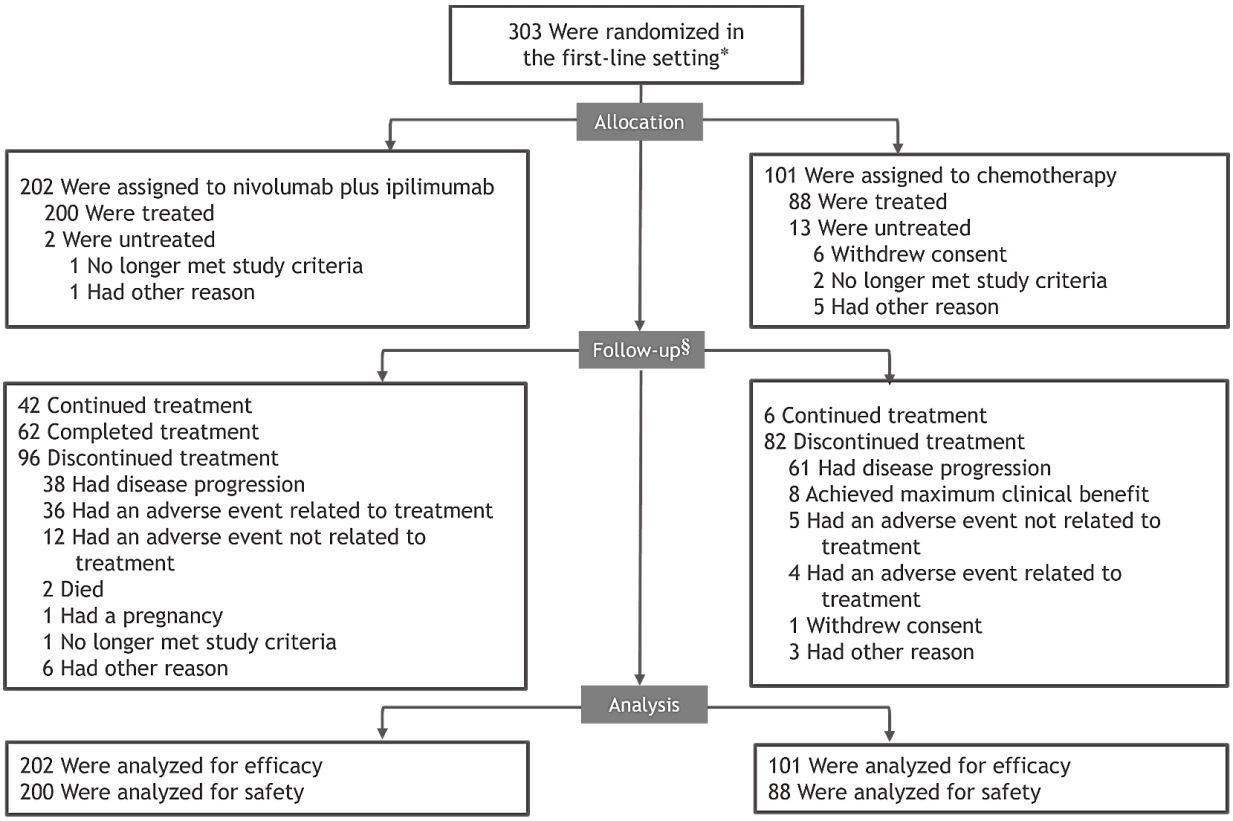
For the analysis of the primary endpoint of PFS per BICR for nivo+ipi vs chemo in 1L patients with centrally confirmed MSI-H/dMMR mCRC, the overall initially allocated alpha of 0.044 will be distributed over the interim and final analysis based on the actual number of PFS by BICR events observed at the interim analysis. If the observed number of PFS by BICR events B vs C in 1L at this interim analysis would have been exactly 106 (85% of the target 125 PFS events), the significance level used for this interim analysis would be 0.0258. However, because the observed number of OFS events is slightly lower than anticipated (100, 80% of the target PFS events), the significance level that is used for this interim analysis is reduced to 0.0209.

Per the SAP, the two interim analyses for the primary objectives were to be event-driven, i.e. performed using separate database locks, but could be combined and conducted at the latest projected time when the projection suggests that they would occur within 3 months from each other.

Results

Participant flow

Figure 4 Subject disposition consort diagram – All 1L randomized subjects – CA2098HW



In CA2098HW, 303 1L patients with MSI-H/dMMR mCRC per local testing were randomized to the nivo+ipi and chemo arms: 202 (nivo+ipi) and 101 (chemo). 288 1L patients in the nivo+ipi and chemo arms were treated: 200 (nivo+ipi) and 88 (chemo). As of the clinical data cutoff (12 October 2023), 21.0% patients in the nivo+ipi arm and 6.8% patients in the chemo arm were continuing in the treatment period. The overall percentage of 1L patients who discontinued treatment was lower in the nivo+ipi arm (48.0%) than the chemo arm (93.2%). This difference was largely due to discontinuation of treatment due to disease progression (19.0% in the nivo+ipi arm and 69.3% in the chemo arm). As of the clinical data cutoff, a higher proportion of patients in the nivo+ipi arm than the chemo arm was ongoing in the study (76.0% vs 56.8%). In both arms, death was a primary reason for discontinuing the study (22.0% in the nivo+ipi arm and 36.4% in the chemo arm).

The disposition summaries for 1L randomized/treated patients with centrally confirmed MSI-H/dMMR (n=255, n=171 nivo+ipi and n=84 chemo) were consistent with those for all 1L randomized/treated patients (Table 5).

Table 5 End of Treatment Period Status Summary - All 1L Randomized and 1L Treated Subjects with MSI-H/dMMR mCRC in the Nivo+Ipi and Chemo Arms in CA2098HW, DCO 12 October 2023

	All 1L Subjects		All 1L Subjects with Centrally Confirmed MSI-H/dMMR	
Status, n (%)	**Nivo+Ipi**	**Chemo**	**Nivo+Ipi**	**Chemo**
Randomized	202	101	171	84
Treated	200 (99.0)	88 (87.1)	170 (99.4)	75 (89.3)
Not Treated	2 (1.0)	13 (12.9)	1 (0.6)	9 (10.7)
Reason for not treated				
Subject withdrew consent	0	6 (5.9)	0	5 (6.0)
Subject no longer meets study criteria	1 (0.5)	2 (2.0)	0	1 (1.2)
Other	1 (0.5)	5 (5.0)	1 (0.6)	3 (3.6)
Ongoing treatment	42 (21.0)	6 (6.8)	41 (24.1)	6 (8.0)
Completed treatment	62 (31.0)	0	60 (35.3)	0
Discontinued treatment	96 (48.0)	82 (93.2)	69 (40.6)	69 (92.0)
Reason for discontinuation of treatment				
Subject withdrew consent	0	1 (1.1)	0	1 (1.3)
Death	2 (1.0)	0	2 (1.2)	0
Pregnancy	1 (0.5)	0	1 (0.6)	0
Subject no longer meets study criteria	1 (0.5)	0	0	0
Other	6 (3.0)	3 (3.4)	6 (3.5)	3 (4.0)
Disease progression	38 (19.0)	61 (69.3)	20 (11.8)	50 (66.7)
Study drug toxicity	36 (18.0)	4 (4.5)	32 (18.8)	3 (4.0)
Adverse event unrelated to study drug	12 (6.0)	5 (5.7)	8 (4.7)	5 (6.7)
Maximum clinical benefit	0	8 (9.1)	0	7 (9.3)
Discontinued treatment due to COVID-19	2 (1.0)	0	2 (1.2)	0
Ongoing study[a]	152 (76.0)	50 (56.8)	140 (82.4)	46 (61.3)
Discontinued study[a]	48 (24.0)	38 (43.2)	30 (17.6)	29 (38.7)
Reason for discontinuation of study				
Death	44 (22.0)	32 (36.4)	26 (15.3)	24 (32.0)
Lost to follow-up	1 (0.5)	0	1 (0.6)	0
Subject withdrew consent	2 (1.0)	3 (3.4)	2 (1.2)	2 (2.7)
Other	1 (0.5)	3 (3.4)	1 (0.6)	3 (4.0)

[a]Includes data from crossover period.

End of treatment status evaluated at the end of main period treatment for subjects continued to crossover.

Only 1L subjects are included for nivo+ipi arm and chemo arm. Percentages based on subjects entering period.

Recruitment

A total of 303 1L patients were randomized to the nivo+ipi and chemo arms: 202 (nivo+ipi) and 101 (chemo). These patients were randomized at 88 sites in 22 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, Romania, Spain, Turkey, United Kingdom [UK], and United States [US]). The first patient with centrally confirmed MSI-H/dMMR CRC in the 1L setting was randomized at 30 Sep 2019 and the last patient for the IA was randomized at 10 April 2023.

Study CA2098HW is ongoing; this report is based on the first interim analysis for PFS with data cutoff date of 12 Oct 2023 . Median duration of follow-up (time from randomization to DCO) at the time of data cutoff was 31.57 months (range: 6.1-48.4). Median survival follow-up (time from randomization to last known alive or death data) was 22.51 months (range 0-48.4).

Conduct of the study

Protocol amendments

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. Information on the key global changes to the protocol, which are relevant to the final study design, and the accrual/randomization numbers at the time of each protocol revision or amendment are summarized below (Table 6).

Table 6 Summary of original global protocol and global changes to protocol CA2098HW

Document /Date	Summary of Key Changes	Rationale for Change(s)	Planned Sample Size	Subjects Randomized at time of Protocol 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	• To fulfill the US FDA PMR associated with the Accelerated Approval of nivo in subjects with previously treated recurrent or metastatic MSI-H	97 treated subjects (with centrally confirmed MSI-H mCRC)	0
Revised Global Protocol 01[a] 16-May-2018	• Modified inclusion criteria to include patients who had received 1L chemo as a triplet chemo combination (FOLFOXIRI).	• To clarify the eligibility criteria permitting enrollment of subjects who received 1L FOLFOXIRI given that these subjects were exposed to both oxaliplatin and irinotecan as part of 1 regimen.	97 treated subjects (with centrally confirmed MSI-H 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** (in all randomized subjects) • Included OS, BICR-assessed ORR, DCR and DoR, and investigator-assessed PFS, ORR, DCR, and DCR as key secondary endpoints.	• To allow for the direct comparison of nivo+ipi with nivo. • To support the analytical and clinical validation of an IHC-based and a PCR-based in vitro diagnostic device essential to the safe and effective use of nivo and/or nivo+ipi in MSI-H/dMMR mCRC.	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 • 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.	• To provide clinical context of current standard of care by generating supportive evidence on the efficacy (BICR- and investigator-assessed PFS, ORR, DCR, and DoR) and safety of immunotherapy (nivo+ipi) vs chemo in 1L and 2L settings in a prospective randomized study. • To ensure that subjects in Arm C (chemo) will have access to immunotherapy treatment after BICR-assessed progression.	447 randomized subjects (with centrally confirmed MSI-H/dMMR mCRC)	0
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 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.	• To power the comparison of nivo+ipi vs chemo in 1L subjects	**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

Table 6 Continued Summary of original global protocol and global changes to protocol CA2098HW

Document /Date	Summary of Key Changes	Rationale for Change(s)	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
Revised Global Protocol 04 17-Jul-2020 (continued)	• 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.	• To include dose modification criteria and AE management algorithms for IO therapy based on CTCAE v5. • To include program level requirements for SARS-CoV-2 and updates regarding male contraception requirements.	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	• To optimize the statistical testing strategy for the primary endpoints. • To decrease the burden on the study subjects by reducing the frequency of tumor assessments after the first 2 years from randomization.	Same as Revised Protocol 04	666
Global Protocol Amendment 07[b] 10-May-2022	• Revised the projection of the number of randomized subjects based on local MSI-H/dMMR. • Updated and streamlined the statistical analyses schedule. • Included additional safety language for oxaliplatin use. • Clarified contraception requirements for study subjects.	• To adjust for higher than initially assumed discordance rate between central and local MSI-H/dMMR testing results, the number of randomized subjects based on local MSI-H/dMMR was increased. • To reflect new enrollment timelines for Part 2, the statistical analyses schedule was updated and streamlined. • To comply with Health Authorities' requests (revised safety language and contraception requirements)	**Part 1:** 560 randomized subjects (local testing) 442 randomized subjects (with centrally confirmed MSI-H/ dMMR mCRC) **Part 2:** 271 randomized subjects (local testing) 230 randomized subjects (with centrally confirmed MSI-H/ dMMR mCRC)	748
Global Protocol Amendment 08[b] 04-Aug-2022	• Specified that a DMC will assess the interim study data and provide a recommendation to BMS on the next steps with regards to study conduct.	• To implement an independent assessment of the interim study data (using an independent data monitoring committee) without unblinding the sponsor.	Same as Protocol Amendment 07	771
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.	• Given the heterogeneity of patient populations (1L and all randomized subjects) and different mode of action of study drugs (chemo and IO therapy), the PFS event accumulation may not align for the 2 primary endpoints. • Conducting the interim analysis of the 2 primary endpoints at separate times would avoid a significant delay if 1 of the 2 primary endpoints had reached the required number of events for its interim analysis.	Same as Protocol Amendment 07	841[d]

[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 number of randomized subjects at the time of Global Protocol Amendment 09 does not include subjects who were randomized in the China substudy.

Protocol deviations

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 patient's rights, safety, or well-being. The MAH has modified the terminology, reporting process, and categorization of protocol deviations. As this study was ongoing at the time of the effective date of the updated procedure for reporting and classifying protocol deviations, both important and significant deviations are included as important protocol deviations in this CSR.

Overall, 51.8% of 1L randomized patients in the nivo+ipi and chemo arms had at least 1 important protocol deviation (Table 8). Important protocol deviations in the category of trial procedures were reported in 39.6% of patients in both the nivo+ipi and chemo arms. Most of these deviations were related to image scans performed outside of the protocol-specified window for some visits (including baseline), survival follow-up performed outside of the protocol-specified window, and QoL questionnaires not completed for some visits. Upon review, important protocol deviations in the inclusion/exclusion category were assigned correctly in 2.5% and 6.9% of patients in the nivo+ipi and chemo arms, respectively.

Table 7 Important protocol deviations: All 1L randomized patients in the nivo+ipi and chemo arms

	Number of Subjects (%)		
Important Protocol Deviations Category	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)
OTHER	0	0	0

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

Relevant protocol deviations are protocol deviations that could affect the interpretability of key study results. Overall, 5.3% of 1L randomized patients in the nivo+ipi and chemo arms had at least 1 relevant protocol deviation and frequencies were comparable between treatment arms (Table 9).

Table 8 Relevant protocol deviations summary: All 1L randomized patients in the nivo+ipi and chemo arms

	Number of Subjects (%)		
	Arm B: Nivo + Ipi N = 202	Arm C: Chemo N = 101	Total N = 303
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 STATUS	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	6 (3.0)	3 (3.0)	9 (3.0)
ON-STUDY			
SUBJECTS RECEIVING CONCURRENT ANTI-CANCER THERAPY	0	1 (1.0)	1 (0.3)

Excludes data collected on or after first crossover dose date.

Baseline data

In 1L randomized patients in the nivo+ipi and chemo arms, baseline characteristics were generally well balanced between the two arms (Table 10). There was a numerically higher proportion of patients in the nivo+ipi arm than the chemo arm with age < 65 years (57.9% vs 45.5%) and PD-L1 ≥ 1% (21.3% vs 11.9%). The nivo+ipi arm had a lower proportion of patients with Lynch syndrome compared with the chemo arm (10.9% vs 16.8%); however, 26.4% of patients overall had unknown or unreported status for

Lynch syndrome. Baseline characteristics for 1L randomized patients with centrally confirmed MSI-H/dMMR were consistent with those for all 1L randomized patients.

Table 9 Selected demographics and baseline characteristics – All 1L randomized subjects with MSI-H/dMMR mCRC in the nivo+ipi and chemo arms – CA2098HW

	All 1L Randomized Subjects			All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	
	Nivo+Ipi N =202	Chemo N = 101	Total N=303	Nivo+Ipi N = 171	Chemo N = 84
AGE (YEARS)					
MEDIAN	62	65	63	62	65
MIN , MAX	21 , 86	26 , 87	21 , 87	21 , 86	26 , 87
AGE CATEGORIZATION (%)					
< 65	117 (57.9)	46 (45.5)	163 (53.8)	98 (57.3)	40 (47.6)
≥ 65	85 (42.1)	55 (54.5)	140 (46.2)	73 (42.7)	44 (52.4)
< 75	165 (81.7)	85 (84.2)	250 (82.5)	137 (80.1)	71 (84.5)
≥ 75	37 (18.3)	16 (15.8)	53 (17.5)	34 (19.9)	13 (15.5)
SEX (%)					
MALE	95 (47.0)	45 (44.6)	140 (46.2)	79 (46.2)	38 (45.2)
FEMALE	107 (53.0)	56 (55.4)	163 (53.8)	92 (53.8)	46 (54.8)
RACE (%)					
WHITE	176 (87.1)	85 (84.2)	261 (86.1)	147 (86.0)	68 (81.0)
BLACK OR AFRICAN AMERICAN	2 (1.0)	2 (2.0)	4 (1.3)	2 (1.2)	2 (2.4)
ASIAN	19 (9.4)	13 (12.9)	32 (10.6)	17 (9.9)	13 (15.5)
OTHER	5 (2.5)	1 (1.0)	6 (2.0)	5 (2.9)	1 (1.2)
ETHNICITY (%)					
HISPANIC OR LATINO	24 (11.9)	8 (7.9)	32 (10.6)	22 (12.9)	7 (8.3)
NOT HISPANIC OR LATINO	96 (47.5)	55 (54.5)	151 (49.8)	79 (46.2)	45 (53.6)
NOT REPORTED	82 (40.6)	38 (37.6)	120 (39.6)	70 (40.9)	32 (38.1)
COUNTRY BY GEOGRAPHIC REGION (%)					
US/CANADA/EUROPE	133 (65.8)	71 (70.3)	204 (67.3)	109 (63.7)	58 (69.0)
ASIA	19 (9.4)	11 (10.9)	30 (9.9)	17 (9.9)	11 (13.1)
REST OF WORLD	50 (24.8)	19 (18.8)	69 (22.8)	45 (26.3)	15 (17.9)
ECOG PERFORMANCE STATUS (%)					
0	111 (55.0)	52 (51.5)	163 (53.8)	97 (56.7)	45 (53.6)
≥ 1 (A)	91 (45.0)	49 (48.5)	140 (46.2)	74 (43.3)	39 (46.4)
WEIGHT (KG)					
MEDIAN	67.45	71	68.00	67.5	71
MIN , MAX	37.0, 178.0	39.3, 128.0	37.0, 178.0	37.0, 178.0	39.3, 128.0
DISEASE STAGE AT INITIAL DIAGNOSIS (%)					
STAGE II	43 (21.3)	17 (16.8)	60 (19.8)	37 (21.6)	16 (19.0)
STAGE III	73 (36.1)	35 (34.7)	108 (35.6)	60 (35.1)	32 (38.1)
STAGE IV	85 (42.1)	49 (48.5)	134 (44.2)	74 (43.3)	36 (42.9)
NOT REPORTED	1 (0.5)	0	1 (0.3)	0	0

	All 1L Randomized Subjects			All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	
	Nivo+Ipi N =202	Chemo N = 101	Total N=303	Nivo+Ipi N = 171	Chemo N = 84
DISEASE STAGE AT STUDY ENTRY (%)					
STAGE IVA	80 (39.6)	43 (42.6)	123 (40.6)	64 (37.4)	35 (41.7)
STAGE IVB	60 (29.7)	27 (26.7)	87 (28.7)	53 (31.0)	22 (26.2)
STAGE IVC	62 (30.7)	31 (30.7)	93 (30.7)	54 (31.6)	27 (32.1)
HISTOLOGICAL GRADE (%)					
GX	28 (13.9)	18 (17.8)	46 (15.2)	23 (13.5)	12 (14.3)
G1	22 (10.9)	13 (12.9)	35 (11.6)	16 (9.4)	11 (13.1)
G2	74 (36.6)	38 (37.6)	112 (37.0)	60 (35.1)	33 (39.3)
G3	71 (35.1)	32 (31.7)	103 (34.0)	65 (38.0)	28 (33.3)
G4	6 (3.0)	0	6 (2.0)	6 (3.5)	0
NOT REPORTED	1 (0.5)	0	1 (0.3)	1 (0.6)	0
CELL TYPE (%)					
ADENOCARCINOMA	193 (95.5)	95 (94.1)	288 (95.0)	162 (94.7)	80 (95.2)
OTHER TYPES	9 (4.5)	6 (5.9)	15 (5.0)	9 (5.3)	4 (4.8)
TUMOR LOCATION (%)					
CECUM	19 (9.4)	15 (14.9)	34 (11.2)	18 (10.5)	13 (15.5)
COLON ASCENDING/HEPATIC FLEXURE	89 (44.1)	40 (39.6)	129 (42.6)	79 (46.2)	36 (42.9)
COLON TRANSVERSE	29 (14.4)	13 (12.9)	42 (13.9)	27 (15.8)	13 (15.5)
COLON DESCENDING/SPLENIC FLEXURE	25 (12.4)	9 (8.9)	34 (11.2)	23 (13.5)	8 (9.5)
COLON SIGMOID	15 (7.4)	13 (12.9)	28 (9.2)	8 (4.7)	8 (9.5)
RECTUM/RECTOSIGMOID JUNCTION	24 (11.9)	11 (10.9)	35 (11.6)	15 (8.8)	6 (7.1)
UNKNOWN	1 (0.5)	0	1 (0.3)	1 (0.6)	0
TUMOR SIDEDNESS (CRF) (%)					
LEFT	64 (31.7)	33 (32.7)	97 (32.0)	46 (26.9)	22 (26.2)
RIGHT	138 (68.3)	68 (67.3)	206 (68.0)	125 (73.1)	62 (73.8)
TIME FROM INITIAL DISEASE DIAGNOSIS TO RANDOMIZATION (%)					
< 1 YEAR	117 (57.9)	64 (63.4)	181 (59.7)	103 (60.2)	51 (60.7)
≥ 1 AND < 3 YEARS	58 (28.7)	24 (23.8)	82 (27.1)	49 (28.7)	22 (26.2)
≥ 3 YEARS	27 (13.4)	12 (11.9)	39 (12.9)	19 (11.1)	11 (13.1)
NOT REPORTED	0	1 (1.0)	1 (0.3)	0	0
LIVER METASTASIS PER BICR (%)					
YES	76 (37.6)	42 (41.6)	118 (38.9)	55 (32.2)	32 (38.1)
NO	123 (60.9)	59 (58.4)	182 (60.1)	114 (66.7)	52 (61.9)
NOT REPORTED	3 (1.5)	0	3 (1.0)	2 (1.2)	0
LUNG METASTASIS PER BICR (%)					
YES	44 (21.8)	25 (24.8)	69 (22.8)	37 (21.6)	16 (19.0)
NO	155 (76.7)	76 (75.2)	231 (76.2)	132 (77.2)	68 (81.0)
NOT REPORTED	3 (1.5)	0	3 (1.0)	2 (1.2)	0
PERITONEAL METASTASIS PER BICR (%)					
YES	84 (41.6)	43 (42.6)	127 (41.9)	76 (44.4)	39 (46.4)
NO	115 (56.9)	58 (57.4)	173 (57.1)	93 (54.4)	45 (53.6)
NOT REPORTED	3 (1.5)	0	3 (1.0)	2 (1.2)	0
PD-L1 STATUS (%)					
≥ 1%	43 (21.3)	12 (11.9)	55 (18.2)	43 (25.1)	12 (14.3)
< 1%	145 (71.8)	80 (79.2)	225 (74.3)	122 (71.3)	69 (82.1)
NOT EVALUABLE/INDETERMINATE	3 (1.5)	0	3 (1.0)	1 (0.6)	0
NOT AVAILABLE	11 (5.4)	9 (8.9)	20 (6.6)	5 (2.9)	3 (3.6)
MSI-H AND/OR DMMR PER CENTRAL ASSESSMENT (%)					
MSI-H and/or dMMR	171 (84.7)	84 (83.2)	255 (84.2)	171 (100)	84 (100)
MSS and pMMR	21 (10.4)	12 (11.9)	33 (10.9)	0	0
OTHER*	10 (5.0)	5 (5.0)	15 (5.0)	0	0

	All 1L Randomized Subjects			All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR	
	Nivo+Ipi N =202	Chemo N = 101	Total N=303	Nivo+Ipi N = 171	Chemo N = 84
MSI TEST RESULTS PER CENTRAL ASSESSMENT (%)					
MSI-H	147 (72.8)	71 (70.3)	218 (71.9)	147 (86.0)	71 (84.5)
MSS	31 (15.3)	15 (14.9)	46 (15.2)	8 (4.7)	3 (3.6)
NOT AVAILABLE	24 (11.9)	15 (14.9)	39 (12.9)	16 (9.4)	10 (11.9)
MMR TEST RESULTS PER CENTRAL ASSESSMENT (%)					
dMMR	163 (80.7)	82 (81.2)	245 (80.9)	163 (95.3)	82 (97.6)
pMMR	28 (13.9)	12 (11.9)	40 (13.2)	3 (1.8)	0
NOT AVAILABLE	11 (5.4)	7 (6.9)	18 (5.9)	5 (2.9)	2 (2.4)
MSI TEST RESULTS PER LOCAL ASSESSMENT (%)					
MSI-H	77 (38.1)	33 (32.7)	110 (36.3)	67 (39.2)	30 (35.7)
MSI-L/MSS	5 (2.5)	1 (1.0)	6 (2.0)	1 (0.6)	0
NOT AVAILABLE	120 (59.4)	67 (66.3)	187 (61.7)	103 (60.2)	54 (64.3)
MMR TEST RESULTS PER LOCAL ASSESSMENT (%)					
dMMR	170 (84.2)	87 (86.1)	257 (84.8)	149 (87.1)	72 (85.7)
pMMR	4 (2.0)	1 (1.0)	5 (1.7)	0	1 (1.2)
NOT AVAILABLE	28 (13.9)	13 (12.9)	41 (13.5)	22 (12.9)	11 (13.1)
BRAF/KRAS/NRAS MUTATION STATUS (%)					
BRAF/KRAS/NRAS ALL WILD TYPE	47 (23.3)	23 (22.8)	70 (23.1)	41 (24.0)	17 (20.2)
BRAF MUTANT	52 (25.7)	24 (23.8)	76 (25.1)	50 (29.2)	22 (26.2)
KRAS OR NRAS MUTANT	43 (21.3)	21 (20.8)	64 (21.1)	30 (17.5)	15 (17.9)
BRAF AND KRAS/NRAS MUTANT	5 (2.5)	2 (2.0)	7 (2.3)	4 (2.3)	2 (2.4)
UNKNOWN	55 (27.2)	31 (30.7)	86 (28.4)	46 (26.9)	28 (33.3)
LYNCH SYNDROME (%) (B)					
YES	22 (10.9)	17 (16.8)	39 (12.9)	18 (10.5)	13 (15.5)
NO	135 (66.8)	49 (48.5)	184 (60.7)	113 (66.1)	39 (46.4)
UNKNOWN	44 (21.8)	30 (29.7)	74 (24.4)	39 (22.8)	27 (32.1)
NOT REPORTED	1 (0.5)	5 (5.0)	6 (2.0)	1 (0.6)	5 (6.0)

(A) All subjects had an ECOG PS of 1.
(B) Information on Lynch syndrome was collected based on the subject's medical history.
For local and central MSI/MMR assessment, not available includes both not evaluable and not tested.
For tumour location, other locations unless listed are included in unknown category.
MSI test per local assessment includes both PCR and NGS test.
*Other, includes all other combinations except mentioned above.
US/Canada/Europe: Austria, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Romania, Spain, UK, and US; **Asia:** China, Japan; **Rest of World:** Argentina, Australia, Brazil, Chile, Turkey

Investigator's choice of chemotherapy

The distribution of type of SOC in the chemo arm is shown in the table below among 1L treated subjects with centrally confirmed dMMR/MSI-h status, a total of n=40 (53%) received mFOLFOX (with or without bevacizumab or cetuximab) and n=35 (47%) received FOLFORI (with or without bevacizumab or cetuximab). Most subjects (n = 56; 74.7%) received a biologic agent, predominantly bevacizumab (n = 48; 64.0%).

Table 10 Summary of standard of care types – All 1L randomized and treated subjects with centrally confirmed dMMR/MSI-H status in chemo arm (Arm C) of CA2098HW

Standard of Care Type n (%)	All Randomized Arm C: Chemo N = 84	All Treated Arm C: Chemo N = 75
FOLFIRI	13 (15.5)	13 (17.3)
FOLFIRI + BEVACIZUMAB	17 (20.2)	17 (22.7)
FOLFIRI + CETUXIMAB	5 (6.0)	5 (6.7)
MFOLFOX	6 (7.1)	6 (8.0)
MFOLFOX + BEVACIZUMAB	31 (36.9)	31 (41.3)
MFOLFOX + CETUXIMAB	3 (3.6)	3 (4.0)
UNTREATED	9 (10.7)	N/A

Prior cancer therapy

Most (96.7%) 1L randomized patients received prior cancer therapy (Table 11). The overall frequency of prior anti-cancer therapy and the types were balanced between 2 arms. In all 1L randomized patients, the most common prior cancer therapies were prior surgery related to current cancer (85.1%) and prior systemic cancer therapy (32.7%), mostly in the adjuvant and neoadjuvant setting. Four patients (two in each arm) received prior systemic cancer therapy in the metastatic setting.

Table 11 Prior Cancer Therapy - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms

	Number of Subjects (%)		
	Arm B: Nivo + Ipi N = 202	Arm C: Chemo N = 101	Total N = 303
SUBJECTS WITH ANY PRIOR THERAPY (A)	198 (98.0)	95 (94.1)	293 (96.7)
SUBJECTS WITH PRIOR SYSTEMIC THERAPY (A)	67 (33.2)	32 (31.7)	99 (32.7)
SUBJECTS WITH PRIOR ADJUVANT/ NEO-ADJUVANT THERAPY (A)	64 (31.7)	31 (30.7)	95 (31.4)
NUMBER OF PRIOR SYSTEMIC CANCER THERAPY REGIMENS RECEIVED (B)			
1	62 (92.5)	29 (90.6)	91 (91.9)
>= 2	5 (7.5)	3 (9.4)	8 (8.1)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING (B)			
ADJUVANT	58 (86.6)	27 (84.4)	85 (85.9)
METASTATIC	2 (3.0)	2 (6.3)	4 (4.0)
NEO-ADJUVANT	7 (10.4)	5 (15.6)	12 (12.1)
MAINTENANCE (C)	2 (3.0)	0	2 (2.0)
TIME FROM COMPLETION OF PRIOR ADJUVANT/ NEO-ADJUVANT THERAPY TO TREATMENT (D)			
< 6 MONTHS	6 (9.4)	2 (6.5)	8 (8.4)
6 -< 12 MONTHS	22 (34.4)	9 (29.0)	31 (32.6)
>= 12 MONTHS	35 (54.7)	17 (54.8)	52 (54.7)
NOT REPORTED	1 (1.6)	3 (9.7)	4 (4.2)
PRIOR SURGERY RELATED TO CURRENT CANCER			
YES	174 (86.1)	84 (83.2)	258 (85.1)
NO	28 (13.9)	17 (16.8)	45 (14.9)
PRIOR RADIOTHERAPY			
YES	16 (7.9)	8 (7.9)	24 (7.9)
NO	186 (92.1)	93 (92.1)	279 (92.1)

(A) Some subjects may have been treated with more than 1 type of therapy.

(B) Percentages are based on subjects with prior systemic therapy.

(C) 2 subjects who were reported to have received prior systemic maintenance therapy, received it in the adjuvant setting.

(D) Percentages are based on subjects with prior adjuvant/neoadjuvant therapy.

Numbers analysed

Table 12 Populations analysed

	Arm B: Nivo + Ipi	Arm C: Chemo	Total
RANDOMIZED	202	101	303
RANDOMIZED WITH CENTRALLY CONFIRMED DMMR/MSI-H	171	84	255
TREATED	200	88	288
PHARMACOKINETICS EVALUABLE	196	43	239
IMMUNOGENICITY EVALUABLE	179	31	210
PD-L1 QUANTIFIABLE	188	92	280

Outcomes and estimation

Table 13 Summary of Efficacy for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC - CA2098HW

	Arm B: Nivo+Ipi N = 171	Arm C: Chemo N = 84
Primary Endpoint		
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
Secondary Endpoint		
PFS (per Investigator, primary definition)		
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
Exploratory Endpoint		
PFS2 (per Investigator)		
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)

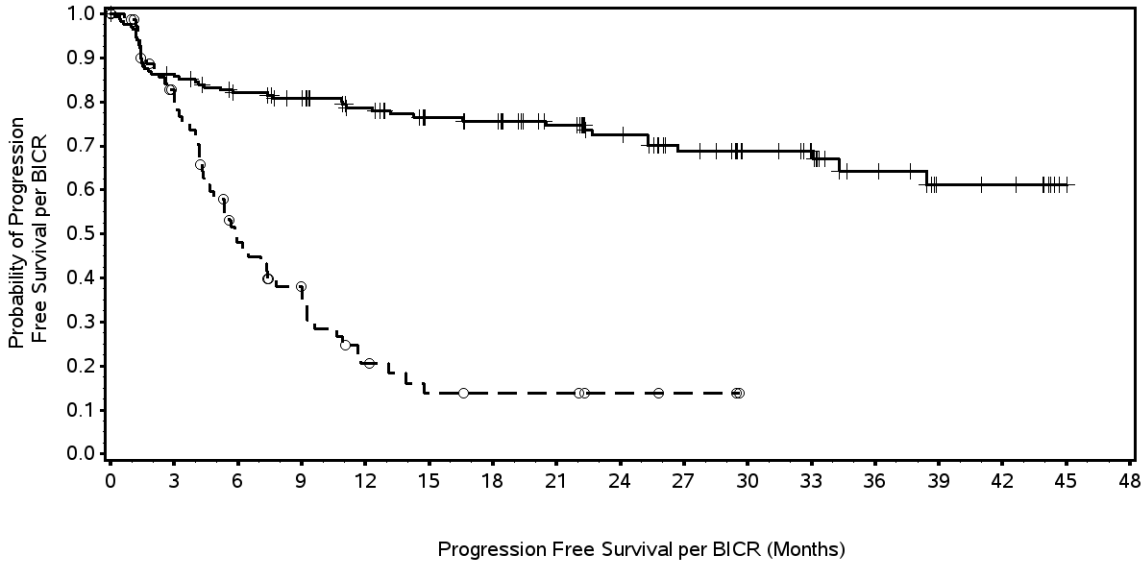
	Arm B: Nivo+Ipi N = 171	Arm C: Chemo N = 84
Number of Subjects at Risk	135	45

[a] Based on KM estimates
[b] HR from a Cox proportional hazard model stratified by tumor sidedness (left vs right) per IRT.
[c] Log-rank test stratified by tumor sidedness (left vs right) per IRT. Boundary for statistical significance p-value was < 0.0209.
Clinical data cutoff was 12-Oct2023.
Minimum follow-up (time from the last subject's randomization date to the clinical cutoff date) was 6.1 months.
Median follow up (time between date of randomization and the clinical cutoff date) was 31.57 (min, max: 6.1, 48.4) months.
Excluded data collected on or after first crossover dose date.

Primary endpoint PFS per BICR – centrally confirmed MSI-H/dMMR mCRC

Nivo+ipi demonstrated a statistically significant improvement in PFS per BICR (primary definition) compared with chemo in all 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC: HR = 0.21 (97.91% CI: 0.13, 0.35; 95% CI: 0.14, 0.32); stratified log-rank test p value < 0.0001, meeting the threshold of significance level of 0.0209. Median PFS was not reached in the nivo+ipi arm and 5.85 months in the chemo arm (Figure 5).

Figure 5 Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC - CA2098HW



Number of Subjects at Risk
Arm B: Nivo + Ipi
171 144 132 122 108 95 92 77 64 53 42 37 22 10 9 1 0
Arm C: Chemo
84 53 29 20 10 6 5 5 3 2 0 0 0 0 0 0 0

Arm B: Nivo + Ipi (events : 48/171), median and 95% CI : N.A. (38.44, N.A.)
Arm C: Chemo (events : 52/84), median and 95% CI : 5.85 (4.37, 7.79)
Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (95% CI): 0.21 (0.14, 0.32)
Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (97.91% CI): 0.21 (0.13, 0.35)
p-value: <0.0001

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.
Excluded data collected on or after first crossover dose date.
KM plot was generated only if there were at least 10 subjects in each treatment arm in population or subgroup.

Reasons for censoring are shown in the Table below (Table 14).

Table 14 Reason for Censoring, Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi vs Chemo- All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

	Arm B: Nivo + Ipi N = 171	Arm C: Chemo N = 84
NUMBER OF EVENTS (%)	48 (28.1)	52 (61.9)
TYPE OF EVENTS (%)		
PROGRESSION (1)	39 (22.8)	45 (53.6)
DEATH	9 (5.3)	7 (8.3)
NUMBER OF SUBJECTS CENSORED (%)	123 (71.9)	32 (38.1)
CENSORED ON DATE OF RANDOMIZATION	3 (1.8)	8 (9.5)
NO BASELINE TUMOR ASSESSMENT (2)	3 (1.8)	2 (2.4)
NEVER TREATED	1 (0.6)	0
OTHER	2 (1.2)	2 (2.4)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	0	6 (7.1)
NEVER TREATED	0	6 (7.1)
OTHER	0	0
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY OR ON DATE OF RANDOMIZATION (3)	120 (70.2)	24 (28.6)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (4)	10 (5.8)	15 (17.9)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	6 (3.5)	11 (13.1)
RECEIVED SUBSEQUENT RADIOTHERAPY	0	1 (1.2)
RECEIVED SUBSEQUENT SURGERY	4 (2.3)	3 (3.6)
STILL ON-TREATMENT	41 (24.0)	4 (4.8)
IN FOLLOW-UP	68 (39.8)	4 (4.8)
OFF STUDY	1 (0.6)	1 (1.2)
LOST TO FOLLOW-UP	0	0
WITHDRAW CONSENT	0	1 (1.2)
OTHER	1 (0.6)	0

(1) RECIST 1.1 criteria

(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy were not considered.

(3) Subjects who received subsequent anti-cancer therapy prior to first on-study scan were censored on randomization date.

(4) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy.

Excludes data collected on or after first crossover dose date.

Secondary endpoints

- PFS per investigator

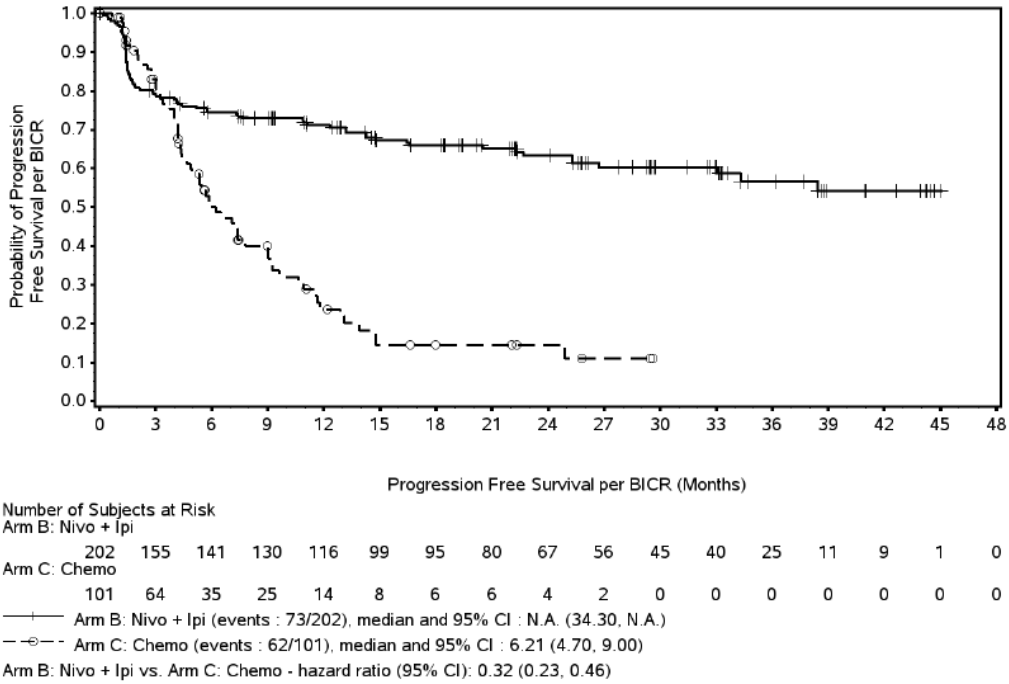
Median PFS per investigator in 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC was not reached in the nivo+ipi arm (95% CI: 38.4.4, NA) and 7.66 (95% CI: 4.21, 9.00) months in the chemo arm; HR = 0.20 (95% CI: 0.14, 0.31). Comparable results were obtained based using a definition of PFS where events (progression or death) and disease assessments that occurred on or after subsequent anti-cancer therapy were considered (no time point truncation).

The agreement between BICR assessment and investigator assessment of the number of PFS events (progression or death) and censoring was 89.5% in the nivo+ipi arm and 86.9% in the chemo arm.

- PFS per BICR in all 1L randomized patients

The median PFS (95% CI) per BICR all 1L randomized patients was not reached in the nivo+ipi arm (34.30, NA) and 6.21 (4.70, 9.00) months in the chemo arm; HR = 0.32 (95% CI: 0.23, 0.46) (Figure 6).

Figure 6 Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects in Arm B and C - CA2098HW



- PFS per BICR using central PCR testing (for MSI-H) or central IHC testing (for dMMR)

Consistent results were obtained independent of type of testing (Table 17).

Table 15 Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with MSI/MMR by Central Testing (PCR or IHC)

	Confirmed MSI-H by PCR		Confirmed dMMR by IHC	
	Nivo+Ipi N = 147	Chemo N = 71	Nivo+Ipi N = 163	Chemo N = 82
PFS (per BICR, primary definition)				
Events, n (%)	39 (26.5)	44 (62.0)	47 (28.8)	50 (61.0)
Median PFS (95% CI), mo.	Not Reached (38.44, NA)	6.21 (4.70, 9.03)	Not Reached (38.44, NA)	5.85 (4.40, 7.79)
HR (95% CI)	0.20 (0.12, 0.31)		0.22 (0.14, 0.34)	

Statistical model for hazard ratio: stratified Cox proportional hazard model by tumor sidedness (left vs. right) as entered into the IRT.

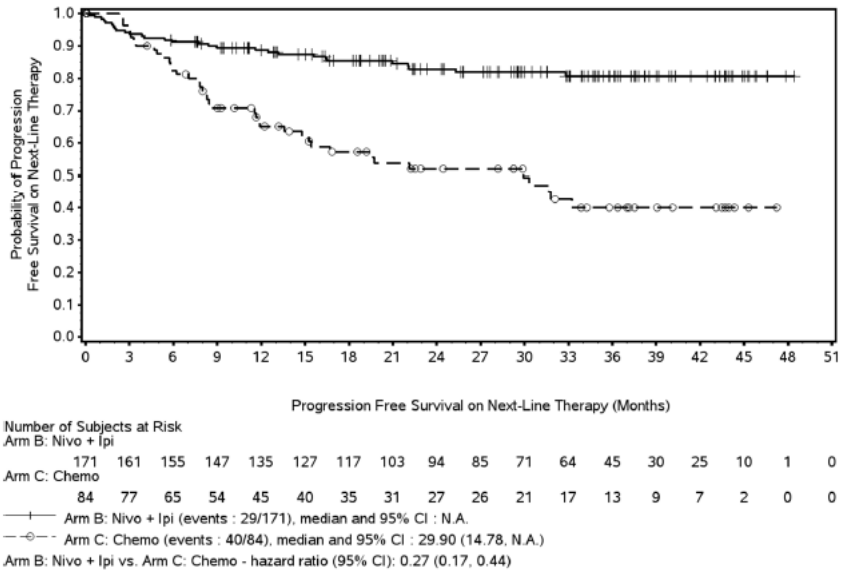
Excludes data collected on or after first crossover dose date.

Exploratory Endpoints

- PFS2 per BICR in patients with centrally confirmed MSI-H/dMMR mCRC

An improvement in PFS2 per investigator was observed with nivo+ipi compared with chemo in all 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC: HR = 0.27 (95% CI: 0.017, 0.44) (Figure 7). PFS2 rates were higher with nivo+ipi than chemo at 6 months (91.22% vs 82.39%) and at 12 months (88.75% vs 65.02%).

Figure 7 Progression-Free Survival on Next Line of Therapy (PFS2) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC



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.

KM plot will be generated only if there are at least 10 subjects in each treatment arm in population or subgroup.

- Recurrence-free survival and pathological response per investigator

In 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC, 5/171 patients in the nivo+ipi arm and 6/84 patients in the chemo arm underwent surgery while on study treatment (potentially curative surgery). Of the patients who underwent on-study surgery, 60.0% (3/5) of patients in nivo+ipi arm and 33.3% (2/6) of patients in the chemo arm had complete pathological response (major pathological response (80.0% [4/5] vs 66.7% [4/6]). RFS was not analysed because there were < 10 patients in each treatment arm who had on-study Surgery. In patients who had on-study surgery, no RFS events (0/5) were reported in the nivo+ipi arm; RFS events were reported in 2 of the 6 patients in the chemo arm.

- PFS by tumour cell PD-L1 at baseline

PFS per BICR benefit of nivo+ipi vs chemo was observed regardless of tumour cell PD-L1 (≥ 1%, < 1%) in 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC.

Table 16 Progression-Free Survival (per BICR) by Tumour Cell PD-L1 at Baseline for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR

	PD-L1 ≥ 1%		PD-L1 < 1%	
	Nivo+Ipi N=43	Chemo N=12	Nivo+Ipi N=122	Chemo N=69
PFS per BICR (primary definition)				
HR (95% CI)	0.11 (0.04, 0.30)		0.22 (0.14, 0.36)	
Events, n	10	9	34	42
Median PFS, (95% CI) mo.	Not Reached (34.30, NA)	3.35 (1.28, 7.10)	Not Reached (38.44, NA)	6.47 (4.70, 9.26)

Statistical model for HR: unstratified Cox proportional hazard model.

Excludes data collected on or after first crossover dose date.

- PFS per BICR in the crossover cohort

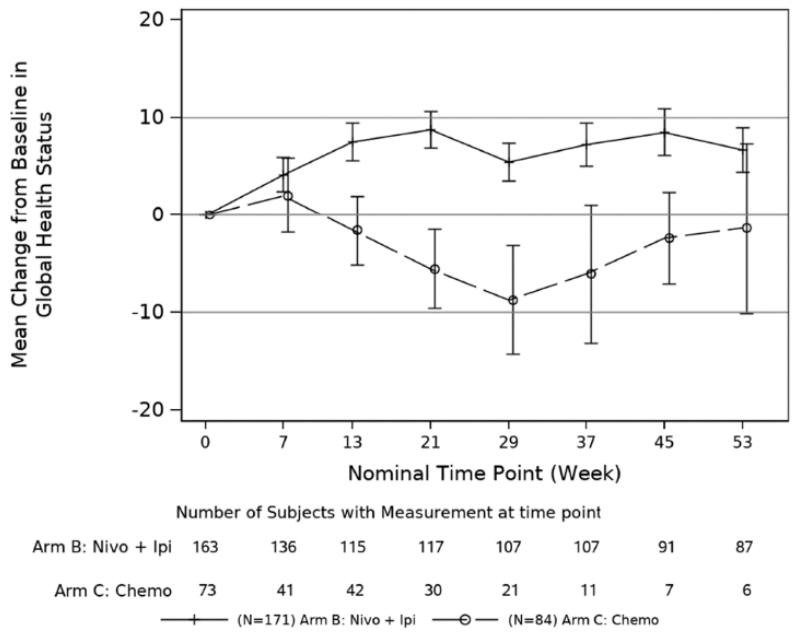
Of the 45 1L crossover treated patients, 11 were ongoing and receiving crossover treatment, 8 completed crossover treatment, and 26 discontinued crossover treatment. The most common reason for study discontinuation was disease progression (11 patients). Baseline and disease characteristics were largely comparable to that of the randomized chemo arm. For crossover treated patients with centrally confirmed MSI-H/dMMR mCRC (n=39), median PFS per BICR (primary definition) was 9.92 (95% CI: 2.73, 30.42) months.

- Patient reported outcome (PRO)

PRO completion rates for the EORTC QLQ-C30 at baseline were 95.3% for patients in the nivo+ipi arm and 86.9% in the chemo arm and completion rates for timepoints where there were at least 10 eligible patients ranged from 84.4% to 94.4% through Week 101 in the nivo+ipi arm, and from 55.0% to 83.3% through Week 37 for the chemo arm. Completion rates at Follow-up visits 1 and 2 were 67.5% and 59.0% for the nivo+ipi arm, and 58.2% and 37.5% for the chemo arm respectively. Compliance rates were in the same order of magnitude for the EORTC QLQ-CR29 and EQ-5D-3L.

EORTC QLQ-C30 Global Health Status: In all 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC, the descriptive PRO results for EORTC QLQ-C30 Global Health Status in the nivo+ipi arm showed a trend for improvement from baseline during the treatment period whereas results for the chemo arm were either stable or showed a trend for worsening from baseline during the treatment period (below MID). Similar trends were observed for most of the EORTC QLQ-C30 subscales in the respective treatment arms.

Figure 8 Mean Change in Scores from Baseline for Global Health Status by Timepoint (EORTC QLQ-C30) - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms with Centrally Confirmed MSI-H/dMMR mCRC

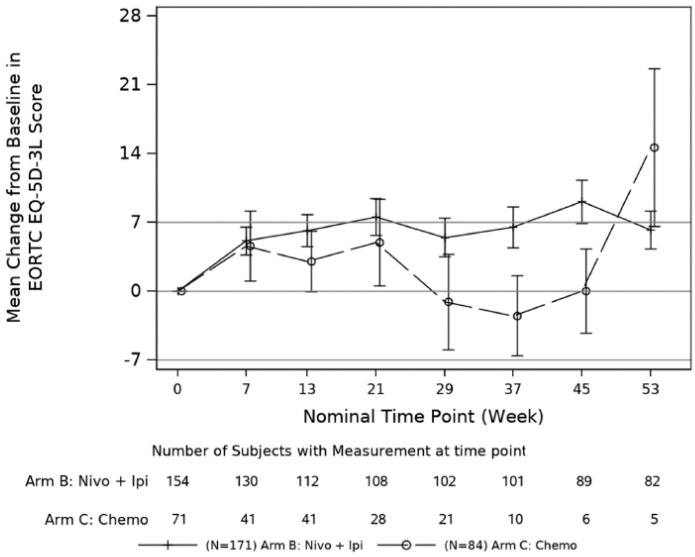


Increases from baseline indicate improvement and decreases from baseline indicate worsening for global health status.
Baseline is defined as the last available assessment on or prior to randomization.
Error bars represent 95% confidence intervals.

EORTC QLQ-CR29: In 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC in both treatment arms, changes from baseline for the majority of the EORTC QLQ-CR29 symptom scores remained stable (close to baseline levels).

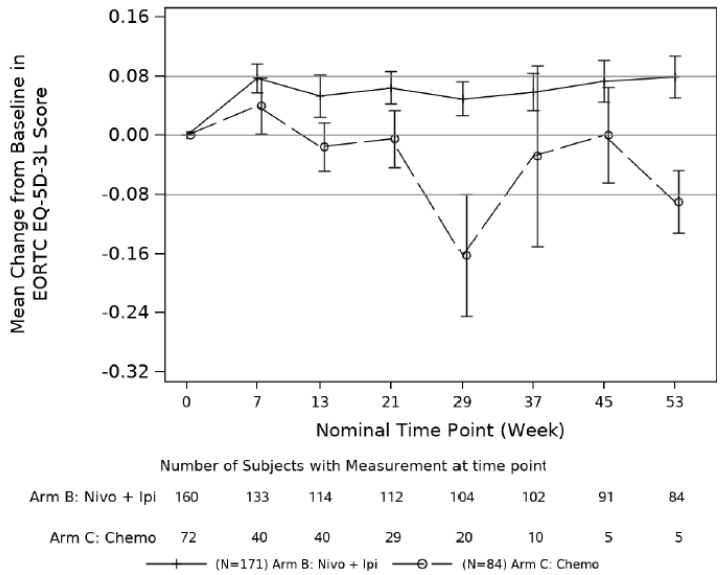
EQ-5D-3L: Overall, the mean EQ-5D-3L VAS and UI scores for all 1L randomized patients with centrally confirmed MSI-H/dMMR mCRC improved (increased) over time during treatment in both arms, but to a greater extent in the nivo+ipi arm compared with the chemo arm. The mean changes from baseline reached the MID for improvement (7 for EQ-5D-3L VAS; 0.08 for EQ-5D-3L UI) in the nivo+ipi arm at several timepoints during the treatment period up to Week 101 and did not reach the MID for improvement at any timepoint during the treatment period in the chemo arm up to Week 37.

Figure 9 Mean Changes from Baseline in EQ-5D-3L Visual Analogue Score (Overall Self-Rated Health Status) - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms with Centrally Confirmed MSIH/dMMR mCRC



Increases indicate improvement.
Error bars represent 95% CI for the mean.
Horizontal reference indicates MID, considered a change of ≥ 7 points from baseline.
Only timepoints with data available for ≥ 5 subjects in each treatment group are plotted.
Excludes data collected on or after first crossover dose date.

Figure 10 Mean Changes from Baseline in EQ-5D-3L Utility Index Score (Overall Self-Rated Health Status) - All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms with Centrally Confirmed MSIH/dMMR mCRC



Increases indicate improvement.
Error bars represent 95% CI for the mean.
Horizontal reference indicates MID, considered a change of ≥ 0.08 points from baseline.
Only timepoints with data available for ≥ 5 subjects in each treatment group are plotted.
Excludes data collected on or after first crossover dose date.

Ancillary analyses

Supportive analyses for PFS by BICR

The results of the primary analysis are corroborated by the results from the 11 supportive analyses, including the analysis in which events (progression or death) and disease assessments that occurred on or after subsequent anti-cancer therapy.

Table 17 Sensitivity Analysis for Progression-Free Survival per BICR (Primary Definition) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

	Arm B over Arm C	
Sensitivity Analysis	HR 97.91% CI	P-VALUE
ANALYSIS OF PFS PER BICR INCLUDING IMBALANCED WITH CENTRALLY CONFIRMED MSI-H/dMMR BASELINE CHARACTERISTICS AS COVARIATES (1) (2)	0.22 (0.13, 0.36)	<0.0001
ANALYSIS OF PFS PER BICR USING UN-STRATIFIED COX MODEL	0.21 (0.13, 0.34)	<0.0001
ANALYSIS OF PFS PER BICR USING STRATIFICATION FACTORS AS COVARIATES	0.21 (0.13, 0.34)	<0.0001
ANALYSIS OF PFS PER BICR ACCOUNTING FOR MISSING TUMOR ASSESSMENT PRIOR TO PFS EVENT (1)	0.22 (0.13, 0.35)	<0.0001

(1) Cox proportional hazard model stratified by time dependent Cox model by tumor sidedness (left vs. right) per IRT.
(2) The following imbalanced baseline characteristics are included in the model: PD-L1
Excludes data collected on or after first crossover dose date.

- PFS per BICR (EMA definition): p < 0.0001; HR (adjusted 95% CI): 0.23 (0.15, 0.34)
- PFS per BICR using the max-combo test: p < 0.0001; HR (adjusted 95% CI): 0.12 (0.07, 0.19).
- In the initial 2 months after randomization, the PFS HR = 1.22 (95% CI: 0.54, 2.72) did not favour nivo+ipi over chemo; after 2 months, the PFS HR = 0.09 (95% CI: 0.05, 0.15) favoured nivo+ipi over chemo.
- Multivariate Cox model: PFS HR = 0.19 (95% CI: 0.13, 0.30) favoured nivo+ipi over chemo when adjusted for the following baseline factors: age (< 65 vs ⩾ 65 years), sex (male, female), ECOG PS (0 vs ⩾ 1), disease stage at initial diagnosis (0/I/II/III vs IV), liver metastasis per BICR (yes vs no/not reported), and tumour cell PD-L1 (⩾ 1% vs < 1%, non-quantifiable vs ⩾ 1%).
- A consistent treatment effect with PFS per BICR was observed across strata (tumour sidedness) as indicated by a p-value > 0.1 (actual p-value = 0.5000) using the Gail-Simon test.

Subsequent cancer therapy

Subsequent cancer therapy was received by a lower proportion of patients in the nivo+ipi arm than the chemo arm (22.3% vs 68.3%), which was mainly due to a lower proportion of patients in the nivo+ipi arm receiving subsequent systemic therapy (19.3% vs 67.3%) (Table 16). In the chemo arm, 44.6% (45/101) of patients crossed over to receive nivo+ipi on-study after BICR-documented progression (Crossover cohort). An additional 20.8% (21/101) of patients in the chemo arm received IO off study. Taken together, 65.4% (66/101) of patients in the chemo arm received subsequent IO therapy.

The frequency of subsequent cancer therapy initiation and the types of treatments for 1L randomized patients with centrally confirmed MSI-H/dMMR were consistent with those for all 1L randomized patients.

Table 18 Subsequent cancer therapy: All 1L randomized subjects in the nivo+ipi and chemo arms.

	Number of Subjects (%)		
	Arm B: Nivo + Ipi N = 202	Arm C: Chemo N = 101	Total N = 303
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1) (2)	45 (22.3)	69 (68.3)	114 (37.6)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	1 (0.5)	1 (1.0)	2 (0.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	5 (2.5)	5 (5.0)	10 (3.3)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%) (2)	39 (19.3)	68 (67.3)	107 (35.3)
CROSSOVER TREATMENT	0	45 (44.6)	45 (14.9)
NON-STUDY SYSTEMIC THERAPY	39 (19.3)	23 (22.8)	62 (20.5)
ANTI-CTLA4	0	2 (2.0)	2 (0.7)
IPILIMUMAB	0	2 (2.0)	2 (0.7)
ANTI-PD1 OR ANTI-PDL1	8 (4.0)	21 (20.8)	29 (9.6)
PEMBROLIZUMAB	6 (3.0)	15 (14.9)	21 (6.9)
NIVOLUMAB	2 (1.0)	4 (4.0)	6 (2.0)
CAMRELIZUMAB	0	1 (1.0)	1 (0.3)
TISLELIZUMAB	0	1 (1.0)	1 (0.3)
EGFR INHIBITORS	11 (5.4)	2 (2.0)	13 (4.3)
CETUXIMAB	9 (4.5)	1 (1.0)	10 (3.3)
PANITUMUMAB	3 (1.5)	1 (1.0)	4 (1.3)
PLATINUM COMPOUNDS	20 (9.9)	5 (5.0)	25 (8.3)
OXALIPLATIN	20 (9.9)	5 (5.0)	25 (8.3)
VEGFR TARGETED THERAPY	15 (7.4)	7 (6.9)	22 (7.3)
BEVACIZUMAB	15 (7.4)	7 (6.9)	22 (7.3)
AFLIBERCEPT	3 (1.5)	0	3 (1.0)
OTHER SYSTEMIC ANTICANCER THERAPY	30 (14.9)	9 (8.9)	39 (12.9)
FLUOROURACIL	25 (12.4)	5 (5.0)	30 (9.9)
IRINOTECAN	18 (8.9)	5 (5.0)	23 (7.6)
CAPECITABINE	4 (2.0)	3 (3.0)	7 (2.3)
IRINOTECAN HYDROCHLORIDE	1 (0.5)	0	1 (0.3)
RALTITREXED	1 (0.5)	0	1 (0.3)
TIPIRACIL HYDROCHLORIDE;TRIFLURIDINE	1 (0.5)	0	1 (0.3)
TIPIRACIL;TRIFLURIDINE	1 (0.5)	0	1 (0.3)
MEK NRAS AND BRAF INHIBITOR	3 (1.5)	1 (1.0)	4 (1.3)
ENCORAFENIB	3 (1.5)	1 (1.0)	4 (1.3)

Clinical Data Cutoff Date: 12-Oct-2023.

Excludes surgery, radiotherapy, or non-study systemic therapy data collected on or after first crossover dose date.

(1) Subject may have received more than 1 type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

(2) Subjects who received Crossover treatment in Arm C are counted.

Subgroup analyses

Figure 11 Progression-Free Survival per BICR (Primary Definition) in Pre-Defined Subsets for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

		Nivo + Ipi			Chemo			Unstratified	
	N	N of Events (N of subjects)	mPFS (95% CI)		N of Events (N of subjects)	mPFS (95% CI)		Hazard Ratio (95% CI) Nivo + Ipi vs. Chemo	
OVERALL	255	48 (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	45 (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	46 (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 (48)	N.A.	(25.30, N.A.)	14 (22)	4.40	(2.07, 9.26)	0.22	(0.10, 0.48)
RIGHT	185	34 (123)	N.A.		38 (62)	7.10	(4.70, 9.03)	0.21	(0.13, 0.34)

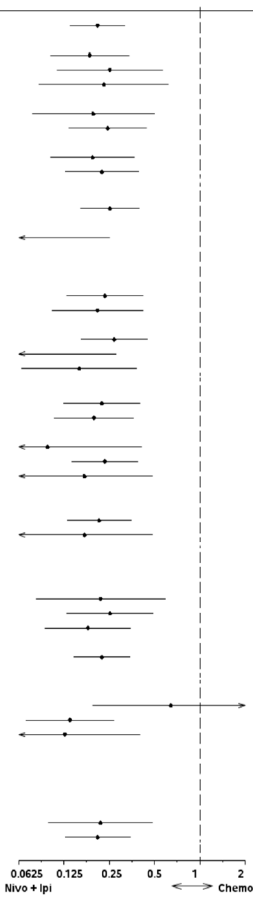
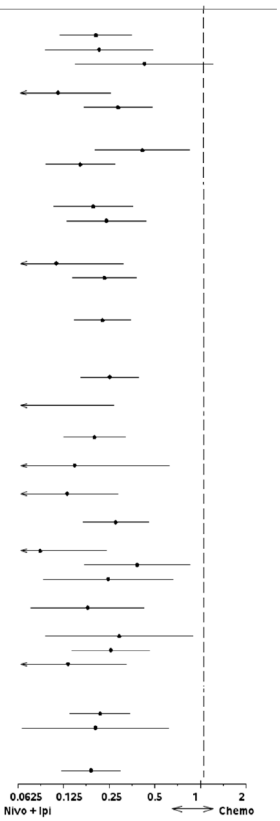


Figure 12 Continued Progression-Free Survival per BICR (Primary Definition) in Pre-Defined Subsets for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

	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	
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	8 (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-L/MSS	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)



HR is not computed for subset category with less than 10 subjects per treatment arm. Excludes data collected on or after first crossover date. 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 is not evaluable, indeterminate, or not available at baseline. MSI test per local assessment includes both PCR and NGS test. Source: Figure 14.2.1.16.2

Post-hoc subgroup analysis of PFS per BICR in 1L randomized subjects with centrally confirmed dMMR/MSI-H mCRC by 6 chemo regimens are shown in Table 19.

Table 19 Summary of progression free survival per BICR (primary definition) by standard of care type – All 1L randomized subjects with centrally confirmed dMMR/MSI-H status in nivo+ipi and chemo arms (Arm B and Arm C) of CA2098HW

	Nivo + Ipi N = 171	Chemo N = 84	FOLFIRI N = 13	FOLFIRI + Bevacizumab N = 17
# EVENTS / # SUBJECTS (%)	48/171 (28.1)	52/84 (61.9)	8/13 (61.5)	10/17 (58.8)
MEDIAN PFS (MONTHS) (1) (95% CI)	N.A. (38.44, N.A.)	5.85 (4.37, 7.79)	5.67 (1.68, N.A.)	9.23 (4.01, 11.63)
HR (95% CI)		0.21 (A) (0.14, 0.32)	0.29 (A) (0.13, 0.62)	0.27 (A) (0.13, 0.55)

	FOLFIRI + Cetuximab N = 5	mFOLFOX N = 6	mFOLFOX + Bevacizumab N = 31	mFOLFOX + Cetuximab N = 3
# EVENTS / # SUBJECTS (%)	5/5 (100.0)	4/6 (66.7)	20/31 (64.5)	3/3 (100.0)
MEDIAN PFS (MONTHS) (1) (95% CI)	2.79 (0.66, N.A.)	2.56 (1.38, N.A.)	5.68 (4.21, 9.03)	4.40 (4.30, N.A.)
HR (95% CI)	0.12 (A) (0.05, 0.32)	0.17 (A) (0.06, 0.52)	0.26 (A) (0.15, 0.46)	0.19 (A) (0.06, 0.61)

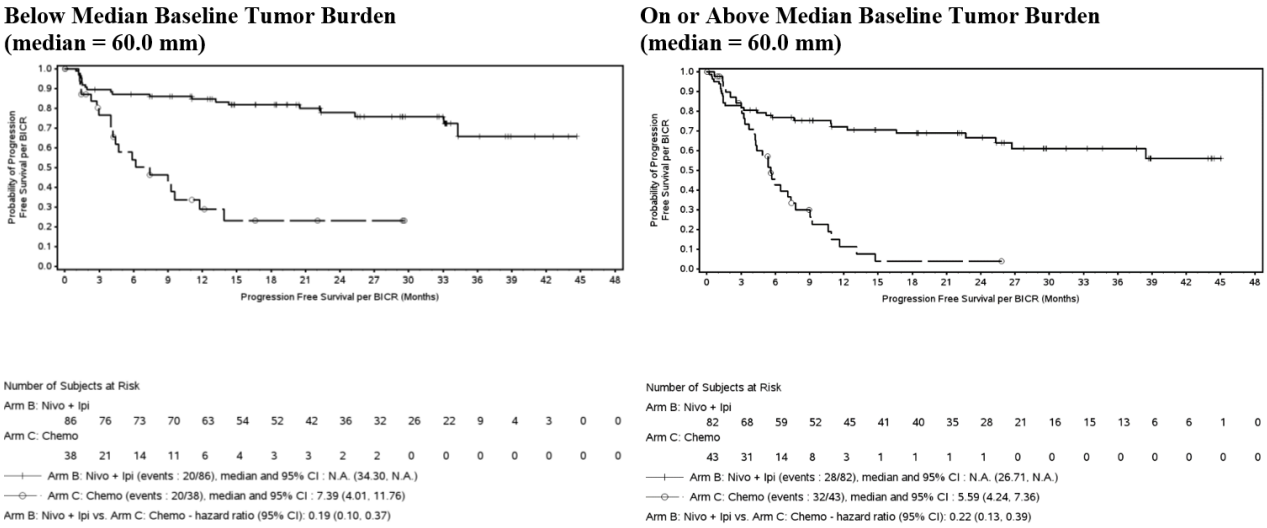
(1) Based on Kaplan-Meier Estimates
(A) Hazard Ratio is Arm B over group of the column from a Cox Model stratified by tumor sidedness (left vs. right) as entered into the IRT.
Excludes data collected on or after first crossover dose date.
Only first line subjects are included for Arm B and Arm C.
DBL: November 2023.

Another post-hoc subgroup analysis concerned the impact of baseline tumour burden on PFS (Table 20). The PFS KM curves are shown in Figure 13 Kaplan-Meier plot of progression free survival per BICR (primary definition) – by baseline tumour burden per BICR – All 1L randomized subjects with centrally confirmed dMMR/MSI-H status in nivo+ipi and chemo arms (Arm B and Arm C) of CA2098HW.

Table 20 Baseline tumour burden per BICR – All 1L randomized subjects with centrally confirmed dMMR/MSI-h status in nivo+ipi and chemo arms (Arm B and Arm C) of CA2098HW

BASELINE TUMOR BURDEN (mm)	Arm B: Nivo + Ipi N = 171	Arm C: Chemo N = 84	Total N = 255
N	168	81	249
MEAN	79.4	79.2	79.3
MEDIAN	58.5	64	60
MIN , MAX	10 , 329	12 , 244	10 , 329
Q1 , Q3	33.0 , 99.5	41.0 , 104.0	34.0 , 100.0
SD	66.57	51.54	61.98

Figure 13 Kaplan-Meier plot of progression free survival per BICR (primary definition) – by baseline tumour burden per BICR – All 1L randomized subjects with centrally confirmed dMMR/MSI-H status in nivo+ipi and chemo arms (Arm B and Arm C) of CA2098HW



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.
Only first line subjects are included for Arm B and Arm C.
Hazard Ratio is Arm B over Arm C from a Cox Model stratified by tumor sidedness (left vs. right) as entered into the IRT.
Excludes data collected on or after first crossover dose date.
DBL: November 2023

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial CA2098HW

Title: A phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (DMMR) metastatic colorectal cancer.		
Study identifier	CA2098HW, EudraCT: 2018-000040-26, NCT04008030	
Design	Randomised, multicentre, open-label, active-controlled, 3-arm phase III study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient randomized 1L 19-aug-2019, ongoing study Not applicable Not applicable
Hypothesis	Superiority Nivolumab plus ipilimumab combination therapy is superior to standard chemotherapy as measured by PFS in participants with recurrent or metastatic dMMR/MSI-H CRC who have not received prior treatment for metastatic disease.	
Treatments groups	Nivolumab + ipilimumab (n=202)	Nivolumab 240 mg Q3W x 4 doses (2 cycles), followed by nivolumab 480 mg Q4W Until disease progression up till a maximum of 24 months
	SoC (n=101)	mFOLFOX6 mFOLFOX6+bevacizumab mFOLFOX6+cetuximab FOLFIRI FOLFIRI+bevacizumab FOLFIRI+cetuximab

Endpoints and definitions	Primary endpoint	PFS (per RECIST 1.1 by BICR)	Time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first.
	Exploratory endpoint	PFS2 (by investigator)	Time from randomization to the date of investigator-defined documented disease progression per RECIST 1.1 during next line of treatment or death due to any cause, whichever comes first.
Data cut-off Database lock	12-Oct-2023 15-Nov-2023		

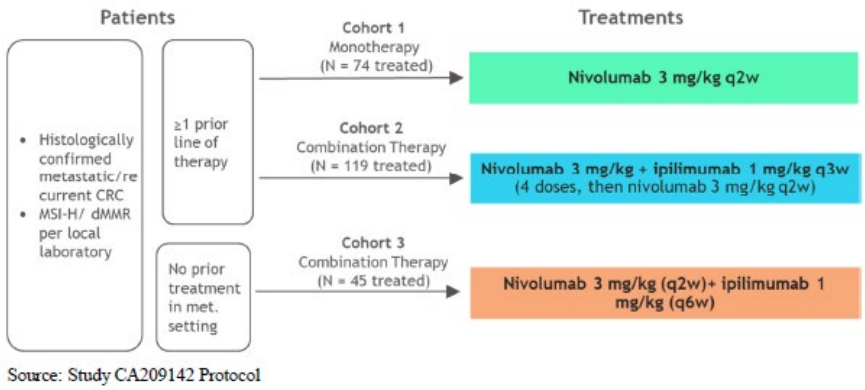
Results and Analysis

Analysis description	**Interim analysis**		
Analysis population and time point description	Intent to treat with centrally confirmed MSI-H/dMMR mCRC		
Descriptive statistics and estimate variability	Treatment group	Nivolumab + ipilimumab	SOC
	Number of patient	171	84
	PFS (median in months)	NR	5.85
	95% CI	(38.44, NA)	(4.37, 7.79)
	PFS2 (median in months)	NR	29.90
	95% CI	(NA, NA)	(14.78, NA)
Effect estimate per comparison	Primary endpoint	Nivolumab+ipilimumab vs SOC	PFS
		HR	0.21
		95% CI	(0.14, 0.32)
		P-value	<0.0001
	Exploratory endpoint	Nivolumab+ipilimumab vs SOC	PFS2
		HR	0.27
		95%CI	(0.17, 0.44)
		P-value	NA
Notes	At the IA, PFS was statistically significant and considered the final analysis. Key secondary endpoints OS and ORR were not tested at this IA, because its precedent endpoints per the testing hierarchy pre-defined in the SAP have not been tested yet. Data will be available at Q2 2025.		

Supportive study – CA209142

CA209142 is a multicohort, nonrandomized, Phase 2 study of nivo, or nivo combinations, in patients with histologically confirmed MSI-H/dMMR mCRC per local testing. MSI-H/dMMR status was also assessed at the central lab retrospectively. Patients with MSI-H/dMMR mCRC who had 1 or more lines of prior therapy (2L+ patients) were treated with either nivo monotherapy in Cohort 1 or nivo+ipi in Cohort 2. Patients who had no prior therapy (1L patients) were treated with nivo+ipi in Cohort 3 (Figure 13).

Figure 14 CA209142 Study design schematic



Source: Study CA209142 Protocol

Contribution of components 2L (cohort 1 and 2)

Results from cohort 2 formed the basis for the approval of nivo+ipi for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high mCRC after prior fluoropyrimidine-based combination chemotherapy (EMEA/H/C/xxxx/WS/1840, 24 Jun 2021). Results from the nivo monotherapy cohort 1 were included in the previous application to justify the contribution of ipilimumab in later line setting. Results were presented based on a DBL of Oct 2020 with a minimum follow-up of 47 months. The MAH submitted an ad-hoc report with updated results at a DBL of Nov 2021 with a minimum follow-up of 66 months in cohort 1 and 60 months in cohort 2. A total of 6.8% and 9.2% were on study treatment in cohort 1 and cohort 2, respectively. Results are shown below (Table 21).

Table 21 Summary of Efficacy Results with Nivo and Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing in CA209142 Cohorts 1 and 2 (Nov-2021 DBL)

Efficacy Parameter	Nivo (Cohort 1) N = 74	Nivo+Ipi (Cohort 2) N = 119
ORR per BICR, n (%)	28/74 (37.8)	74/119 (62.2)
95% CI	(26.8, 49.9)	(52.8, 70.9)
DCR per BICR, n (%)	48/74 (64.9)	98/119 (82.4)
95% CI	(52.9, 75.6)	(74.3, 88.7)
BOR per BICR, n (%)		
CR (95% CI)	13 (17.6) (9.7, 28.2)	32 (26.9) (19.2, 35.8)
PR (95% CI)	15 (20.3) (11.8, 31.2)	42 (35.3) (26.8, 44.6)
SD	22 (29.7)	26 (21.8)
PD, n (%)	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 (min, max), months	4.42 (1.2, 27.9)	3.86 (1.1, 43.0)
DoR per BICR		
Median (95% CI), months	NR (29.86, NA)	NR (NA, NA)
min, max	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, NA)
Rate (95% CI), %		
12-month	45.8 (34.1, 56.8)	71.5 (62.3, 78.8)
24-month	41.2 (29.7, 52.4)	64.1 (54.5, 72.2)

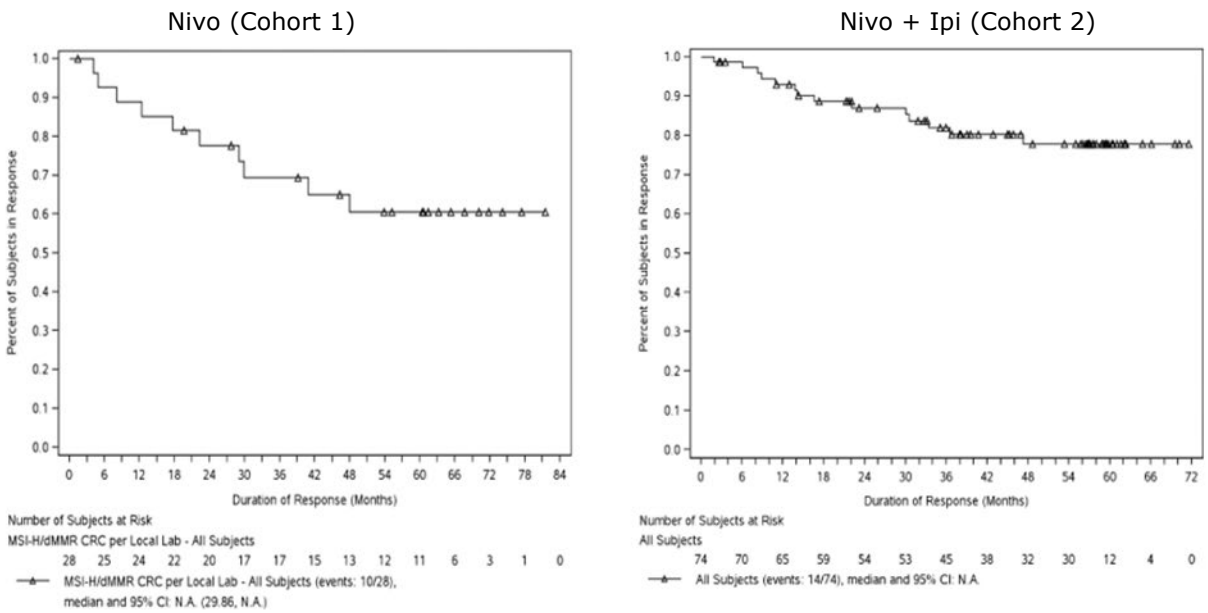
Efficacy Parameter	Nivo (Cohort 1) N = 74	Nivo+Ipi (Cohort 2) N = 119
36-month	36.1 (25.0, 47.4)	59.0 (49.2, 67.5)
60-month	29.3 (18.8, 40.5)	53.2 (43.1, 62.2)
OS		
Median (95% CI), months	44.2 (20.9, 75.1)	NR (NA, NA)
Rate (95% CI), %		
12-month	68.9 (57.0, 78.1)	84.9 (77.1, 90.2)
24-month	58.1 (46.1, 68.4)	74.8 (66.0, 81.6)
36-month	54.1 (42.1, 64.6)	71.4 (62.4, 78.7)
60-month	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 KM method
Ongoing Response included responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excluded responders censored prior to 8 weeks of the clinical data cutoff date if a patient was still in the first 24 weeks follow-up period, otherwise, the window was 14 weeks.
[a] The percentages of subjects with ongoing response were calculated based on number of responders.
Symbol + indicates a censored value.

Data cutoff was 22-Sep-2022 for both Cohorts 1 and 2.

Minimum follow-up (time from the last subject's first dose date to the clinical cutoff date) was 66.2 months for Cohort 1 and 60 months for Cohort 2. Median follow up (time between first subject's first dose date and the clinical cutoff date) was 70.0 (min, max: 66.2, 88.7) months for Cohort 1 and 64.0 (min, max: 60.0, 75.8) months for Cohort 2.

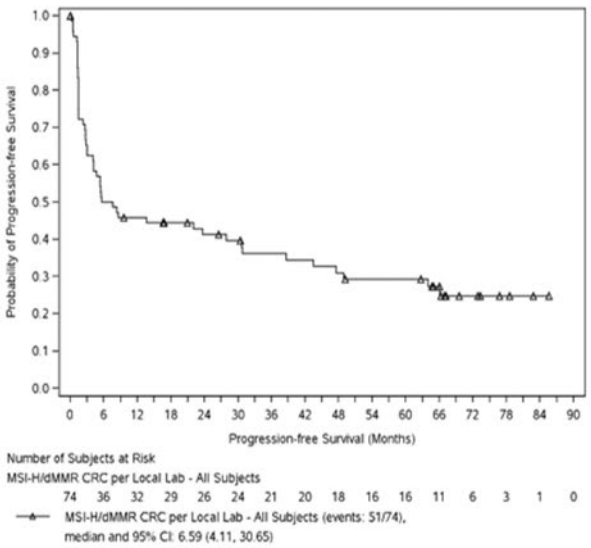
Figure 15 Kaplan-Meier Plot of Duration of Response per BICR with Nivo and Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing in CA209142 Cohorts 1 and 2 (Nov-2021 DBL)



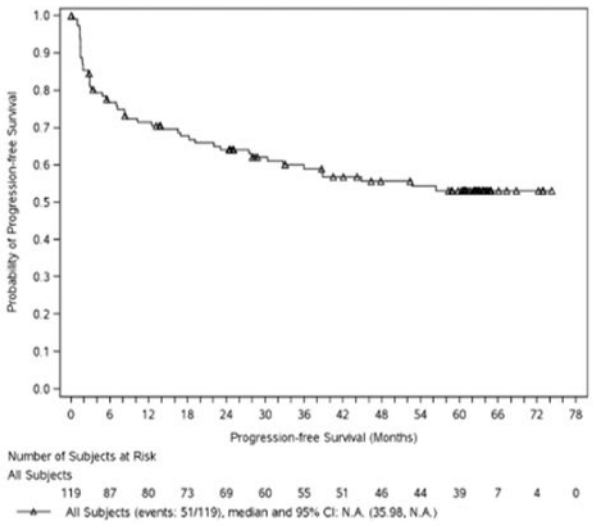
Symbols represent censored observations.

Figure 16 Kaplan-Meier Plot of Progression-free Survival per BICR with Nivo and Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing in CA209142 Cohorts 1 and 2 (Nov-2021 DBL)

Nivo (Cohort 1)



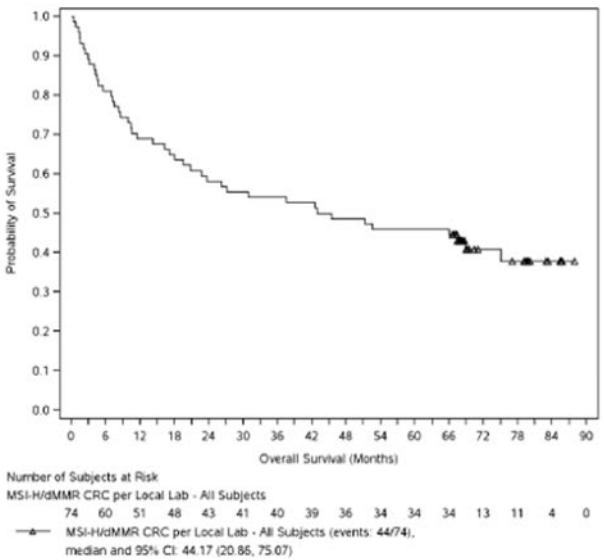
Nivo + Ipi (Cohort 2)



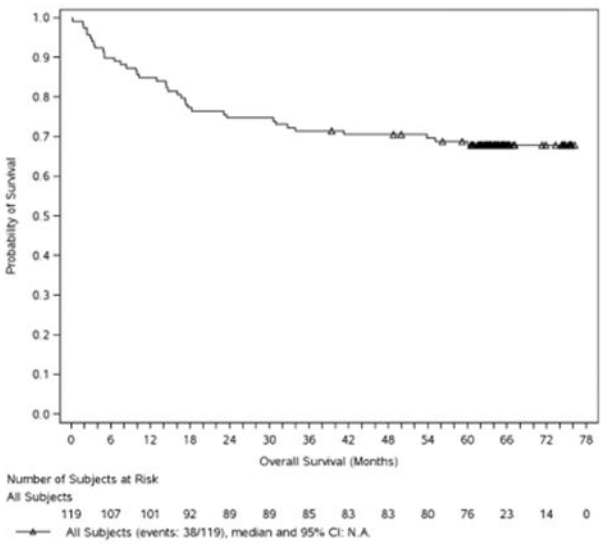
Symbols represent censored observations.

Figure 17 Kaplan-Meier Plot of Overall Survival with Nivo and Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing in CA209142 Cohorts 1 and 2 (Nov-2021 DBL)

Nivo (Cohort 1)



Nivo + Ipi (Cohort 2)



Symbols represent censored observations.

Long-term efficacy nivo+ipi 1L (cohort 3)

A total of 45 patients with MSI-H/dMMR mCRC per local testing who received no prior therapies for metastatic disease were treated with nivo+ipi. As for cohort 1 and 2, treatment with nivo+ipi could be discontinued (optional) in case of maximum clinical benefit per investigator. Minimum treatment duration was 24 months and a minimum of 12 months after date of first response (PR or CR).

At the Oct 2020 DBL with a minimum follow-up of 34.5 months, 2 (4.4%) patients were still receiving treatment and 95.6% of patients discontinued study treatment. The most common reasons for discontinuation of study treatment were: reaching maximum clinical benefit (37.8%), disease progression (17.8%), and study drug toxicity (15.6%).

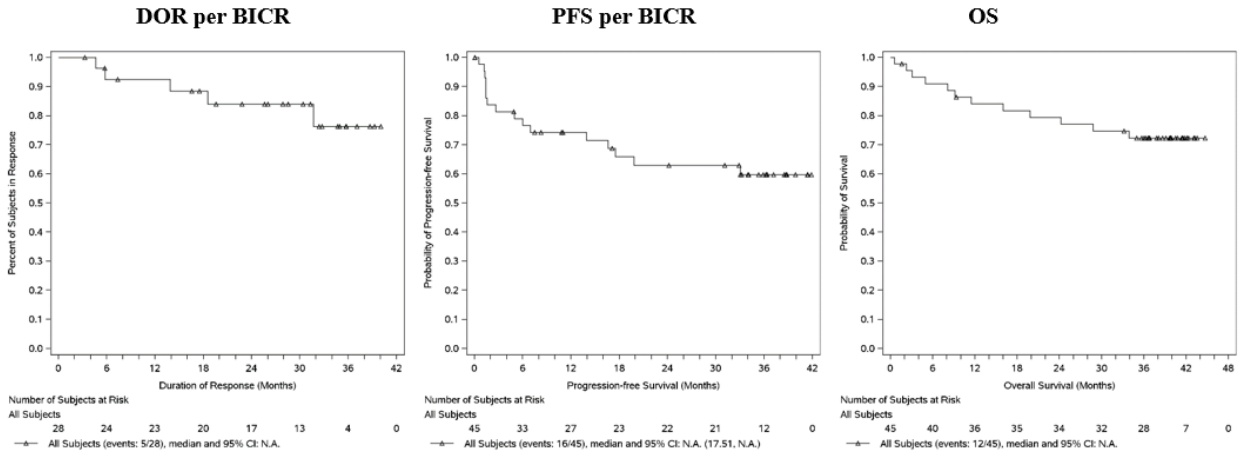
Baseline demographic and disease characteristics largely resemble that of the patients included in the pivotal study CA2098HW. Efficacy results are shown below (Table 22 and Figure 17).

Table 22 Summary of Efficacy Results with Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing (Oct-2020 DBL) in CA209142 Cohort 3

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 per BICR	
Number of responders	28
Median (min, max), months	1.97 (1.2, 16.6)
DoR per BICR	
Median (95% CI), months	NR (NA, NA)
min, max	(3.3+, 40.0+)
Subjects with ongoing response, n (%)[a]	15 (53.6%)
PFS per BICR	
Median (95% CI), months	NR (17.5, NA)
Rate (95% CI), %	
12-month	74.2 (58.3, 84.8)
24-month	63.0 (46.0, 75.9)
36-month	59.7 (42.4, 73.3)
OS	
Median (95% CI), months	NR (NA, NA)
Rate (95% CI), %	
12-month	84.1 (69.5, 92.1)
24-month	79.4 (64.1, 88.7)
36-month	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 KM method; Ongoing Response included responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excluded responders censored prior to 8 weeks of the clinical data cutoff date if a patient was still in the first 24 weeks follow-up period, otherwise, the window was 14 weeks.
[a] The percentages of subjects with ongoing response were calculated based on number of responders.
Symbol + indicates a censored value.
Clinical data cutoff was 25-Sep-2020.
Minimum follow-up (time from the last subject's first dose date to the clinical cutoff date) was 34.5 months.
Median follow up (time between first subject's first dose date and the clinical cutoff date) was 39.3 (min, max: 34.5, 44.0) months.

Figure 18 Kaplan-Meier Plot of DoR per BICR, PFS per BICR, and OS with Nivo+Ipi - All Treated Subjects with MSI-H/dMMR mCRC per Local Testing (Oct-2020 DBL) - CA209142 Cohort 3



Symbols represent censored observations.

In vitro biomarker test for patient selection for efficacy

Patients were required to have known tumour MSI-H or dMMR per local standard of practice testing to be eligible for enrolment. Tumour specimen acquisition was mostly (87.0% (n = 262) from the primary site and balanced between treatment arms; 88.5% (177/200) subjects in the nivo+ipi arm (Arm B), and 84.2% (85/101) subjects in the chemo arm (Arm C). Tissue samples for study patients were then sent to the central lab (LabCorp) for a retrospective confirmation of MSI-H/dMMR. The central labs used in this study were LabCorp, Indianapolis, IN, USA and Shanghai, China for testing of MSI-H by PCR and LabCorp, Torrance, CA USA and Shanghai, China for testing of dMMR by IHC. Both assays are classified as investigational use only (IUO).

The primary population for efficacy analysis was patients with centrally confirmed MSI-H and/or dMMR. Additional efficacy analyses were performed on all randomized patients. To fulfil a post marketing commitment with the US FDA to support labelling of a nucleic acid-based in vitro diagnostic and an IHC based in vitro diagnostic device, supportive efficacy analyses were performed on patients with centrally confirmed MSI-H by PCR and patients with centrally confirmed dMMR by IHC.

Table 23 Concordance between baseline MSI status reported through local vs. central lab summary - All first line randomized subjects.

Treatment Group: Total N = 303

	Number of Subjects (%)			
	MSI Test Results per Central Assessment			
	MSI-H	MSS	Not Evaluable	Not Tested
MSI TEST RESULTS PER LOCAL ASSESSMENT				
MSI-H	87 (28.7)	9 (3.0)	0	14 (4.6)
MSI-L	0	2 (0.7)	0	0
MSS	0	3 (1.0)	0	1 (0.3)
NOT EVALUABLE	0	0	0	0
NOT TESTED	131 (43.2)	32 (10.6)	0	24 (7.9)

Table 24 Concordance between baseline MMR status reported through local vs. central lab summary - All first line randomized subjects.

Treatment Group: Total N = 303

	Number of Subjects (%)			
	MMR Test Results per Central Assessment			
	dMMR	pMMR	Not Evaluable	Not Tested
MMR TEST RESULTS PER LOCAL ASSESSMENT				
DMMR	213 (70.3)	30 (9.9)	13 (4.3)	1 (0.3)
PMMR	1 (0.3)	3 (1.0)	1 (0.3)	0
NOT EVALUABLE	0	0	0	0
NOT TESTED	31 (10.2)	7 (2.3)	3 (1.0)	0

Assays used

MSI was determined on pre-treatment FFPE tissues using the Biocartis Idylla™ MSI Test by a central laboratory. The Idylla™ MSI Test uses FFPE tissue sections from human cancer tissue, from which nucleic acids are liberated, then analyzed by PCR amplification and high-resolution melting detection.

MMR was determined using the Agilent MMR IHC Panel pharmDx (Dako Omnis) assay; a qualitative IHC test intended for use in the assessment of MMR proteins (MLH1, PMS2, MSH2, and MSH6) in formalin-fixed, paraffin-embedded CRC tissue sections

The presence ("intact") or absence ("loss") of target proteins was determined by visual examination of the specimen slide under a light microscope by a qualified pathologist.

Intact:

a. Nuclear staining in viable malignant cells must be unequivocal, with at least the same overall staining intensity as in adjacent internal positive controls.

b. If focal staining is present, the tissue is considered intact if:
- Continuous in multiple glands/nests and
- Equal or stronger in intensity than internal positive controls.

Loss:

a. No or equivocal nuclear staining in viable malignant cells compared to moderate or strong nuclear staining in adjacent internal positive controls.

b. If focal staining is present, the tissue is considered loss if:
- Continuous in only a single gland/nest, or
- Discontinuous in multiple glands/nests, or
- Weaker in intensity than internal positive controls.

Table 25 MMR Panel Assay Diagnosis

Observations or Results	Interpretations	Reporting
Intact for all four biomarkers (MLH1, PMS2, MSH2 and MSH6)	MMR Proficient	MMR Proficient
Loss of one or more biomarkers (MLH1, PMS2, MSH2 and MSH6)	MMR Deficient	MMR Deficient
H&E result failed or any reasons described in Section 3.3	N/A	Not Evaluable

The percentage positive agreement (PPAs) for Idylla MSI and for Omnis MMR tests were estimated using the samples of the 837 enrolled subjects with locally confirmed dMMR/MSI-H (CTA+) status and randomized into the three arms of CA2098HW. The negative percentage agreement (NPAs) were assessed using the commercially procured samples that were predetermined as pMMR/MSS using test methods representative of the CTA. The PPAs and NPAs for the tests are displayed in Table 26

Concordance results between CTA and Omnis MMR/Idylla MSI tests in CA2098HW

Performance Criteria	Omnis MMR		Idylla MSI	
	N[c]	Point Estimate (95% CI[d])	N[c]	Point Estimate (95% CI[d])
PPA[a]	662/777	85.2% (82.5, 87.5)	600/725	82.8% (79.8, 85.3)
NPA[b]	199/204	97.5% (94.4, 98.9)	152/155	98.1% (94.5, 99.3)

[a] Analysis used CA2098HW clinical study specimens.
[b] Analysis used commercially procured tissue specimens.
[c] Analysis based on the evaluable samples.
[d] CI, confidence interval by Wilson Score method

Table 26 Concordance results between CTA and Omnis MMR/Idylla MSI tests in CA2098HW

Performance Criteria	Omnis MMR		Idylla MSI	
	N[c]	Point Estimate (95% CI[d])	N[c]	Point Estimate (95% CI[d])
PPA[a]	662/777	85.2% (82.5, 87.5)	600/725	82.8% (79.8, 85.3)
NPA[b]	199/204	97.5% (94.4, 98.9)	152/155	98.1% (94.5, 99.3)

[a] Analysis used CA2098HW clinical study specimens.
[b] Analysis used commercially procured tissue specimens.
[c] Analysis based on the evaluable samples.
[d] CI, confidence interval by Wilson Score method

Clinical validation

The clinical performance bridged the efficacies from the clinical trial positive (CTA+, local testing) population to the Idylla and Omnis assays intended use population with the interim analysis results in PFS per BICR for nivo+ipi vs chemo in 1L randomized patients with mCRC. Furthermore, positive percent agreement (PPA) was evaluated using specimens from all randomized patients (CTA+) while negative percent agreement (NPA) was evaluated using commercially procured specimens (CTA-), reflective of the intended use population. For the PPA, specimens obtained from patients enrolled in the study CA2098HW were tested retrospectively in central laboratories with the Idylla and Omnis assays. The patients enrolled based on local testing are referred to as CTA+. For the NPA, specimens were tested retrospectively in central laboratories with the Idylla and Omnis assays and compared to results used to characterize the specimens as either MSS or pMMR.

A total of 839 patients were randomized to CA2098HW, and of those, 837 were CTA+. Of the 837 CTA+ randomized patients in Arms A (nivo), B (nivo+ipi) and C (chemo), 13.4% had missing assessments by Idylla, and 7.2% had missing assessments by Omnis. The missing assessments were due to the fact that some patients did not have sufficient tissue for testing or resulted in an invalid test status by Idylla or Omnis assays even with sufficient tissues collected. The missing assessments may potentially introduce bias to the concordance and the clinical performance evaluation, and hence imputations and sensitivity analyses were conducted after these analyses were done with the available data and reflected in the clinical performance results given below.

The clinical utility of Idylla™ MSI Test and Omnis CDx were evaluated in CA2098HW. A total of 301 patients were randomized per CTA+ (nivo+ipi: 200 patients; chemo: 101 patients).

IDYLLA MSI

Nivo+ipi demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR over chemo in 1L randomized patients with centrally confirmed MSI-H status by the Idylla MSI test (Figure 18), consistent with the PFS benefit observed in all 1L clinical trial assay positive (CTA+, local testing) patients randomized to nivo+ipi and chemo (Table 27). Median PFS was not reached vs 6.21 months for nivo+ipi and chemo, respectively (HR: 0.20 [95% CI: 0.12, 0.31]).

The clinical performance of the MSI-H status resulted by Idylla MSI in the intended use population showed consistent and clinically meaningful PFS benefit with nivo+ipi vs chemo in 1L patients, consistent with the PFS benefits observed in all 1L CTA+ randomized patients in Arms B and C in CA2098HW and all 1L randomized patients with centrally confirmed MSI-H/dMMR in Arms B and C in CA2098HW (study defined primary population) (Figure 18). Note: The reported tipping point analysis to assess the impact of the effect in the unobserved discordant subpopulation follows was performed following 'Statistical Consideration and Challenges in Bridging Study of Personalized Medicine' (2015, Journal of Biopharmaceutical Statistics, 25:3, 397-407, DOI: 10.1080/10543406.2014.920340) by Meijuan Li (FDA).

Table 27 Progression-free Survival per BICR for Nivo+Ipi vs Chemo in 1L CTA+ Subjects - CA2098HW

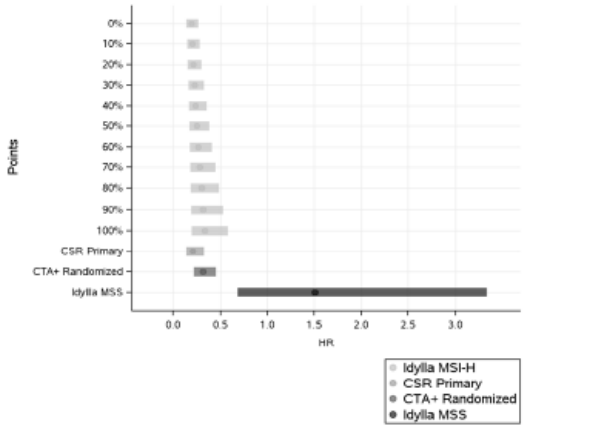
	1L Randomized Subjects (CTA+) with Centrally Confirmed MSI-H Status by Idylla		1L Randomized Subjects (CTA+)	
	Nivo+ Ipi N=147	Chemo N=71	Nivo+ Ipi N=200	Chemo N=101
PFS Events, n (%)	39 (26.5)	44 (62.0)	72 (36.0)	62 (61.4)
Median PFS (95% C.I.), mo[a]	N.A. (38.44, N.A.)	6.21 (4.70, 9.03)	N.A. (34.30, N.A.)	6.21 (4.70, 9.00)
HR (95% CI)[b]	0.20 (0.12, 0.31)		0.32 (0.22, 0.45)	

[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: 12-Oct-2023.

Figure 19 Forest Plot of Progression Free Survival per BICR for Idylla MSI-H of the Intended Use – Nivo+Ipi over Chemo in 1L Subjects



Populations: [Idylla MSI-H] Intended use population of Idylla MSI-H; [CSR Primary] Subjects who were randomized in CA2098HW with centrally confirmed MSI-H/dMMR status; [CTA+ Randomized] Subjects who were randomized in CA2098HW with locally confirmed MSI-H/dMMR status; [Idylla MSS] Subjects who were randomized in CA2098HW with centrally tested MSS status and locally confirmed MSI-H/dMMR status

Tipping point analysis results range from the best to the worst scenario, where the best scenario represents HR equal to the estimated value from the data of the concordant population and the worst scenario represents HR equal to 1.

The results are based on the data from a database lock when only the 1L subjects in Arm B and Arm C are unblinded.

OMNIS MMR

Nivo+ipi demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR over chemo in 1L randomized patients with centrally confirmed dMMR status by Omnis (Figure 19), consistent with the PFS benefit observed in all 1L CTA+ patients randomized to nivo+ipi and chemo

(Table 29). Median PFS was not reached vs 5.85 months for nivo+ipi and chemo, respectively (HR: 0.22 [95% CI: 0.14, 0.34]).

The clinical performance of the dMMR status resulted by Omnis MMR in the intended use population showed consistent and clinically meaningful PFS benefit with nivo+ipi vs chemo in 1L patients, consistent with the PFS benefits observed in all 1L CTA+ randomized patients in Arms B and C in CA2098HW and all 1L randomized patients with centrally confirmed MSI-H/dMMR in Arms B and C in CA2098HW (Figure 19).

Table 28 Progression-free Survival per BICR for Nivo+Ipi vs Chemo in 1L CTA+ Subjects - CA2098HW

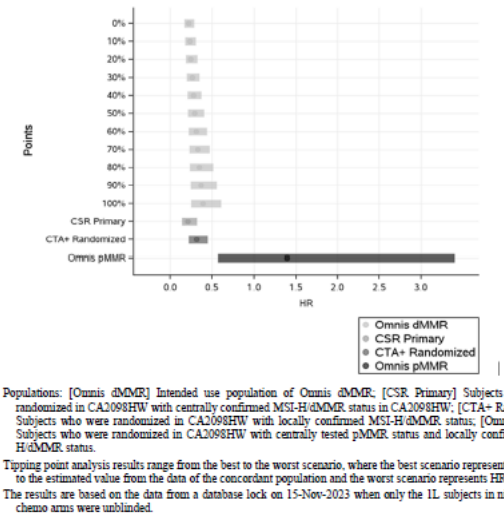
	1L Randomized Subjects (CTA+) with Centrally Confirmed dMMR Status by Omnis		1L Randomized Subjects (CTA+)	
	Nivo+Ipi N=163	Chemo N=82	Nivo+Ipi N=200	Chemo N=101
PFS Events, n (%)	47 (28.8)	50 (61.0)	72 (36.0)	62 (61.4)
Median PFS (95% C.I.), mo[a]	NR (38.44, NA)	5.85 (4.40, 7.79)	NR (34.30, NA)	6.21 (4.70, 9.00)
HR (95% CI)[b]	0.22 (0.14, 0.34)		0.32 (0.22, 0.45)	

[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: 12-Oct-2023

Figure 20 Forest Plot of Progression Free Survival per BICR for Omnis dMMR of the Intended Use – Nivo+Ipi vs Chemo in 1L Subjects



Populations: [Omnis dMMR] Intended use population of Omnis dMMR; [CSR Primary] Subjects who were randomized in CA2098HW with centrally confirmed MSI-H/dMMR status in CA2098HW; [CTA+ Randomized] Subjects who were randomized in CA2098HW with locally confirmed MSI-H/dMMR status; [Omnis pMMR] Subjects who were randomized in CA2098HW with centrally tested pMMR status and locally confirmed MSI-H/dMMR status.

Tipping point analysis results range from the best to the worst scenario, where the best scenario represents HR equal to the estimated value from the data of the concordant population and the worst scenario represents HR equal to 1.

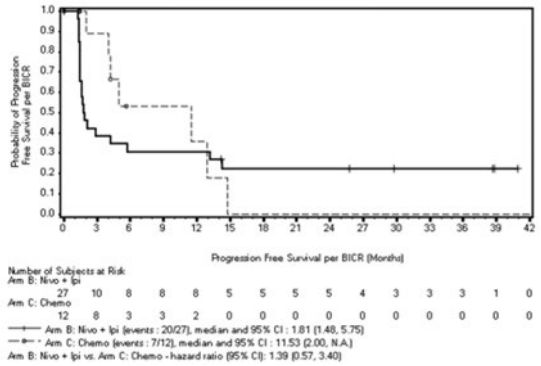
The results are based on the data from a database lock on 15-Nov-2023 when only the 1L subjects in nivo+ipi and chemo arms were unblinded.

PFS in the MSS/pMMR population

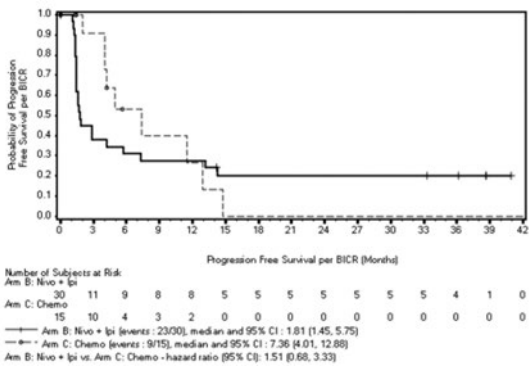
In 1L randomized CTA+ subjects with centrally confirmed Omnis pMMR status, the median PFS for nivo+ipi vs chemo was 1.81 months (95% CI: 1.48, 5.75) vs 11.53 months (95% CI: 2.00, not reached). In 1L randomized CTA+ subjects with centrally confirmed Idylla MMS status, the median PFS was 1.81 months (95% CI: 1.45, 5.75) for nivo+ipi, and 7.36 months (95% CI: 4.01, 12.88) for chemo. PFS KM-curves are shown below.

Figure 21 Progression free survival per BICR for nivo+ipi vs chemo – 1L randomized CTA+ subjects with centrally confirmed Omnis pMMR (A) or Idylla MSS (B) status in CA2098WH

A:



B:



Topline results IA DCO (28 Aug 2024)

During the procedure, the MAH provided topline results of the nivo+ipi vs nivo comparison. Study CA2098HW met its dual primary endpoint demonstrating statistically significant improvement in PFS by BICR with nivo+ipi compared to nivo across all lines of therapy in patients with centrally confirmed MSI-H/dMMR mCRC. PFS HR = 0.62 (95%CI: 0.48, 0.81), p = 0.0003; median PFS Not Reached (95%CI: 53.8, NE) vs 39.3 months (95%CI: 22.1, NE) with nivo+ipi vs nivo. The secondary endpoint ORR by BICR with nivo+ipi vs nivo across all lines of therapy also met statistical significance (70.6% vs 57.7%, p=0.0011).

PFS for nivo+ipi vs nivo (Arm B vs Arm A) in the 1L setting did not reach statistical significance and will therefore remain blinded until PFS FA (clinical cut off April 2025) with data being available in 4Q2025.

2.4.3. Discussion on clinical efficacy

The scope of this variation is to support the extension of indication for Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for the first-line treatment of adults with unresectable or metastatic dMMR or MSI-H CRC, based on the results of the pivotal study CA2098HW, an ongoing phase 3 open-label randomized 2:2:1 study of nivolumab alone vs nivolumab in combination with ipilimumab vs investigator's choice SOC chemotherapy. The clinical data cutoff for this submission was 12 Oct 2023, median follow-up was 31.57 months (minimum 6.1 months) in 1L randomized patients.

Design and conduct of clinical studies

The dosing regimen of nivo 240 mg + ipi 1 mg/kg Q3W for a maximum of 4 doses, followed by nivo 480 mg Q4W was expected to have similar exposures of both nivo and ipi as the approved combination dosing regimen for 2L+ patients with dMMR or MSI-H mCRC, which is nivo 3 mg/kg + ipi 1 mg/kg Q3W for 4 doses, followed by nivo 240 mg Q2W. The maintenance dose of 480 mg Q4W is approved for RCC indication and expected to have similar exposure as 240 mg Q2W based on prior popPK analysis. Overall, this is acceptable as benefit has been shown and no major safety issues were observed in the pivotal clinical study CA2098HW.

Study CA2098HW consisted of two sequential parts; Part 1 included patients across all lines of therapy whereas Part 2 only included 1L patients. Eligible 1L and 2L patients were randomized to Arm A (nivo), Arm B (nivo+ipi), or Arm C (chemo) in a 2:2:1 ratio and ≥ 3L patients were randomized to Arm A (nivo)

and Arm B (nivo+ipi) in a 1:1 ratio. Randomization was stratified by tumour location (right vs left) and by the number of prior treatments for metastatic disease (none, 1, ≥ 2, for Part 1 only). Patients in the SOC arm had the option to crossover to nivo+ipi at disease progression (PD). Patients 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. This information however is not reflected in section 5.1 SmPC as there is no sound evidence to support this treatment strategy. The study design is overall acceptable as it allows the assessment of the contribution of ipilimumab to the combination treatment, given the nivolumab monotherapy arm. The study did not include an ipilimumab monotherapy arm which is agreed since adequate efficacy would not be anticipated, as already stated in the previous SA (EMEA/H/SA/3330/4/2019/II). However, as discussed below on the statistical analyses, the multiple objectives (all lines and 1L setting) and the chosen hierarchical testing strategy limit the data available at the time of assessment hampering the interpretation of the results.

The eligibility criteria are considered overall appropriate to define the target population, although mostly reflecting relatively fit patients (ECOG 0-1). Information that only patients with ECOG 0 or 1 were enrolled is included in section 5.1 of the SmPC. Baseline ECOG performance status was 0 (54%) and ≥ 1 (46%). Inclusion was based on known tumour MSI/MMR per local standard of practice testing and MSI-H/dMMR CRC was retrospectively confirmed by central testing using PCR and IHC. Both type of tests are acceptable. The ESMO consensus panel recommends the use of both MMR-IHC and MSI-PCR to assess the eligibility to treatment with immune checkpoint inhibitors of mCRC. Tumour specimen acquisition was mostly (87.0%) from the primary tumour and balanced between the two arms. Of the 303 randomized patients, 87 (28.7%) were MSI-H and 213 (70.3%) were dMMR according to local testing.

The primary population for efficacy analysis concerned patients with centrally confirmed MSI-H and/or dMMR. Additional efficacy analyses were performed on all randomized patients and centrally confirmed by test (PCR or IHC). During the study, concordance between local and central testing for MSI-H/dMMR was lower than expected (15%) and the number of randomized patients based on local testing was increased (protocol amendment 7, 10 May 2022; from 492 to 560 patients in part 1 and 256 to 271 in part 2). Ultimately, 255/301 (84.7%) had centrally confirmed MSI-H/dMMR in the 1L setting. It is known that several factors may influence concordance such as type of test used, expertise of pathologists, and the quality of the tissue sample.

The comparator arm consisted of an investigator's choice treatment (chosen before randomization) among 6 different polychemotherapy regimens, each acceptable as 1L regimen at the time of start of the study (first patient enrolled August 2019). It is noted that the cetuximab dosing regimen of 500 mg/m^2 is currently not approved in the EU. However, the dose is commonly used in clinical practice and recommended in the ESMO guideline during COVID-19 and FDA.

The open label design is acknowledged given the marked differences of the treatments in the three treatment arms. The primary endpoint PFS was assessed per BICR which is preferred in view of the open-label design.

The study was set up to investigate nivo+ipi in all lines of treatment and in 1L with two dual primary endpoints; PFS of the nivo+ipi combination vs nivolumab monotherapy in all lines and PFS of nivo+ipi vs chemo in 1L setting. ORR and OS were to be analysed as secondary endpoints as part of the hierarchical testing strategy. A comparison of nivo+ipi vs nivolumab monotherapy is a secondary endpoint in the 1L setting which allows the assessment of the contribution of ipilimumab to the combination treatment. These data are currently not available and not expected until April 2025 due to slow PFS event accumulation causing delay in performing the first interim analysis of the other primary endpoint. Instead, the MAH has presented the results from the 2L setting to support the contribution of the

components which is further discussed in the results section below. A formal analysis of nivolumab monotherapy vs chemotherapy is lacking and would have been welcomed to assess the benefit-risk profile of the monotherapy given the additional toxicity of the combination treatment. However, secondary objectives include comparisons of arm A vs arm C for PFS, ORR and OS (SAP section 3.2).

The primary endpoint PFS per RECIST 1.1 by BICR is considered an acceptable primary endpoint for this study but would in general need support from sufficiently mature OS data. Due to the testing hierarchy, no OS data are currently available and the MAH expects that the earliest scenario for OS analysis would be April 2025. Formal testing of OS endpoints would also depend on whether the precedent endpoint in the testing hierarchy achieve significance and pass over the alpha. In addition, no information is available on ORR from the pivotal study so there will be limited supportive data for the primary endpoint PFS. PFS2 is available as exploratory endpoint providing some support for long-term efficacy. This is further discussed below.

Crossover from the SOC to nivo+ipi at PD was allowed which will confound OS. Although combination treatment was not yet approved for the 2L setting at the start of the study (Approval May 2021, EMEA/H/C/WS1840), checkpoint inhibitors and ipilimumab could be available for cross-over in clinical practice and cross-over can thus be acceptable from a pragmatic point of view (EMEA/H/SA/3330/4/2019/II). Sensitivity analysis to address the impact of crossover on OS will be performed at the time of IA OS (April 2025) and submitted by Q4 2025 (REC).

The statistical methods used for the analysis of primary and secondary PFS outcomes in this interim analysis are in general accepted, although the implausibility of the proportional hazards assumption should be taken into account when interpreting the estimated hazard ratios. In addition, by censoring patients with missing PFS duration in the analyses, it is assumed that the missingness is uninformative. This assumption is plausible when the outcome status is missing due to administrative reasons, but not, in general, when missingness is non-administrative (EMA/CHMP/27994/2008/Rev.1). Regarding the analysis of BICR-PFS according to the EMA definition, non-administrative censoring appears limited in the nivo+ipi arm (4/171, i.e. 2.3%, counting the patients censored at randomization and those off-study), but more substantial in the chemo arm (9/84, 10.7%). However, sensitivity analyses provided by the MAH indicated that the reported results were robust.

The testing strategy used to protect the type I error across primary and secondary outcomes in the study is accepted, as is the approach used to conduct the interim analyses. The small discrepancy between the prespecified (106) and observed (100) number of events was because the date of database lock was based on (blinded) event projection (performed by an independent vendor), not on the actual event count.

There were several changes to the study design and statistical analyses. When the first patient included in the current analysis was randomized (19 Aug 2019), the most recent protocol version was Revised Global Protocol 03. At that point, the study was designed as a 3-arm RCT, with the primary endpoint defined as "PFS per BICR for nivo+ipi vs nivo in patients across lines of therapy (in all randomized patients)". Adjustments were made in subsequent revisions, including the addition of a second primary objective (as well as an updated recruitment strategy), a change in the statistical testing procedure, and a change in the timing of the interim analyses. Such changes bear the risk of increased type 1 error, particularly given the open-label nature of the study. Sensitivity analyses suggest that the adjustments did not affect the conclusion regarding the currently reported primary endpoint. The choice to consider the comparison of BICR-PFS in nivo+ipi vs. chemotherapy in the subset of 1L patients with centrally confirmed dMMR/MSI-H mCRC as a primary objective was made in Revised Global Protocol 04 (17 Jul 2020), approximately 11 months after the first patient was randomized. However, results from additional sensitivity analyses provided by the MAH indicate consistency of the reported primary PFS analysis results

between the subgroup of subjects randomized up to 17 Jul 2020 (HR = 0.20 (95% CI 0.09, 0.45)) and those in the subgroup randomized on or after 17 Jul 2020 (HR = 0.22 (95% CI 0.13, 0.36), respectively.

Overall, the rate of protocol deviations was comparable between the treatment arms and no concern is raised over the possible impact of protocol deviations on efficacy results.

Efficacy data and additional analyses

A total of 303 1L patients with MSI-H/dMMR mCRC per local testing were randomized to the nivo+ipi (n=202) and chemo arms (n=101). Information on the number of patients screened and reasons for not meeting eligibility criteria were not available for the 1L setting as line of therapy was not collected at enrolment. Nevertheless, information from the all randomized subjects did not raise specific concerns (data not shown). More patients in the chemo arm did not receive treatment (n=13 vs n=2), which may be due to the open-label design and patients not willing to receive the SOC. Main reasons for discontinuation of treatment were disease progression in the chemo arm (69.3% vs 19.0% nivo+ipi) and adverse events in the nivo+ipi arm (related or unrelated to study drug; 24% vs. 10.2% chemo). About a quarter of patients is still on treatment in the nivo+ipi arm.

Baseline characteristics were generally well balanced between the two arms, except for (differences ≥5%) age < 65 years (57.9% vs 45.5%), PD-L1 ≥ 1% (21.3% vs 11.9%), and Lynch syndrome (10.9% vs 16.8%; overall 26.5% unknown/unreported), geographic region ROW (24.8% vs 18.8%), in nivo+ipi vs chemo, respectively. Comparable results were observed for patients with centrally confirmed MSI-H/dMMR, except for an additional difference in unknown BRAF/KRAS/NRAS mutation status (26.9% vs 33.3%). Unfortunately about 30% of patients had unknown BRAF/KRAS/NRAS mutational status, as this was not mandatory for enrolment. Baseline tumour burden per BICR in all 1L randomized subjects with centrally confirmed dMMR/MSI-H status was generally balanced between the 2 treatment arms, with an overall median of 60 mm.

The MAH presented the results of the 1st interim analysis for PFS in the 1L setting at a DCO date of 12 Oct 2023, with a median follow-up duration of 31.57 months (range: 6.1-48.4). The primary efficacy analysis population consisted of patients with centrally confirmed MSI-H/dMMR mCRC. Median PFS was not reached for nivo+ipi (95% CI: 38.44, NA) and was 5.85 (95% CI: 4.37, 7.79) months for chemo. PFS events occurred in 28.1% vs 61.9% in the nivo+ipi vs chemo arm. As the threshold for statistical significance was reached, this is also considered the final PFS analysis. The KM-curves show a pronounced difference between the treatment arms starting around 3 months of treatment with 12-month PFS rates of 79% vs 21% and the PFS benefit of nivo+ipi is considered compelling in the proposed target population. A high number of patients on nivo+ipi is censored and 24.1% is still ongoing on treatment which may be partly explained by the late enrolment in part 2 of the study (last patient enrolled April 2023). Updated PFS results (including PFS2) will be available at the time of the next IA PFS analyses across all lines of treatment. These data will therefore be submitted by Q4 2025 which is acceptable (REC). Within the initial two months after randomization, results did not favour nivo+ipi over chemo, however, KM-curves did not cross as observed in the Keynote-177 study where pembrolizumab was administered as monotherapy.

The mPFS in the control arm is somewhat lower than assumed for the sample size calculation (9 months) and observed in the Keynote-177 study (8.2 months). This is not further pursued as it will not impact the conclusion on the PFS benefit. Results for PFS per BICR without censoring at subsequent anti-cancer therapy initiation were consistent with the primary analysis. Also other supportive analyses support the primary analysis.

The results for the primary endpoint were supported by the secondary endpoints PFS per BICR in all randomized patients, and PFS per investigator in patients with centrally confirmed MSI-H/dMMR mCRC.

PFS results by central biomarker test for dMMR/MSI-H (ICH or PCR) showed similar results. It is noted that for the all randomized patients early crossing of the KM PFS curves was observed in the first 3-6 months. Additional analysis of baseline characteristics of 84 patients (47 nivo+ipi and 37 chemo arm) with early PFS events prior to or on week 13 indicate that the absence of biomarker (i.e. subjects without centrally confirmed dMMR/MSI-H status) most likely contributed to the early crossing of the KM curves observed in all 1L randomized subjects.

The lack of OS data is a current uncertainty in the assessment. However, given the compelling PFS benefit observed and provided that the apparent substantially prolonged effect is sustained with longer follow-up, a detrimental effect on OS is unlikely and PFS can be viewed as a benefit on its own (EMEA/H/SA/3330/4/2019/II). A long term benefit is supported by PFS2 (exploratory endpoint; HR = 0.27 (95% CI: 0.017, 0.44)) with 12-month PFS rates of 89% vs 65%. Some additional support for long-term benefit is derived from the single arm cohort 3 in study CA209142 including 45 1L patients, however, the lack of a control arm hampers interpretation. As discussed before, crossover to nivo+ipi likely confounds OS. In the chemo arm, 44.6% of patients crossed over and an additional 20.8% of patients in the chemo arm received IO off study. Overall 65.4% received subsequent IO therapy. Given that nivo+ipi is currently approved in 2L setting, this is considered to reflect clinical practice. It is reassuring that PFS2 still favours nivo+ipi and the PFS of nivo+ipi appears favourable compared to PFS2 of the SOC. Results from cohort 3 suggest an ORR of about 62%, comparable to that observed in the 2L setting for nivo+ipi. However, this is based on a limited number of patients. Overall, given the outstanding PFS benefit, it is acceptable to obtain OS data post-approval. The MAH has committed to submit the interim OS data by Q4 2025 (**REC**).

The contribution of ipilimumab to the efficacy of the combination treatment in the 1L setting has not been established as no data are available yet on nivolumab monotherapy. The contribution of ipilimumab to the efficacy of the combination treatment is of relevance given that it is known that the addition of ipilimumab leads to a more unfavourable safety profile. The MAH submitted the results of the nivo+ipi cohort and the nivolumab monotherapy cohort from the nonrandomized phase 2 study CA209142 in later line setting to support the contribution of ipilimumab. This was previously accepted by the CHMP based on an increase in ORR (59.7% vs 37.8%), although based on non-randomized comparisons (EMEA/H/C/WS1840). It is agreed that these data partly support the contribution of ipilimumab to the combination in the 1L setting, although some uncertainty remains based on the non-randomized comparisons, the different lines of treatment and the uncertainty whether an increase in ORR translates into an increase in long-term endpoints like PFS and OS. Nevertheless, given the compelling PFS results observed, and the biological rationale to combine treatments in the target population, together with some support from the 2L setting, it is considered acceptable to obtain information on the contribution of ipilimumab to the combination treatment in the proposed target population post-approval. PFS for nivo+ipi vs nivo (Arm B vs Arm A) in the 1L setting did not reach statistical significance at the IA PFS (DCO 28 Aug 2024) for the all lines population and will therefore remain blinded until PFS FA (clinical cut off April 2025) with data being available in Q4 2025. The MAH has committed to present these data (**REC**) by Q4 2025. ORR data will be submitted as well post-marketing with the same timeline. Further, the safety profile of the combination treatment does not seen worse compared to SOC and might even be favourable in terms of grade 3-4 events.

Subgroup analyses were pre-specified in the SAP. Beneficial effects were seen in important subgroups such as patients with Lynch syndrome, patients with hepatic or pulmonary metastases, and patients with BRAF or KRAS/NRAS mutations. There were no subgroups with a point estimate HR>1. HR could not be calculated in patients with prior radiotherapy given the limited size of this subgroup. Post-hoc subgroup analyses also showed a consistent benefit of nivo+ipi over SOC, independent of type of SOC, and regardless of tumour burden. A beneficial effect was also seen independent of tumour PD-L1 expression. The fact that most patients (74.9%) had low PD-L1 levels (<1%) might also support on an added benefit

of ipilimumab as it is known that nivolumab monotherapy especially performs well in the PD-L1 high population (e.g. melanoma). It remains, however, to be seen whether there are additional biomarkers that predict response to immunotherapy. Exploratory biomarker analyses are planned which is endorsed and additional information is estimated to be available in Q4 2024 (inflammatory gene signature) and Q3 2025 (select gene alterations and TMB).

Patients were allowed to undergo resection of primary tumour or metastases with curative intent if deemed eligible after responding to treatment. The possibility to be treated with curative intent after systemic treatment-induced response is considered clinically relevant as this can result in long term survival. Results show that only a limited number of patients underwent curative surgery in both arms and numerically less in the nivo+ipi arm (n=5 (2.9%) vs n=6 (7.1%)). Therefore, based on the current data the possibility to undergo curative surgery does not seem to increase with nivo+ipi treatment.

PRO data showed stable results or a trend for improvement with nivo+ipi over time. The most notable changes were as follows: improvements in abdominal pain and bloating in the nivo+ipi arm, worsening of hair, taste and sexual interest for women in the chemo arm, and improvement in anxiety for both arms. Overall, PRO data support the benefit of nivo+ipi over SOC in terms of efficacy and safety, although data should be interpreted cautiously due to the open-label design and the number of missing data over time. No claims are made in the SmPC which is agreed given the study design (not formal testing and open-label study).

In vitro biomarker test MSI-H/dMMR: Testing for MSI-H/dMMR is clinical practice in CRC to guide use of immunotherapy and both IHC and PCR are acceptable tests. A PFS benefit was seen both in the centrally confirmed population and the all randomized population (local testing). Additional analyses were performed to account for missing samples and the results of tipping point analyses were presented in the forest plots. Additional analyses in subjects classified as MMS/pMMR based on central testing indicate lack of a beneficial effect of nivo+ipi over chemo in the absence of the biomarker, which is in line with the biological rationale.

Target population: The proposed indication concerns unresectable or metastatic MSI-H/dMMR CRC. Study CA2098HW permitted enrolment of patients with metastatic or recurrent MSI-H/dMMR CRC not amenable to surgery, with patients having local recurrence qualifying for advanced unresectable disease. However, only patients with mCRC were enrolled. Extrapolation to patients with unresectable MSI-H/dMMR CRC (encompassing both recurrent and non-recurrent unresectable disease) is based on published data from the use of IO in the neoadjuvant setting in patients with stage II-III disease, and especially NICHE-2 showing a high rate of complete pathologic response and encouraging disease free survival (DFS) results were reported after 2 doses of nivo and one dose of ipi followed by surgery. Further, the NCCN guidelines[19], while acknowledging a lack of data in this setting, recommend pembrolizumab, dostarlimab or nivo as a monotherapy or in combination with ipi, as options for treatment of unresectable advanced CRC or potentially resectable mCRC with MSI-H/dMMR tumours. The possibility to be treated with curative intent surgeries is considered clinically relevant as this can result in long term survival. Within the current metastatic setting only a limited number of patients underwent curative surgery in both arms. Overall, available data in earlier setting provide additional support for efficacy of nivo+ipi in MSI-H/dMMR CRC and given the observed high efficacy in this biomarker defined population in mCRC, extrapolation to the advanced unresectable MSI-H/dMMR CRC population in need of first line systemic treatment is considered acceptable.

2.4.4. Conclusions on the clinical efficacy

The efficacy of nivo+ipi in the proposed target population of first-line treatment of adults with

[19] NCCN-2024-colon-cancer-version-1

unresectable or metastatic dMMR or MSI-H CRC has been demonstrated. Data from the pivotal Study CA2098HW indicate a statistically significant and clinically relevant benefit of PFS of nivo+ipi over SOC. The PFS benefit is considered compelling and clinically meaningful.

2.5. Clinical safety

Introduction

Nivolumab in combination with ipilimumab is already approved for the treatment of patients with dMMR or MSI-H after prior fluoropyrimidine-based combination therapy (EMEA/H/C/xxxx/WS/1840, 24 Jun 2021).

The safety data in the current report focused on the use of nivo+ipi for 1L treatment of patients with unresectable or metastatic mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal carcinoma. Main safety results were obtained from the pivotal study CA2098HW which is an ongoing phase 3 open-label randomized 2:2:1 study of nivolumab alone vs nivolumab in combination with ipilimumab vs investigator's choice SOC chemotherapy. The currently submitted safety data includes 200 patients treated with nivo+ipi and 88 patients treated with chemo. The safety data for the chemo arm excludes data after the first Crossover dose, except for the death summaries.

Patient exposure

In 1L treated patients, the median duration of therapy was longer in the nivo+ipi arm than the chemo arm: 13.52 (nivo: 13.52 months; ipi: 2.10 months) vs 3.96 months. Approximately twice as many 1L treated patients in the nivo+ipi arm vs the chemo arm received study drug for > 6 months: 68.5% vs 36.4% (Table 29).

Most 1L nivo+ipi-treated patients received ≥ 90% of the intended dose intensity (Table 30): 82.5% for nivo and 85.0% for ipi. In the chemo arm, 34.1% to 58.9% of 1L treated patients 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 chemotherapies.

In the chemo arm, a larger proportion of 1L treated patients received oxaliplatin-containing regimens (58.0%, 51/88) than irinotecan-containing regimens (42.0%, 37/88). The median duration of oxaliplatin exposure was slightly shorter compared with irinotecan (2.83 vs 3.45 months). In the chemo arm, 75.0% (66/88) of 1L treated patients received a biologic agent; this includes bevacizumab (63.6%, 56/88) and cetuximab (11.4%, 10/88).

Table 29 Duration of Study Therapy - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

	Arm B: Nivo + Ipi N = 200		
	Nivolumab N = 200	Ipilimumab N = 200	Overall N = 200
DURATION OF THERAPY (MONTHS)			
MEAN (MIN, MAX)	13.26 (0.0, 32.3)	1.96 (0.0, 3.7)	13.26 (0.0, 32.3)
MEDIAN	13.52	2.10	13.52
> 3 MONTHS (%)	151 (75.5)	7 (3.5)	151 (75.5)
> 6 MONTHS (%)	137 (68.5)	0	137 (68.5)
> 9 MONTHS (%)	122 (61.0)	0	122 (61.0)
> 12 MONTHS (%)	106 (53.0)	0	106 (53.0)

	Arm C: Chemo N = 88			
	Oxaliplatin N = 51	Leucovorin N = 87	Fluorouracil N = 86	Fluorouracil (cont.) N = 88
DURATION OF THERAPY (MONTHS)				
MEAN	3.30	5.43	4.87	5.41
(MIN, MAX)	(0.0, 11.5)	(0.0, 27.4)	(0.0, 27.4)	(0.1, 27.5)
MEDIAN	2.83	3.94	3.56	3.96
> 3 MONTHS (%)	24 (47.1)	50 (57.5)	46 (53.5)	50 (56.8)
> 6 MONTHS (%)	8 (15.7)	32 (36.8)	27 (31.4)	32 (36.4)
> 9 MONTHS (%)	1 (2.0)	16 (18.4)	13 (15.1)	15 (17.0)
> 12 MONTHS (%)	0	7 (8.0)	6 (7.0)	7 (8.0)

	Bevacizumab N = 56	Cetuximab N = 10	Irinotecan N = 37	Overall N = 88
DURATION OF THERAPY (MONTHS)				
MEAN	5.57	3.19	4.62	5.44
(MIN, MAX)	(0.0, 22.1)	(0.0, 8.8)	(0.0, 20.8)	(0.1, 27.5)
MEDIAN	3.83	2.66	3.45	3.96
> 3 MONTHS (%)	31 (55.4)	5 (50.0)	19 (51.4)	50 (56.8)
> 6 MONTHS (%)	20 (35.7)	2 (20.0)	11 (29.7)	32 (36.4)
> 9 MONTHS (%)	10 (17.9)	0	6 (16.2)	16 (18.2)
> 12 MONTHS (%)	7 (12.5)	0	1 (2.7)	7 (8.0)

Excludes data collected on or after first crossover dose date.

Table 30 Cumulative Dose and Relative Dose Intensity - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

	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(cont.) (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)

	Arm C: Chemo N = 88		
	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	42.729	2278.309	1303.523
(MIN - MAX)	(5.00 - 210.47)	(502.13 - 9005.10)	(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.

Dose modifications

Dose escalation or reductions of nivo or ipi were not permitted. However, dose adjustments of ipi (1 mg/kg) were permitted if the patient'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. For chemo dose reductions were permitted.

Dose delays were frequently reported in both arms and dose reductions were frequently reported in the chemo arm (Table 31).

Table 31 Dose Delay - All 1L Treated Subjects in the Nivo+Ipi Arm

	Arm B: Nivo + Ipi N = 200	
	Nivolumab N = 200	Ipilimumab N = 200
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	113 (56.5)	43 (21.5)
NUMBER OF DOSES DELAYED PER SUBJECT (%)		
0	87 (43.5)	157 (78.5)
1	57 (28.5)	40 (20.0)
2	32 (16.0)	3 (1.5)
3	11 (5.5)	0
>= 4	13 (6.5)	0
TOTAL NUMBER OF DOSES DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	218/2908 (7.5)	46/521 (8.8)
REASON FOR DOSE DELAY (%) (B)		
ADVERSE EVENT	135 (61.9)	29 (63.0)
OTHER	72 (33.0)	11 (23.9)
NOT REPORTED	11 (5.0)	6 (13.0)
LENGTH OF DOSE DELAY (%) (B)		
4 - 7 DAYS	83 (38.1)	16 (34.8)
8 - 14 DAYS	48 (22.0)	10 (21.7)
15 - 42 DAYS	72 (33.0)	18 (39.1)
> 42 DAYS	15 (6.9)	2 (4.3)
SUBJECTS WITH AT LEAST ONE DOSE DELAYED DUE TO COVID-19 (%)	23 (11.5)	5 (2.5)
NUMBER OF DOSES DELAYED DUE TO COVID-19 PER SUBJECT (%)		
0	177 (88.5)	195 (97.5)
1	20 (10.0)	5 (2.5)
2	2 (1.0)	0
3	1 (0.5)	0
TOTAL NUMBER OF DOSES DELAYED DUE TO COVID-19/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	27/2908 (0.9)	5/521 (1.0)
REASON FOR DOSE DELAY DUE TO COVID-19 (%) (C)		
ADVERSE EVENT	16 (59.3)	3 (60.0)
OTHER	11 (40.7)	2 (40.0)
LENGTH OF DOSE DELAY DUE TO COVID-19 (%) (C)		
4 - 7 DAYS	7 (25.9)	2 (40.0)
8 - 14 DAYS	10 (37.0)	2 (40.0)
15 - 42 DAYS	8 (29.6)	1 (20.0)
> 42 DAYS	2 (7.4)	0

Excludes data collected on or after first crossover dose date.

A dose was considered as actually delayed if the delay is exceeding 3 days.

(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.

(B) Percentages are computed out of the total number of doses delayed.

(C) Percentages are computed out of the total number of doses delayed due to COVID-19.

Concomitant therapy

Most (91.7%) 1L randomized patients in the nivo+ipi and chemo arms received concomitant medications.

Among all 1L treated patients in the nivo+ipi and chemo arms, Immune-Modulating Medications (IMMs) were administered for management of certain AEs in 50.0% of patients in the nivo+ipi arm and 39.8% of patients in the chemo arm.

In all 1L treated patients in the nivo+ipi and chemo arms, the most frequently reported AEs that required IMM were:

- **Nivo+ipi:** adrenal insufficiency (9.5%), hypophysitis, and rash (4.5% each)

- **Chemo:** neutropenia (9.1%), abdominal pain (4.5%), anemia and neutrophil count decreased (3.4% each)

The use of concomitant IMMs in 1L randomized patients with centrally confirmed MSI-H/dMMR) was consistent with those for all 1L randomized patients.

Adverse events

AEs (all causality) were reported for most 1L treated patients in both arms (98.5% vs 97.7%)(Table 32). Grade 3-4 AEs were reported in a lower proportion of patients in the nivo+ipi arm compared with the chemo arm (48.0% vs 67.0%).

Table 32 Safety Results - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms - CA2098HW

	Number (%) of Subjects			
Safety Parameters	**Arm B: Nivo+Ipi (N = 200)**		**Arm C: Chemo (N = 88)**	
Deaths	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
Diarrhoea	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)
Anaemia	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

Safety Parameters	Number (%) of Subjects			
	Arm B: Nivo+Ipi (N = 200)		Arm C: Chemo (N = 88)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality Select AEs, by Category (continued)				
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)
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)
All-causality Non-Endocrine IMAEs within 100 days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhoea/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

Safety Parameters	Number (%) of Subjects			
	Arm B: Nivo+Ipi (N = 200)		Arm C: Chemo (N = 88)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
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, 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; CTC version 5.0. Includes events reported between first dose and 30 days after last dose of study therapy, unless otherwise indicated. Excludes data collected on or after first crossover dose date, except for the summary of deaths.

For nivo+ipi, the most frequently reported AEs (all grades, PTs) were diarrhoea (33.5%), pruritus (27.0%), asthenia (22.0%), nausea (20.0%), fatigue (19.0%), abdominal pain (17.0%), and hypothyroidism (16.0%). The most frequently reported Grade 3-4 AEs (PTs) were abdominal pain (3.5%), anaemia (3.5%), and lipase increased and adrenal insufficiency (3.0% each) (Table 33).

For chemo the most frequently reported AEs (all grades, PTs) were diarrhea (56.8%), nausea (48.9%) and asthenia (39.8%). The most frequently reported Grade 3-4 AEs (PTs) were neutropenia (10.2%), neutrophil count decreased (6.8%), hypertension (6.8%), and asthenia (5.7%).

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 patients.

COVID-19 AEs between first treatment and 30 days after last dose of study therapy were reported in 12.0% of patients in the nivo+ipi arm and 6.8% of patients in the chemo arm.

Table 33 Adverse Events by Worst CTC Grade with 10% Cutoff - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

System Organ Class (%) Preferred Term (%)	Arm B: Nivo + Ipi N = 200			Arm C: Chemo N = 88		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	197 (98.5)	96 (48.0)	8 (4.0)	86 (97.7)	59 (67.0)	1 (1.1)
Gastrointestinal disorders	126 (63.0)	31 (15.5)	1 (0.5)	74 (84.1)	14 (15.9)	0
Diarrhoea	67 (33.5)	4 (2.0)	0	50 (56.8)	4 (4.5)	0
Nausea	40 (20.0)	3 (1.5)	0	43 (48.9)	3 (3.4)	0
Abdominal pain	34 (17.0)	7 (3.5)	0	21 (23.9)	2 (2.3)	0
Constipation	28 (14.0)	1 (0.5)	0	19 (21.6)	1 (1.1)	0
Vomiting	20 (10.0)	1 (0.5)	0	22 (25.0)	1 (1.1)	0
Stomatitis	3 (1.5)	0	0	11 (12.5)	0	0
General disorders and administration site conditions	103 (51.5)	9 (4.5)	2 (1.0)	61 (69.3)	8 (9.1)	0
Asthenia	44 (22.0)	4 (2.0)	0	35 (39.8)	5 (5.7)	0
Fatigue	38 (19.0)	2 (1.0)	0	16 (18.2)	0	0
Pyrexia	21 (10.5)	0	0	10 (11.4)	1 (1.1)	0
Infections and infestations	100 (50.0)	22 (11.0)	0	33 (37.5)	13 (14.8)	0
COVID-19	25 (12.5)	2 (1.0)	0	7 (8.0)	1 (1.1)	0
Skin and subcutaneous tissue disorders	100 (50.0)	6 (3.0)	0	33 (37.5)	3 (3.4)	0
Pruritus	54 (27.0)	0	0	6 (6.8)	0	0
Rash	27 (13.5)	2 (1.0)	0	8 (9.1)	1 (1.1)	0
Alopecia syndrome	4 (2.0)	0	0	10 (11.4)	0	0
Metabolism and nutrition disorders	80 (40.0)	9 (4.5)	0	41 (46.6)	8 (9.1)	0
Decreased appetite	31 (15.5)	1 (0.5)	0	27 (30.7)	1 (1.1)	0
Hypokalaemia	13 (6.5)	4 (2.0)	0	14 (15.9)	3 (3.4)	0
Investigations	75 (37.5)	21 (10.5)	0	37 (42.0)	10 (11.4)	0
Alanine aminotransferase increased	28 (14.0)	4 (2.0)	0	6 (6.8)	1 (1.1)	0
Aspartate aminotransferase increased	25 (12.5)	3 (1.5)	0	5 (5.7)	1 (1.1)	0
Lipase increased	23 (11.5)	6 (3.0)	0	4 (4.5)	0	0
Neutrophil count decreased	3 (1.5)	1 (0.5)	0	14 (15.9)	6 (6.8)	0
Endocrine disorders	66 (33.0)	12 (6.0)	0	2 (2.3)	0	0
Hypothyroidism	32 (16.0)	2 (1.0)	0	1 (1.1)	0	0
Adrenal insufficiency	20 (10.0)	6 (3.0)	0	0	0	0
Musculoskeletal and connective tissue disorders	65 (32.5)	3 (1.5)	0	16 (18.2)	0	0
Arthralgia	36 (18.0)	2 (1.0)	0	4 (4.5)	0	0
Back pain	19 (9.5)	0	0	10 (11.4)	0	0
Nervous system disorders	56 (28.0)	4 (2.0)	0	45 (51.1)	6 (6.8)	0
Headache	24 (12.0)	1 (0.5)	0	8 (9.1)	0	0
Neuropathy peripheral	0	0	0	12 (13.6)	1 (1.1)	0
Blood and lymphatic system disorders	42 (21.0)	10 (5.0)	0	36 (40.9)	14 (15.9)	0
Anaemia	29 (14.5)	7 (3.5)	0	18 (20.5)	4 (4.5)	0
Neutropenia	6 (3.0)	2 (1.0)	0	23 (26.1)	9 (10.2)	0
Thrombocytopenia	1 (0.5)	0	0	9 (10.2)	0	0
Vascular disorders	30 (15.0)	4 (2.0)	1 (0.5)	17 (19.3)	8 (9.1)	0
Hypertension	14 (7.0)	3 (1.5)	0	12 (13.6)	6 (6.8)	0

MedDRA Version: 26.1, CTC Version 5.0

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

Excludes data collected on or after first crossover dose date.

Drug-related AEs were reported in a lower proportion of 1L treated patients in the nivo+ipi arm compared with the chemo arm (all grades: 80.0% vs 94.3%; Grade 3-4 AEs (23.0% vs 47.7%).

For nivo+ipi the most frequently reported drug-related AEs (all grades, PTs) were pruritus (22.5%), diarrhoea (21.0%), and hypothyroidism (16.0%). The most frequently reported drug-related Grade 3-4 AEs (PTs) were adrenal insufficiency (3.0%), lipase increased (2.5%), and ALT increased (1.5%).

For chemo the most frequently reported drug-related AEs (all grades, PTs) were diarrhoea (51.1%), nausea (46.6%), and asthenia (35.2%). The most frequently reported drug-related Grade 3-4 AEs (PTs) were neutropenia (10.2%), neutrophil count decreased (6.8%), and asthenia (5.7%).

Serious adverse event/deaths/other significant events

Grade 3-4 SAEs were reported in a lower proportion of patients in the nivo+ipi arm compared with the chemo arm (34.5% vs 42.0%) (Table 34).

For 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%) (Table 35).

For 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).

SAEs of COVID-19 infection (between the first treatment and 30 days after last dose of study therapy) were reported in 1.0% of patients in the nivo+ipi arm and 1.1% of patients in the chemo arm.

Table 34 Serious Adverse Events by Worst CTC Grade Reported in > 2% of Subjects - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

System Organ Class (%) Preferred Term (%)	Arm B: Nivo + Ipi N = 200			Arm C: Chemo N = 88		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	91 (45.5)	69 (34.5)	8 (4.0)	45 (51.1)	37 (42.0)	1 (1.1)
Gastrointestinal disorders	31 (15.5)	27 (13.5)	1 (0.5)	12 (13.6)	11 (12.5)	0
Abdominal pain	5 (2.5)	5 (2.5)	0	3 (3.4)	2 (2.3)	0
Immune-mediated enterocolitis	5 (2.5)	5 (2.5)	0	0	0	0
Diarrhoea	4 (2.0)	3 (1.5)	0	2 (2.3)	1 (1.1)	0
Small intestinal obstruction	4 (2.0)	3 (1.5)	0	0	0	0
Intestinal obstruction	2 (1.0)	2 (1.0)	0	3 (3.4)	2 (2.3)	0
Ileus	0	0	0	2 (2.3)	2 (2.3)	0
Infections and infestations	22 (11.0)	20 (10.0)	0	13 (14.8)	10 (11.4)	0
Pneumonia	3 (1.5)	3 (1.5)	0	3 (3.4)	3 (3.4)	0
Vascular device infection	2 (1.0)	1 (0.5)	0	2 (2.3)	2 (2.3)	0
Endocrine disorders	11 (5.5)	9 (4.5)	0	0	0	0
Adrenal insufficiency	8 (4.0)	6 (3.0)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (4.0)	2 (1.0)	4 (2.0)	6 (6.8)	2 (2.3)	1 (1.1)
Malignant neoplasm progression	5 (2.5)	0	4 (2.0)	2 (2.3)	1 (1.1)	1 (1.1)
Colon neoplasm	1 (0.5)	0	0	2 (2.3)	1 (1.1)	0
Renal and urinary disorders	7 (3.5)	6 (3.0)	0	1 (1.1)	0	0
Acute kidney injury	4 (2.0)	3 (1.5)	0	1 (1.1)	0	0
Respiratory, thoracic and mediastinal disorders	6 (3.0)	5 (2.5)	0	3 (3.4)	3 (3.4)	0
Pleural effusion	0	0	0	2 (2.3)	2 (2.3)	0
Metabolism and nutrition disorders	4 (2.0)	3 (1.5)	0	5 (5.7)	5 (5.7)	0
Hyponatraemia	0	0	0	2 (2.3)	2 (2.3)	0
Injury, poisoning and procedural complications	2 (1.0)	1 (0.5)	0	6 (6.8)	4 (4.5)	0
Infusion related reaction	0	0	0	2 (2.3)	1 (1.1)	0

MedDRA version 26.1; CTC version 5.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Excludes data collected on or after first crossover dose date.

Table 35 Drug-Related Serious Adverse Events by Worst CTC Grade Reported in at Least 2 Subjects - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

System Organ Class (%) Preferred Term (%)	Arm B: Nivo + Ipi N = 200			Arm C: Chemo N = 88		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	38 (19.0)	32 (16.0)	0	17 (19.3)	14 (15.9)	0
Endocrine disorders	11 (5.5)	9 (4.5)	0	0	0	0
Adrenal insufficiency	8 (4.0)	6 (3.0)	0	0	0	0
Hypophysitis	3 (1.5)	3 (1.5)	0	0	0	0
Gastrointestinal disorders	11 (5.5)	9 (4.5)	0	3 (3.4)	3 (3.4)	0
Immune-mediated enterocolitis	5 (2.5)	5 (2.5)	0	0	0	0
Colitis	2 (1.0)	1 (0.5)	0	1 (1.1)	1 (1.1)	0
Diarrhoea	1 (0.5)	1 (0.5)	0	2 (2.3)	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders	4 (2.0)	3 (1.5)	0	0	0	0
Pneumonitis	3 (1.5)	2 (1.0)	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	3 (3.4)	2 (2.3)	0
Infusion related reaction	0	0	0	2 (2.3)	1 (1.1)	0

MedDRA version 26.1; CTC version 5.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Excludes data collected on or after first crossover dose date.

Deaths

As of the 12 Oct 2023 clinical data cutoff, a lower proportion of 1L treated patients in the nivo+ipi arm died (any time after randomization up to the clinical data cutoff date: 12 Oct 2023) compared with the chemo arm: 22.0% vs 42.0%. Disease progression was the most frequently reported cause of death in both arms (Table 36).

Table 36 Death Summary - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

	Arm B: Nivo + Ipi N = 200	Arm C: Chemo N = 88
NUMBER OF SUBJECTS WHO DIED (%) (A)	44 (22.0)	37 (42.0)
PRIMARY REASON FOR DEATH (%)		
DISEASE	28 (14.0)	24 (27.3)
STUDY DRUG TOXICITY (B)	2 (1.0)	1 (1.1)
UNKNOWN	5 (2.5)	4 (4.5)
OTHER	9 (4.5)	8 (9.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%) (C)	9 (4.5)	6 (6.8)
PRIMARY REASON FOR DEATH (%)		
DISEASE	4 (2.0)	2 (2.3)
STUDY DRUG TOXICITY	0	1 (1.1)
UNKNOWN	2 (1.0)	1 (1.1)
OTHER	3 (1.5)	2 (2.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%) (C)	21 (10.5)	18 (20.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	11 (5.5)	11 (12.5)
STUDY DRUG TOXICITY	1 (0.5)	1 (1.1)
UNKNOWN	2 (1.0)	1 (1.1)
OTHER	7 (3.5)	5 (5.7)

(A) Deaths at any time after randomization up to the clinical cutoff date: 12-Oct-2023.

(B) 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, died while receiving Crossover therapy (nivo+ipi). This death (due to acute myocarditis) was considered to be related to nivo+ipi per the investigator.

(C) Last dose of chemo for 1L treated subjects in Arm C who did not crossover to nivo+ipi, or last dose of nivo+ipi for 1L treated subjects in Arm C who crossed over to nivo+ipi.

Two (1.0%) patients (1 due to myocarditis and 1 due to pneumonitis) in the nivo+ipi arm and 1 (1.1%) patient (due to acute myocarditis) in the chemo arm died due to study drug toxicity (per the investigator). The latter patient was reported to have progressed while receiving chemo, crossed over and received 2 doses of nivo (240 mg each), 1 dose of ipi (74 mg), and died 16 days after the last dose. This death was considered to be related to nivo+ipi per the investigator.

In 1L treated patients, deaths attributed to other reasons (per the investigator) were reported in 4.5% of patients in the nivo+ipi arm and 9.1% of patients in the chemo arm. The events that were included in the verbatim terms for the 'other' reasons for death, contain necrohaemorrhagic pancreatitis, sepsis, COVID-19 infection, mesenteric ischemia, internal jugular DV with death due to presumed pulmonary embolism, abdominal focus septic shock, pulmonary embolism, cardiac arrest and brain stem infarction for nivo+ipi. For chemo, death considered "for other reasons" included, ileus, sepsis, colon perforation, acute coronary syndrome, cerebrovascular accident complications, post-op complications, pulmonary focus sepsis and cardiac arrest. None of these events were considered related to study drug per the investigators.

Other Significant Events

Across select AE categories, most select AEs reported in all 1L treated patients were Grade 1-2. The majority were considered drug-related by the investigator.

For nivo+ipi the most frequently reported drug related selected AE categories (any grade) were: skin (34.5%), endocrine (33.5%) and gastrointestinal (23.0%) (Table 37).

For the chemo arm those were; gastrointestinal (52.3%), skin (20.5%), and hypersensitivity/infusion reactions (9.1%).

The most frequently reported drug-related select AEs by PT (any grade) were for nivo+ipi; pruritus (22.5%), diarrhea (21.0%), and hypothyroidism (16.0%).

For the chemo arm the most frequently reported drug-related AEs by PT were diarrhea (51.1%), rash (8.0%), and infusion related reaction (6.8%)

Drug-related serious select AEs were infrequent in the nivo+ipi (≤ 5.5%) and chemo (≤ 3.4%) arms).

Table 37 Onset, Management, and Resolution of Drug-Related Select AEs - All 1L Treated Subjects in the Nivo+Ipi Arm (N = 200)

Category	N (%) Treated Subj. with Any Grade/ Grade 3-4 Drug-Related Select AE	Median Time to Onset of Drug-Related Select AE (range), wks	% Treated Subj. with Drug-Related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time [b] to Resolution of Drug-Related Select AE (range), wks [c,d,e]	% Subj. with Drug-Related Select AE that Resolved[d,e]
Endocrine	67 (33.5)/ 11 (5.5)	12.43 (3.0-102.4)	6 (3.0)	40.3 / 16.4	NA (0.9+ - 201.6+)	27 (40.3)
Gastrointestinal	46 (23.0)/ 9 (4.5)	12.36 (0.3-80.6)	6 (3.0)	23.9 / 19.6	4.14 (0.1 - 93.0+)	43 (93.5)
Hepatic	39 (19.5)/ 9 (4.5)	12.14 (1.9-68.7)	5 (2.5)	28.2 / 25.6	7.14 (0.9 - 98.3+)	36 (92.3)
Pulmonary	5 (2.5)/ 2 (1.0)	6.00 (5.3-12.0)	2 (1.0)	60.0 / 60.0	7.14 (4.0 - 20.1)	5 (100)
Renal	7 (3.5)/ 1 (0.5)	19.86 (2.6-76.1)	2 (1.0)	28.6 / 28.6	1.14 (0.3 - 12.3)	7 (100)
Skin	69 (34.5)/ 5 (2.5)	5.29 (0.1-63.7)	2 (1.0)	27.5 / 7.2	11.86 (0.1 - 154.6+)	52 (75.4)
Hypersensitivity/ Infusion Reaction	8 (4.0)/ 0	3.36 (0.1-93.3)	0	25.0 / 25.0	0.14 (0.1 - 88.4+)	7 (87.5)

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

[d] Subjects reported with a select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.

+ indicates a censored value

MedDRA Version: 26.1, CTC 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.

Immune-Mediated Adverse Events

IMAE analyses included events, all causality, reported within 100 days of the last dose (i.e., with extended follow-up). These analyses include patients who received Immune-Modulating Medications (IMM) for treatment of the event, except for 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 identified by the investigator as IMAEs with no clear alternate etiology and an immune-mediated component.

The majority of non-endocrine IMAEs were Grade 3-4 except for rash. Grade 3-4 non-endocrine IMAEs were reported in a small proportion of patients (≤ 4.5%).

The majority of endocrine IMAEs were Grade 1-2 (except for hypophysitis; Grade 3-4 hypophysitis was reported in 2.5% of patients).

In 1L treated patients, the most frequently reported IMAEs (any grade, by category) were for nivo+ipi; hypothyroidism/thyroiditis (17.0%), adrenal insufficiency (10.5%) and hyperthyroidism (9.0%) Table 38).

Across IMAE categories, all events in the nivo+ipi arm were manageable using the established IMAE treatment algorithms, with resolution reported when IMMs (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

For chemo, the most frequently reported IMAEs were; diarrhoea/colitis, hypersensitivity/infusion reactions, hypothyroidism/thyroiditis, and hyperthyroidism (1.1% each).

Table 38 Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All 1L Treated Subjects in the Nivo+Ipi Arm (N = 200)

IMAE Category	N (%) Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[b,c]	Median[d] Time to Resolution (range), wks[b,c]
Pneumonitis	4 (2.0)/ 3 (1.5)	6.57 (5.3 - 27.9)	2 (1.0)/ 0	4 (100.0)/ 4 (100.0)	8.57 (4.9 - 68.6)	50.0	13.29 (5.9+ - 69.7+)
Diarrhea/Colitis	13 (6.5)/ 9 (4.5)	13.29 (0.9 - 77.0)	8 (4.0)/ 6 (3.0)	13 (100.0)/ 10 (76.9)	6.71 (0.1 - 119.4)	84.6	8.29 (1.9 - 93.0+)
Hepatitis	11 (5.5)/ 6 (3.0)	12.00 (1.9 - 48.9)	5 (2.5)/ 5 (2.5)	11 (100.0)/ 10 (90.9)	4.43 (0.4 - 96.6)	90.9	10.0 (0.9 - 98.3+)
Nephritis/Renal Dysfunction	2 (1.0)/ 1 (0.5)	11.36 (2.6 - 20.1)	2 (1.0)/ 0	2 (100.0)/ 2 (100.0)	8.21 (1.1 - 15.3)	100.0	6.71 (1.1 - 12.3)
Rash	11 (5.5)/ 3 (1.5)	4.86 (0.3 - 43.0)	2 (1.0)/ 5 (2.5)	11 (100.0)/ 4 (36.4)	36.00 (0.7 - 141.1)	72.7	16.14 (0.7 - 143.9+)
Hypersensitivity/ Infusion Reaction	0/ 0	-	-	-	-	-	-
Adrenal Insufficiency	21 (10.5)/ 7 (3.5)	15.00 (4.6 - 96.6)	5 (2.5)/ 5 (2.5)	20 (95.2)/ 7 (33.3)	101.14 (0.4 - 195.9)	38.1	NA (0.4 - 196.1+)
Hypothyroidism/ Thyroiditis	34 (17.0)/ 3 (1.5)	12.64 (5.3 - 102.4)	0/ 6 (3.0)	2 (5.9)/ 2 (5.9)	38.21 (1.6 - 74.9)	38.2	NA (2.1 - 201.6+)
Diabetes Mellitus	2 (1.0)/ 0	15.36 (12.1 - 18.6)	0/ 0	0/ 0	-	0	NA (44.0+ - 78.3+)
Hyperthyroidism	18 (9.0)/ 0	6.14 (3.0 - 33.6)	0/ 3 (1.5)	1 (5.6)/ 0	112.29 (112.3 - 112.3)	72.2	6.29 (0.9+ - 195.9+)
Hypophysitis	10 (5.0)/ 5 (2.5)	14.29 (8.0 - 32.0)	1 (0.5)/ 3 (1.5)	10 (100.0)/ 5 (50.0)	119.21 (4.6 - 181.3)	50.0	86.29 (1.1 - 174.3+)

[a] Denominator is based on the number of subjects who experienced the event.

[b] Reported IMAEs that did not worsen from baseline grade were excluded from time to resolution analysis.

[c] Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.

[d] From Kaplan-Meier estimation. Note that the number of events was very low for most categories.

MedDRA version 26.1: CTC version 5.0.

Other Events of Special Interest

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 patients in the nivo+ipi arm and no patients in the chemo arm. Of the 11 OESIs, 1 event was Grade 5, 8 were Grade 3-4, and 2 were Grade 2. Seven of the 11 events were reported to have resolved (Table 39).

Table 39 Other Events of Special Interest Reported in Nivo+Ipi-Treated Subjects

Events	Grade	Treated with IMM (yes/no)	Outcome
1 Subject with 3 OESIs			
Myasthenic syndrome	Grade 4	No	Death due to myasthenic syndrome
Myocarditis	Grade 4	Yes	Did not resolve
Myositis	Grade 3	No	Did not resolve
1 subject with 2 OESIs			
Encephalitis	Grade 3	Yes	Resolved
Myocarditis	Grade 4	No	Resolved
1 subject with 2 OESIs			
Encephalitis	Grade 3	No	Resolved
Myocarditis	Grade 3	Yes	Resolved
2 subjects with Pancreatitis	Grade 5	No	Death due to hemorrhagic necrotic pancreatitis
	Grade 2	No	Resolved
1 subject with Myositis	Grade 2	No	Resolved
1 subject with Encephalitis	Grade 3	Yes	Resolved

Laboratory findings

Laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) including Grade 3-4 events, seen in 1L treated patients in the nivo+ipi and chemo arms during the treatment period or within 30 days of last dose of study drug are displayed in Table 40.

Table 40 On-Treatment Worst CTC Grade Laboratory Parameters within 30 Days Follow-up (SI Units) – All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

Lab Test Description (%)	Arm B: Nivo + Ipi			Arm C: Chemo			Total		
	N	Grades 1–4	Grades 3–4	N	Grades 1–4	Grades 3–4	N	Grades 1–4	Grades 3–4
HEMOGLOBIN (A)	195	72 (36.9)	6 (3.1)	84	37 (44.0)	7 (8.3)	279	109 (39.1)	13 (4.7)
PLATELET COUNT	195	19 (9.7)	1 (0.5)	84	31 (36.9)	0	279	50 (17.9)	1 (0.4)
LEUKOCYTES, LOCAL LAB	195	25 (12.8)	0	84	45 (53.6)	3 (3.6)	279	70 (25.1)	3 (1.1)
LYMPHOCYTES (ABSOLUTE), TOTAL	195	58 (29.7)	7 (3.6)	83	36 (43.4)	8 (9.6)	278	94 (33.8)	15 (5.4)
ABSOLUTE NEUTROPHIL COUNT	195	36 (18.5)	2 (1.0)	84	50 (59.5)	15 (17.9)	279	86 (30.8)	17 (6.1)
ALKALINE PHOSPHATASE, LOCAL LAB	195	48 (24.6)	3 (1.5)	83	30 (36.1)	0	278	78 (28.1)	3 (1.1)
ASPARTATE AMINOTRANSFERASE, LOCAL LAB	194	78 (40.2)	7 (3.6)	84	28 (33.3)	1 (1.2)	278	106 (38.1)	8 (2.9)
ALANINE AMINOTRANSFERASE, LOCAL LAB	195	80 (41.0)	8 (4.1)	84	29 (34.5)	1 (1.2)	279	109 (39.1)	9 (3.2)
BILIRUBIN, TOTAL, LOCAL LAB	195	34 (17.4)	4 (2.1)	84	10 (11.9)	3 (3.6)	279	44 (15.8)	7 (2.5)
CREATININE, LOCAL LAB	195	56 (28.7)	6 (3.1)	84	18 (21.4)	0	279	74 (26.5)	6 (2.2)
AMYLASE LOCAL LAB	101	40 (39.6)	4 (4.0)	38	12 (31.6)	2 (5.3)	139	52 (37.4)	6 (4.3)
LIPASE, TOTAL	103	43 (41.7)	10 (9.7)	41	17 (41.5)	6 (14.6)	144	60 (41.7)	16 (11.1)
HYPERNATREMIA	194	13 (6.7)	0	84	5 (6.0)	0	278	18 (6.5)	0
HYPONATREMIA	194	65 (33.5)	7 (3.6)	84	23 (27.4)	2 (2.4)	278	88 (31.7)	9 (3.2)
HYPERKALEMIA	194	57 (29.4)	2 (1.0)	83	17 (20.5)	3 (3.6)	277	74 (26.7)	5 (1.8)
HYPOKALEMIA	194	26 (13.4)	2 (1.0)	83	28 (33.7)	8 (9.6)	277	54 (19.5)	10 (3.6)
HYPERCALCEMIA	194	35 (18.0)	0	82	11 (13.4)	0	276	46 (16.7)	0
HYPOCALCEMIA	194	50 (25.8)	1 (0.5)	82	20 (24.4)	0	276	70 (25.4)	1 (0.4)
HYPOGLYCEMIA	189	25 (13.2)	0	78	7 (9.0)	0	267	32 (12.0)	0

Toxicity Scale: CTC version 5.0 Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Excludes data collected on or after first crossover dose date. Percentages are based on subjects with on-treatment laboratory results and CTC grade criteria available.
(A) Per anemia criteria in CTC version 5.0, there is no Grade 4 for hemoglobin.

Hematology

In 1L treated patients, Grade 3 abnormalities in hemoglobin levels were reported in a smaller proportion of patients in the nivo+ipi arm than the chemo arm (3.1% vs 8.3%) during the treatment period or within 30 days of last dose of study drug. Per the anemia criteria in CTC version 5.0, there is no Grade 4 for hemoglobin.

Serum Chemistry

Liver Function Tests

The incidence of grade ¾ hepatic abnormalities (AST, ALT, ALP, total bilirubin) in patients treated with 1L nivo+ipi were; increased ALT (4.1%), increased AST (3.6%), increased bilirubin (2.1%), and increased ALP (1.5%).

For patients treated with chemo, grade 2/4 hepatic abnormalities were; increased bilirubin (3.6%), increased ALT and increased AST (1.2% each)

Six (3.1%) patients in the nivo+ipi arm and 3 (3.6%) patients in the chemo arm were reported with concurrent ALT or AST > 3 x ULN with total bilirubin > 2 x ULN within 1 day and within 30 days of last dose of study therapy. These hepatic abnormalities for the 6 patients in the nivo+ipi arm were not considered to be related to study drug (per the investigator. Among these 6 patients, 4 had advanced malignant disease with the presence of liver metastasis and signs of cholestasis; 1 patient had gallstone disease, and the remaining patient had multiorgan failure in the context of disseminated intravascular coagulation.

Table 41 On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) – All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

Abnormality (%)	Arm B: Nivo + Ipi N = 200	Arm C: Chemo N = 88	Total N = 288
	N = 195	N = 84	N = 279
ALT OR AST > 3XULN	30 (15.4)	8 (9.5)	38 (13.6)
ALT OR AST > 5XULN	10 (5.1)	2 (2.4)	12 (4.3)
ALT OR AST > 10XULN	5 (2.6)	1 (1.2)	6 (2.2)
ALT OR AST > 20XULN	2 (1.0)	0	2 (0.7)
	N = 195	N = 84	N = 279
TOTAL BILIRUBIN > 2XULN	11 (5.6)	4 (4.8)	15 (5.4)
	N = 195	N = 84	N = 279
ALP > 1.5XULN	42 (21.5)	26 (31.0)	68 (24.4)

Table 42 On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) – All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

Abnormality (%)	Arm B: Nivo + Ipi N = 200	Arm C: Chemo N = 88	Total N = 288
	N = 195	N = 84	N = 279
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	6 (3.1)	3 (3.6)	9 (3.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	6 (3.1)	3 (3.6)	9 (3.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	6 (3.1)	3 (3.6)	9 (3.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	6 (3.1)	3 (3.6)	9 (3.2)

Excludes data collected on or after first crossover dose date.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.

Kidney Function Tests

Most 1L treated patients (with at least 1 on-treatment measurement) were reported with normal creatinine values during the treatment period. Grade ¾ abnormalities in creatinine (increases) were reported in six (3.1%) of the 1L treated patients in the nivo+ipi arm (3.1%) and in no patients in the chemo arm.

Thyroid Function Tests

In 1L treated patients, TSH increases to > ULN from a baseline level £ ULN were reported in 20.9% of patients in the nivo+ipi arm and 9.3% of patients in the chemo arm. TSH decreases to < LLN from a baseline level < LLN were reported in 31.9% of in the nivo+ipi arm and 2.3% of patients in the chemo arm (Table 43).

Table 43 On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All 1L Treated Subjects with at Least 1 On-Treatment TSH Measurement in the Nivo+Ipi and Chemo Arms

Abnormality (%)	Arm B: Nivo + Ipi N = 182	Arm C: Chemo N = 43	Total N = 225
TSH > ULN	50 (27.5)	4 (9.3)	54 (24.0)
TSH > ULN WITH TSH <= ULN AT BASELINE	38 (20.9)	4 (9.3)	42 (18.7)
TSH > ULN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	25 (13.7)	0	25 (11.1
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	15 (8.2)	4 (9.3)	19 (8.4
WITH FT3/FT4 TEST MISSING (A) (B)	10 (5.5)	0	10 (4.4
TSH < LLN	66 (36.3)	1 (2.3)	67 (29.8)
TSH < LLN WITH TSH >= LLN AT BASELINE	58 (31.9)	1 (2.3)	59 (26.2)
TSH < LLN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	31 (17.0)	0	31 (13.8)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	28 (15.4)	1 (2.3)	29 (12.9)
WITH FT3/FT4 TEST MISSING (A) (B)	7 (3.8)	0	7 (3.1)

Excludes data collected on or after first crossover dose date.

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

(A) Within a 2-week window after the abnormal TSH test date.

(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Pancreas Function Tests

Most 1L treated patients were reported with normal amylase and lipase levels during the treatment period. Abnormalities in amylase and lipase that were reported during treatment were primarily Grade 1-2. In the nivo+ipi and chemo arms, Grade 3/4 amylase elevation was reported for respectively 4.0% vs 5.3% of the patients. Lipase elevation was reported in respectively 9.7% vs 14.6% of the patients during the treatment period or within 30 days of last dose of study drug.

Electrolytes

Most 1L treated patients were reported with normal electrolyte levels during the treatment period. When electrolyte levels were abnormal, the events were mostly Grade 1-2. In the nivo+ipi and chemo arms, ≤ 10% of patients were reported with Grade 3/4 abnormal electrolyte values during the treatment period or within 30 days of last dose of study drug.

Glucose

Most 1L treated patients were reported with normal fasting glucose levels during the treatment period; abnormalities in glucose (low) during treatment were all Grade 1-2.

Pregnancy Tests

One patient 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 patient had received the last dose of ipi on Day 66 and the last dose of nivolumab on Day 604. The pregnancy was terminated on Day 674.

Safety in special populations

Subgroup Analysis by Intrinsic and Extrinsic Factors

Summary of on-treatment adverse events by age group for all patients who received nivo+ipi or chemo as first line treatment in study CA209HW is provided in the table below.

Table 44 All-Causality Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

	Number (%) of Subjects							
	Nivo+Ipi				Chemo			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	200	197 (98.5)	96 (48.0)	8 (4.0)	88	86 (97.7)	59 (67.0)	1 (1.1)
By Age (years)								
< 65	115	113 (98.3)	52 (45.2)	4 (3.5)	42	41 (97.6)	27 (64.3)	1 (2.4)
≥ 65	85	84 (98.8)	44 (51.8)	4 (4.7)	46	45 (97.8)	32 (69.6)	0
≥ 65 and < 75	48	47 (97.9)	22 (45.8)	2 (4.2)	34	33 (97.1)	25 (73.5)	0
≥ 75 and < 85	35	35 (100.0)	20 (57.1)	2 (5.7)	10	10 (100.0)	6 (60.0)	0
≥ 85	2	2 (100.0)	2 (100.0)	0	2	2 (100.0)	1 (50.0)	0
By Sex								
Male	94	92 (97.9)	40 (42.6)	6 (6.4)	43	42 (97.7)	30 (69.8)	0
Female	106	105 (99.1)	56 (52.8)	2 (1.9)	45	44 (97.8)	29 (64.4)	1 (2.2)
By Race								
White	175	173 (98.9)	87 (49.7)	7 (4.0)	77	75 (97.4)	52 (67.5)	1 (1.3)
Black or African American	1	1 (100.0)	0	0	2	2 (100.0)	1 (50.0)	0
Asian	19	18 (94.7)	6 (31.6)	1 (5.3)	8	8 (100.0)	6 (75.0)	0
Other	5	5 (100.0)	3 (60.0)	0	1	1 (100.0)	0	0
By Region								
US/Canada/Europe	131	129 (98.5)	68 (51.9)	6 (4.6)	65	63 (96.9)	40 (61.5)	1 (1.5)
Asia	19	18 (94.7)	6 (31.6)	1 (5.3)	7	7 (100.0)	5 (71.4)	0
Rest of World	50	50 (100.0)	22 (44.0)	1 (2.0)	16	16 (100.0)	14 (87.5)	0

MedDRA version 26.1; CTC 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.

Table 45 Drug-Related Adverse Events, Worst CTC Grade by Age, Sex, Race, and Region - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

	Number (%) of Subjects							
	Nivo+Ipi				Chemo			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	200	160 (80.0)	46 (23.0)	0	88	83 (94.3)	42 (47.7)	0
By Age (years)								
< 65	115	93 (80.9)	22 (19.1)	0	42	40 (95.2)	19 (45.2)	0
≥ 65	85	67 (78.8)	24 (28.2)	0	46	43 (93.5)	23 (50.0)	0
≥ 65 and < 75	48	36 (75.0)	13 (27.1)	0	34	32 (94.1)	17 (50.0)	0
≥ 75 and < 85	35	29 (82.9)	10 (28.6)	0	10	9 (90.0)	5 (50.0)	0
≥ 85	2	2 (100)	1 (50.0)	0	2	2 (100)	1 (50.0)	0
By Sex								
Male	94	74 (78.7)	21 (22.3)	0	43	42 (97.7)	19 (44.2)	0
Female	106	86 (81.1)	25 (23.6)	0	45	41 (91.1)	23 (51.1)	0
By Race								
White	175	140 (80.0)	42 (24.0)	0	77	72 (93.5)	35 (45.5)	0
Black or African American	1	0	0	0	2	2 (100.0)	1 (50.0)	0
Asian	19	16 (84.2)	3 (15.8)	0	8	8 (100.0)	6 (75.0)	0
Other	5	4 (80.0)	1 (20.0)	0	1	1 (100.0)	0	0
By Region								
US/Canada/Europe	131	105 (80.2)	31 (23.7)	0	65	60 (92.3)	24 (36.9)	0
Asia	19	16 (84.2)	3 (15.8)	0	7	7 (100.0)	5 (71.4)	0
Rest of World	50	39 (78.0)	12 (24.0)	0	16	16 (100.0)	13 (81.3)	0

MedDRA version 26.1; CTC 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.

Table 46 Summary of On-treatment Adverse Events by Age Group All First Line Nivolumab and Ipilimumab Treated Subjects and Chemotherapy Treated Subjects in CA209HW

Treatment Group: Nivo + Ipi: 1L N = 200

MedDRA Terms (%)	Age Group (Years) < 18 N = 0	>=18 and <65 N = 115	>=65 and <75 N = 48	>=75 and <85 N = 35	>= 85 N = 2	Total N = 200
TOTAL SUBJECTS WITH AN EVENT	0	113 (98.3)	47 (97.9)	35 (100.0)	2 (100.0)	197 (98.5)
SERIOUS AE - TOTAL	0	49 (42.6)	22 (45.8)	19 (54.3)	1 (50.0)	91 (45.5)
FATAL (DEATH)	0	5 (4.3)	4 (8.3)	3 (8.6)	0	12 (6.0)
HOSPITALIZATION/PROLONGATION	0	44 (38.3)	21 (43.8)	18 (51.4)	1 (50.0)	84 (42.0)
LIFE THREATENING	0	2 (1.7)	4 (8.3)	2 (5.7)	0	8 (4.0)
CANCER	0	13 (11.3)	2 (4.2)	2 (5.7)	1 (50.0)	18 (9.0)
DISABILITY/INCAPACITY	0	0	2 (4.2)	0	0	2 (1.0)
IMPORTANT MEDICAL EVENT	0	13 (11.3)	4 (8.3)	3 (8.6)	0	20 (10.0)
AE LEADING TO DISCONTINUATION	0	18 (15.7)	13 (27.1)	8 (22.9)	1 (50.0)	40 (20.0)
PSYCHIATRIC DISORDERS	0	18 (15.7)	4 (8.3)	4 (11.4)	0	26 (13.0)
NERVOUS SYSTEM DISORDERS	0	28 (24.3)	10 (20.8)	17 (48.6)	1 (50.0)	56 (28.0)
ACCIDENT AND INJURIES	0	3 (2.6)	1 (2.1)	4 (11.4)	1 (50.0)	9 (4.5)
CARDIAC DISORDERS	0	6 (5.2)	2 (4.2)	4 (11.4)	0	12 (6.0)
VASCULAR DISORDERS	0	18 (15.7)	4 (8.3)	7 (20.0)	1 (50.0)	30 (15.0)
CEREBROVASCULAR DISORDERS	0	1 (0.9)	0	1 (2.9)	0	2 (1.0)
INFECTIONS AND INFESTATIONS	0	59 (51.3)	25 (52.1)	14 (40.0)	2 (100.0)	100 (50.0)
ANTICHOLINERGIC SYNDROME	0	28 (24.3)	11 (22.9)	11 (31.4)	2 (100.0)	52 (26.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	0	8 (7.0)	4 (8.3)	7 (20.0)	1 (50.0)	20 (10.0)

MedDRA Version: 26.1; CTC Version: 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.
For CA209-8HW, only first line subjects are included.
Excludes data collected on or after first crossover dose date.
CA209-8HW DBL: November 2023

Treatment Group: Chemo: 1L N = 88

MedDRA Terms (%)	Age Group (Years) < 18 N = 0	>=18 and <65 N = 42	>=65 and <75 N = 34	>=75 and <85 N = 10	>= 85 N = 2	Total N = 88
TOTAL SUBJECTS WITH AN EVENT	0	41 (97.6)	33 (97.1)	10 (100.0)	2 (100.0)	86 (97.7)
SERIOUS AE - TOTAL	0	22 (52.4)	18 (52.9)	4 (40.0)	1 (50.0)	45 (51.1)
FATAL (DEATH)	0	2 (4.8)	0	0	0	2 (2.3)
HOSPITALIZATION/PROLONGATION	0	20 (47.6)	16 (47.1)	3 (30.0)	1 (50.0)	40 (45.5)
LIFE THREATENING	0	1 (2.4)	3 (8.8)	1 (10.0)	0	5 (5.7)
CANCER	0	5 (11.9)	2 (5.9)	0	0	7 (8.0)
DISABILITY/INCAPACITY	0	0	1 (2.9)	0	0	1 (1.1)
IMPORTANT MEDICAL EVENT	0	4 (9.5)	3 (8.8)	2 (20.0)	0	9 (10.2)
AE LEADING TO DISCONTINUATION	0	15 (35.7)	16 (47.1)	3 (30.0)	1 (50.0)	35 (39.8)
PSYCHIATRIC DISORDERS	0	6 (14.3)	6 (17.6)	0	0	12 (13.6)
NERVOUS SYSTEM DISORDERS	0	26 (61.9)	10 (29.4)	7 (70.0)	2 (100.0)	45 (51.1)
ACCIDENT AND INJURIES	0	0	1 (2.9)	1 (10.0)	1 (50.0)	3 (3.4)
CARDIAC DISORDERS	0	2 (4.8)	2 (5.9)	1 (10.0)	0	5 (5.7)
VASCULAR DISORDERS	0	6 (14.3)	6 (17.6)	4 (40.0)	1 (50.0)	17 (19.3)
CEREBROVASCULAR DISORDERS	0	1 (2.4)	1 (2.9)	0	0	2 (2.3)
INFECTIONS AND INFESTATIONS	0	16 (38.1)	10 (29.4)	6 (60.0)	1 (50.0)	33 (37.5)
ANTICHOLINERGIC SYNDROME	0	9 (21.4)	8 (23.5)	3 (30.0)	0	20 (22.7)
QUALITY OF LIFE DECREASED	0	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	0	0	1 (2.9)	3 (30.0)	1 (50.0)	5 (5.7)

MedDRA Version: 26.1; CTC Version: 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.
For CA2098HW, only first line subjects are included.
Excludes data collected on or after first crossover dose date.
CA2098HW DBL: November 2023

Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab or ipilimumab. This is reflected in the approved SmPC in section 4.5, no new information has been submitted.

Discontinuation due to adverse events

In 1L treated patients, 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 in the chemo arm (all causality: 20.0% vs 39.8%; drug-related: 16.5% vs 31.8%) (Table 47). Grade 3-4 AEs leading to discontinuation of study drug (all causality and drug-related) were reported in a similar proportion of patients in both arms.

AEs leading to discontinuation related to COVID-19 infection were reported in 0.5% of patients in the nivo+ipi arm and no patients in the chemo arm.

Table 47 Adverse Events Leading to Discontinuation by Worst CTC Grade Reported in ≥1% of Subjects - All 1L Treated Subjects in the Nivo+Ipi and Chemo Arms

System Organ Class (%) Preferred Term (%)	Arm B: Nivo + Ipi N = 200			Arm C: Chemo N = 88		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	40 (20.0)	29 (14.5)	0	35 (39.8)	13 (14.8)	0
Gastrointestinal disorders	9 (4.5)	8 (4.0)	0	6 (6.8)	2 (2.3)	0
Immune-mediated enterocolitis	4 (2.0)	4 (2.0)	0	0	0	0
Diarrhoea	1 (0.5)	1 (0.5)	0	2 (2.3)	0	0
Abdominal pain	0	0	0	2 (2.3)	0	0
Colitis	0	0	0	1 (1.1)	1 (1.1)	0
Ileus	0	0	0	1 (1.1)	1 (1.1)	0
Intestinal haemorrhage	0	0	0	1 (1.1)	0	0
Endocrine disorders	6 (3.0)	4 (2.0)	0	0	0	0
Adrenal insufficiency	5 (2.5)	3 (1.5)	0	0	0	0
Hepatobiliary disorders	4 (2.0)	4 (2.0)	0	1 (1.1)	1 (1.1)	0
Hepatitis	2 (1.0)	2 (1.0)	0	0	0	0
Biliary obstruction	0	0	0	1 (1.1)	1 (1.1)	0
Infections and infestations	4 (2.0)	4 (2.0)	0	2 (2.3)	1 (1.1)	0
Anal abscess	0	0	0	1 (1.1)	0	0
Pneumonia	0	0	0	1 (1.1)	1 (1.1)	0
Investigations	3 (1.5)	2 (1.0)	0	2 (2.3)	0	0
Neutrophil count decreased	0	0	0	2 (2.3)	0	0
White blood cell count decreased	0	0	0	2 (2.3)	0	0
Respiratory, thoracic and mediastinal disorders	3 (1.5)	3 (1.5)	0	2 (2.3)	1 (1.1)	0
Pneumonitis	2 (1.0)	2 (1.0)	0	0	0	0
Pulmonary embolism	0	0	0	2 (2.3)	1 (1.1)	0
Cardiac disorders	2 (1.0)	2 (1.0)	0	1 (1.1)	1 (1.1)	0
Cardiac failure	0	0	0	1 (1.1)	1 (1.1)	0
Nervous system disorders	2 (1.0)	1 (0.5)	0	12 (13.6)	1 (1.1)	0
Lethargy	0	0	0	1 (1.1)	0	0
Neuropathy peripheral	0	0	0	4 (4.5)	1 (1.1)	0
Neurotoxicity	0	0	0	4 (4.5)	0	0
Peripheral sensory neuropathy	0	0	0	3 (3.4)	0	0
Renal and urinary disorders	2 (1.0)	1 (0.5)	0	2 (2.3)	1 (1.1)	0
Acute kidney injury	0	0	0	1 (1.1)	0	0
Proteinuria	0	0	0	1 (1.1)	1 (1.1)	0
Skin and subcutaneous tissue disorders	2 (1.0)	1 (0.5)	0	1 (1.1)	0	0
Rash	2 (1.0)	1 (0.5)	0	0	0	0
Skin exfoliation	0	0	0	1 (1.1)	0	0
Blood and lymphatic system disorders	1 (0.5)	1 (0.5)	0	4 (4.5)	1 (1.1)	0
Febrile neutropenia	0	0	0	1 (1.1)	1 (1.1)	0
Neutropenia	0	0	0	2 (2.3)	0	0
Thrombocytopenia	0	0	0	1 (1.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	0	0	3 (3.4)	1 (1.1)	0
Breast cancer	0	0	0	1 (1.1)	0	0
Colon neoplasm	0	0	0	2 (2.3)	1 (1.1)	0
General disorders and administration site conditions	0	0	0	4 (4.5)	0	0
Asthenia	0	0	0	2 (2.3)	0	0
Non-cardiac chest pain	0	0	0	2 (2.3)	0	0
Immune system disorders	0	0	0	1 (1.1)	1 (1.1)	0
Anaphylactic shock	0	0	0	1 (1.1)	1 (1.1)	0
Injury, poisoning and procedural complications	0	0	0	1 (1.1)	1 (1.1)	0
Infusion related reaction	0	0	0	1 (1.1)	1 (1.1)	0
Metabolism and nutrition disorders	0	0	0	2 (2.3)	0	0
Decreased appetite	0	0	0	2 (2.3)	0	0
Malnutrition	0	0	0	1 (1.1)	0	0
Reproductive system and breast disorders	0	0	0	1 (1.1)	0	0
Ovarian haemorrhage	0	0	0	1 (1.1)	0	0
Vascular disorders	0	0	0	1 (1.1)	1 (1.1)	0
Hypertension	0	0	0	1 (1.1)	1 (1.1)	0

MedDRA version 26.1; CTC version 5.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Excludes data collected on or after first crossover dose date.

Adverse Events Leading to Dose Delay or Reduction

In 1L treated patients, AEs (all causality) leading to a dose delay or reduction were reported in 98 (49.0%) patients in the nivo+ipi arm and 60 (68.2%) patients in the chemo arm.

The most frequently reported AEs (all causality) leading to a dose delay or reduction were for nivo+ipi COVID-19 (8.0%), diarrhoea (6.0%), and ALT increased and AST increased (4.0% each)

For chemo, the most frequently reported AEs leading to a dose delay or reduction were, neutropenia (15.9%), asthenia (12.5%), diarrhoea (11.4%), and neutrophil count decreased (10.2%); note that COVID-19 was reported in 3.4% of patients.

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

For nivo+ipi, the most frequently reported drug-related AEs leading to a dose delay or reduction were diarrhoea (4.0%), and adrenal insufficiency, ALT increased, and AST increased (3.0% each).

For nivo+ipi, the most frequently reported drug-related AEs leading to a dose delay or reduction were neutropenia (14.8%), asthenia (11.4%), and diarrhoea and neutrophil count decreased (10.2% each).

Immunogenicity

Effect of Immunogenicity on Safety

Of the 1L treated patients in the nivo+ipi arm who were evaluable for ADA, hypersensitivity/infusion reaction AEs were reported in a similar proportion of nivo ADA-negative patients (5.9%) and nivo ADA-positive patients (4.0%) and in a comparable proportion of ipi ADA-negative patients (5.7%) and ipi ADA-positive patients (7.1%) (Table 48).

Table 48 Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All 1L Nivo+Ipi-Treated Subjects

	Arm B: Nivo + Ipi			
	Nivolumab		Ipilimumab	
Preferred Term (%)	ADA Positive N = 25	ADA Negative N = 152	ADA Positive N = 14	ADA Negative N = 159
TOTAL SUBJECTS WITH AN EVENT	1 (4.0)	9 (5.9)	1 (7.1)	9 (5.7)
Bronchospasm	0	1 (0.7)	0	1 (0.6)
Hypersensitivity	1 (4.0)	3 (2.0)	0	4 (2.5)
Infusion related reaction	0	6 (3.9)	1 (7.1)	5 (3.1)

MedDRA Version: 26.1; CTC Version 5.0

Includes events between first dose and within the last dose of therapy + 100 days.

Subjects who received nivo and ipi in the Crossover period are not included.

Adverse drug reactions in the SmPC

In line with "A guideline on summary of product characteristics (SmPC), September 2009" and the EMA guideline on the evaluation of anticancer medicinal products in man [EMA/CHMP/205/95 Rev.6], the following methodology was used to generate the adverse reactions with nivo + ipi for Section 4.8 of the OPDIVO SmPC and Section 4.8 of the YERVOY SmPC.

- Integrate all-causality AEs data from CA2098HW (MSI-H/dMMR mCRC) and the completed studies across multiple indications.
- Programmatically remap MedDRA PTs representing the same or similar clinical conditions for the integrated AE data and generate summary tables.

- Identify clinically relevant events based on applicants medical review of the all-causality re-mapped AE summary table.
- Present resulting clinically relevant re-mapped events by SOC and all-causality frequency grouping (ie, common, uncommon, rare, or very rare).
- To calculate the frequencies of laboratory ADR, the applicant used the laboratory abnormality change from baseline tables.

Post marketing experience

Based on pharmacovigilance activities, post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab and ipilimumab.

2.5.1. Discussion on clinical safety

Nivolumab in combination with ipilimumab is already approved for the treatment of patients with dMMR or MSI-H mCRC after prior fluoropyrimidine-based combination therapy (EMEA/H/C/xxxx/WS/1840, 24 Jun 2021).

The safety data in the current report focused on the use of nivo+ipi for 1L treatment of patients with unresectable or metastatic dMMR or MSI-H colorectal carcinoma. Main safety results were obtained from the pivotal study CA2098HW. The currently submitted safety data includes 200 patients treated with nivo+ipi and 88 patients treated with chemo. The safety data for the chemo arm excludes data after the first crossover dose, except for the death summaries. Results for patients treated with nivolumab alone are not yet available.

In 1L treated patients, the median duration of therapy was longer in the nivo+ipi arm than the chemo arm: 13.52 (nivo: 13.52 months; ipi: 2.10 months) vs 3.96 months. Approximately twice as many 1L treated patients in the nivo+ipi arm vs the chemo arm received study drug for > 6 months: 68.5% vs 36.4%.

Almost all patients reported at least one adverse event (98.5% and 97.7% for respectively patients treated with nivo+ipi and chemotherapy). Grade 3-4 AEs were reported in a lower proportion of patients in the nivo+ipi arm compared with the chemo arm (48.0% vs 67.0%).

For nivo+ipi, the most frequently reported (≥15%) AEs (all grades, PTs) were diarrhoea (33.5%), pruritus (27.0%), and asthenia (22.0%), nausea (20.0%), fatigue (19.0%), abdominal pain (17.0%), and hypothyroidism (16.0%). The most frequently reported Grade 3-4 AEs (PTs) were abdominal pain (3.5%), anaemia (3.5%), and lipase increased and adrenal insufficiency (3.0% each).

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 patients.

The safety profile of nivolumab + ipilimumab is characterised by immune-related adverse events (IMAEs). IMAE analyses included events, all causality, reported within 100 days of the last dose (i.e., with extended follow-up). The most commonly reported select IMAEs were skin events (42%), gastrointestinal (35.5%), endocrine (34.0%) and hepatic events (28.0%). Most of these events were considered drug-related (34.5%, 23.0%, 33.5%, and 19.5%, respectively).

In 1L treated patients, the most frequently reported IMAEs (any grade, by category) were for nivo+ipi; hypothyroidism/thyroiditis (17.0%), adrenal insufficiency (10.5%) and hyperthyroidism (9.0%).

Across IMAE categories, all events in the nivo+ipi arm were manageable using the established IMAE treatment algorithms, with resolution reported when Immune-Modulating Medications (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the

continuing need for hormone replacement therapy.

Grade 3-4 SAEs were reported in a lower proportion of patients in the nivo+ipi arm compared with the chemo arm (34.5% vs 42.0%).

All causality and drug-related SAEs and AEs in the subset of 1L treated patients with centrally confirmed MSI-H/dMMR mCRC (n=170 for the nivo+ipi arm and n=75 for the chemo arm) were consistent with those for all 1L treated .

For 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%).

As of the DCO 12 Oct 2023, a lower proportion of 1L treated patients in the nivo+ipi arm died (any time after randomization up to the clinical DCO: 12 Oct 2023) compared with the chemo arm: 22.0% vs 42.0%. Two (1.0%) patients (1 due to myocarditis and 1 due to pneumonitis) in the nivo+ipi arm and 1 (1.1%) patient (due to acute myocarditis) in the chemo arm died due to study drug toxicity (per the investigator). The lower percentage of total deaths and patients who died due to disease progression in the nivo+ipi arm in comparison to the chemo arm, does currently not raise concerns of an overall detrimental effect of nivo+ipi treatment on OS in comparison to chemotherapy.

In 1L treated patients, 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 in 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 patients in both arms.

For nivo+ipi, the most frequently reported all causality and drug-related AEs leading to discontinuation were adrenal insufficiency (2.5%) and immune mediated enterocolitis (2.0%).

Pooled safety data, in which safety data obtained in different studies are combined, was compared to the safety data obtained in the current study. Incidence of immune-mediated enterocolitis including grade 3-4 events, is higher for the study CA2098HW than in the pooled safety database (2.5% vs 0.3% and 2.5% vs 0.2% for respectively any immune related enterocolitis and grade 3-4 events). Also for blood bilirubin increase (7.0% vs 2.2% and 1.5% vs 0.2% for respectively any blood bilirubin increase and grade 3-4 events), gamma-glutamyltransferase increased (4.5% vs 2.2% and 1.5% vs 1.0% for respectively any gamma-glutamyltransferase increase and grade 3-4 events), hepatotoxicity (2.5% vs 1.2% and 0% vs 0.7% for respectively any hepatotoxicity and grade 3-4 events), adrenal insufficiency (10% vs 4.5% and 3% vs 1.6% for respectively any adrenal insufficiency and grade 3-4 events) higher incidences were seen in the current study for recurrent or mCRC with MSI-H or dMMR than in the pooled safety data. However, these increased incidences are not considered concerning, incidences were mostly (except for adrenal insufficiency) under 5% and absolute numbers of patients with one of these events were limited. Overall, the safety profile of nivolumab + ipilimumab in1L treatment of patients with dMMR or MSI-H mCRC appears consistent with the already known safety profile of each mono-component and with the known safety profile of the combination.

Safety data per age group does not show concerning differences between age groups. More patients older than 65 years of age had an AE leading to discontinuation, this is not unexpected and accounts both for patients treated with nivolumab and ipilimumab and for patients treated with chemotherapy. Further, in the nivo+ipi study arm, the percentage fatal events was higher in patients above the age of 65 years than in patients below the age of 65 years. In the chemotherapy arm no fatal events were seen in the group of patients older than 65 years of age. The number of patients per age group is limited, so no robust conclusions can be drawn regarding differences in risk of death due to a drug related AE, per age

group. The AEs in study CA2098HW and in pooled safety database show for the age group below 65 years and the age group between 65-75 years, in general comparable data as the table with AEs for the all treated patients in study CA2098HW with the pooled safety data of patients treated with nivo+ipi. Only limited number of elderly (above the age of 75 years) are included in the current study, which hampers a proper characterisation of the safety profile in this patient population.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of nivolumab + ipilimumab in 1L treatment of patients with dMMR or MSI-H mCRC appears consistent with the already known safety profile of each mono-component and with the known safety profile of the combination. No new safety signals were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP for nivolumab (version 37.3) and an updated RMP for ipilimumab (version 41.3) with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the RMP version 37.3 for nivolumab and RMP version 41.3 for ipilimumab are acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to the separate attachments which include all proposed changes to the Product Information with comments from the Rapporteur.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The readability of the PL of Opdivo (nivolumab)/YERVOY (ipilimumab), in English, was assessed during the assessment of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline titled: *A guideline on the readability of the label and package leaflet of medicinal products for human use, Revision 1, 12 January 2009*.
    - For Opdivo: the final report was then submitted to the EMA on 02 September 2014 as part of the initial MAA dossier (EMEA/H/C/3985, MAA approved on 19 June 2015).
    - For Yervoy: the final report was then submitted to the EMA in January 2011 (Response to the List of Questions, original MAA) as per EMA operational procedure guidance

(EMEA/277378/2005). YERVOY (ipilimumab) was approved on 13 July 2011.

- The new indication in adults that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications (i.e., key safety messages for the existing and new applied for indication are essentially the same).
- Administration of Opdivo (nivolumab) and YERVOY (ipilimumab) is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL were also successfully tested as part of the user consultation performed for the initial MAA and remain unchanged.
- The general design and layout of the proposed PL have not changed compared to the tested one.
- Overall, the proposed leaflet shares large text sections with the reference one. The modifications now proposed in the PL (i.e., those relevant to the new indication) do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is "*Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adults with unresectable or metastatic mismatch repair deficient or microsatellite instability-high colorectal cancer.*"

CRC is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease. MSI-H/dMMR colorectal tumours are identified in approximately 15% of CRC patients. Among patients with mCRC, those with MSI-H/dMMR tumours comprise approximately 4-7%. MSI-H/dMMR is a form of genetic instability due to a dysfunction of a DNA repair system (mismatch repair proteins), which causes an accumulation of repetitive DNA units called microsatellites. Molecular diagnosis can be performed either with IHC (analysing MMR proteins) or PCR (evaluating panels of microsatellites). MSI CRC can be hereditary (Lynch syndrome) or sporadic, leading to heterogeneity of this disease. Patients with Lynch-like mCRC are associated with younger age, higher frequency of liver metastasis, more frequent resection of metastatic disease, thus more favourable prognosis compared to those with sporadic dMMR or MSI-H mCRC. In general, MSI-H/dMMR cancer can be associated with a favourable prognosis in early-stage disease. MSI-H/dMMR in stage IV CRC seems to be associated with a worse prognosis (or unclear association with prognosis).

3.1.2. Available therapies and unmet medical need

Combination chemotherapy in the form of FOLFOX (oxaliplatin, 5-FU, and leucovorin/folinic acid) or FOLFIRI (irinotecan, 5-FU, and leucovorin/folinic acid) has been established as first-line SOC chemotherapy options for metastatic CRC and may be used interchangeably depending on the physician's recommendation and regional preference. The median TTP (7 vs 7 months, respectively) and median OS (15 vs 14 months, respectively) were comparable between the 2 regimens. Targeted treatments such as bevacizumab (EMEA/H/C/000582/II/0014, 25/01/2008) and cetuximab (EMEA/H/C/000558, 29/06/2004) are approved in the EU for use in combination with chemotherapy as first-line treatment in CRC resulting in PFS ranging from 7.2 to 10.6 months and median OS ranging from 18.3 to 28.7 months. Following recent approval of pembrolizumab in the EU for the first-line treatment of metastatic MSI-H or dMMR CRC in adults (EMEA/H/C/003820/II/0091, 21/01/2021), the ESMO guidelines have been updated to

recommend pembrolizumab as 1L therapy for MSI-H/dMMR mCRC. Median PFS was 16.5 months (95% CI: 5.4, 32.4) with pembrolizumab versus 8.2 months (95% CI: 6.1, 10.2) with chemo (HR 0.60, 95% CI: 0.45, 0.80) in the pivotal KEYNOTE-177 study. The study showed a trend for 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).

There is still an unmet medical need, as more than half of the patients do not respond to pembrolizumab and 52% progress or die within 2 years. High rates of primary disease progression with pembrolizumab compared with chemo manifested as early detriment on PFS and OS curves, highlighting the remaining unmet need. Several factors such as presence of RAS-mutations, high tumour burden, or liver/lung metastases were associated with a lesser PFS benefit with IO monotherapy across multiple studies.

3.1.3. Main clinical studies

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) in patients with histologically confirmed recurrent or metastatic CRC with known tumour MSI-H or dMMR status (local testing). dMMR/MSI-H status was to be confirmed retrospectively by central testing. Patients across all lines of treatment could be enrolled in the first part of the study, the second part of the study enrolled only 1L patients. Eligible 1L patients were randomized to Arm A (nivo), Arm B (nivo+ipi), or Arm C (chemo) in a 2:2:1, stratified by tumour location (right vs left). The primary objective for the 1L setting was PFS by BICR per RECIST 1.1 for nivo+ipi vs SOC. The other dual primary endpoint was PFS for nivo+ipi vs nivo in all randomized patients. The primary analysis population consisted of patients with centrally confirmed MSI-H/dMMR mCRC. Secondary endpoints included ORR and OS.

A total of 303 participants were randomized in a 2:1 ratio to receive nivo+ipi (n=202/n=171 centrally confirmed MSI-H/dMMR) or investigator's choice of SOC (6 regimens allowed: mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab) (n=101/n=84 centrally confirmed MSI-H/dMMR). The MAH submitted results of the preplanned IA of the primary endpoint of PFS per BICR for nivo+ipi vs chemo in 1L randomized patients with centrally confirmed MSI H/dMMR mCRC. Median follow-up was 31.57 months (range: 6.1-48.4). At the time of this planned IA (DCO: 12 Oct 2023), however, the results for OS (along with the other secondary endpoints) were not tested, because its precedent endpoints per the testing hierarchy pre-defined in the SAP have not been tested yet.

3.2. Favourable effects

- Statistically significant and clinically relevant PFS benefit of nivo+ipi vs SOC in 1L randomized patients with centrally confirmed MSI H/dMMR mCRC: HR 0.21 (95%CI 0.14, 0.32), p<0.0001, median PFS NR (95%CI 38.44, NA) vs 5.85 (95%CI 4.37, 7.79) months. Kaplan-Meier PFS curves demonstrate an increasingly pronounced separation from month 3 onwards (PFS rate at 6 months 82.08% vs 48.18%, PFS rate at 12 months 78.69% vs 20.62%). PFS results were consistent across supportive analyses.
- Supported by PFS per investigator and in all randomized patients.
- PFS benefit was seen among all subgroups, including patients with Lynch syndrome, hepatic or pulmonary metastases, and patients with BRAF or KRAS/NRAS mutations. Further, a benefit was observed independent of tumour PD-L1 expression.
- PFS2 favours nivo+ipi over SOC; mPFS NR (NA, NA) vs 29.90 (14.78, NA) months (HR 0.27; 95%CI: 0.17, 0.44).

3.3. Uncertainties and limitations about favourable effects

- OS data are currently not available due to the testing hierarchy in the SAP. The MAH will submit the results of the IA of OS data by Q4 2025 **(REC).** Sensitivity analysis to address the impact of crossover on OS will be performed at the time of IA OS.
- The exact contribution of ipilimumab is unknown. The MAH will submit the results of the nivo+ipi vs nivolumab monotherapy in 1L setting from study CA2098HW post-marketing by Q4 2025 **(REC).** There is some support for an added benefit of ipilimumab from the 2L setting where ORR was higher in the nivo+ipi cohort vs the nivo cohort (62.2% vs 37.8%, non-randomized comparison).

3.4. Unfavourable effects

The pooled safety dataset of nivolumab in combination with ipilimumab (regardless of posology and with or without chemotherapy) includes 2294 patients across several tumour types with minimum follow-up ranging from 6 to 47 months. The main safety dataset for the target population is based on the all randomized population in which 200 patients received nivo+ipi at the proposed dose. Median treatment duration was 13.52 months (range: 0-32.3 months) for nivolumab and 2.10 months for ipilimumab (range: 0-3.7 months).

Almost all patients reported at least one AE (98.5%). The most frequently reported (≥15%) AEs were diarrhoea (33.5%), pruritus (27.0%), asthenia (22.0%), nausea (20.0%), fatigue (19.0%), abdominal pain (17.0%), and hypothyroidism (16.0%). AEs of Grade 3-4 were reported in 48.0% of patients, the most frequently reported Grade ≥3 AEs were abdominal pain and anaemia (3.5% each), and lipase increased and adrenal insufficiency (3.0% each). Most AEs were considered treatment-related and known for nivo+ipi combination treatment. No new safety signals were identified.

Select immune-mediated AEs (IMAE) in patients treated with nivo+ipi include endocrine, gastrointestinal, hepatic, pulmonary, renal, skin events and hypersensitivity/infusion reactions. The most commonly reported select AEs were skin events (42%), gastrointestinal (35.5%), endocrine (34.0%) and hepatic events (28.0%). Most of these events were considered drug-related. The most frequent drug-related select AEs were pruritus (22.5%), diarrhoea (21.0%), and hypothyroidism (16.0%). Most of events were Grade 1 or 2, the frequency of Grade 3-4 drug-related select AE in each category was ≤5.5%. No AEs of Grade 5 were reported.

There were 7 (3.5%) patients that reported 11 events of other events of special interest (OESI), including encephalitis (3 patients), myocarditis (3 patients), myositis (2 patients), and pancreatitis (2 patients).

Serious adverse events (SAEs) were reported by 45.5% of patients, 19.0% patients reported a drug-related SAE. Most frequently reported SAEs by PT were adrenal insufficiency (4.0%), abdominal pain and immune-mediated enterocolitis (2.5% each).

There were two patients (1.0%) in the nivo+ipi arm for which the primary cause of death was study drug toxicity (n=1 myocarditis and n=1 pneumonitis). One patient (1.1%) died in the chemo arm during the cross-over period and the event of acute myocarditis was considered related to nivo+ipi.

Treatment discontinuation due to AEs occurred in 20.0% of patients (16.5% drug-related), most frequently due to adrenal insufficiency (2.5%) and immune mediated enterocolitis (2.0%).

The tolerability of nivo+ipi was overall improved compared to the SOC with lower frequencies of Grade ≥3 events (48.0% vs. 67.0%) and discontinuation due to AEs (20.0% vs. 39.8%), while the frequency of SAEs was comparable (45.5% vs. 51.1%). The safety profile is clinically different from SOC with fewer haematological toxicities, especially neutropenia.

3.5. Uncertainties and limitations about unfavourable effects

- Safety data of the combination of nivolumab + ipilimumab in the applied indication is limited in elderly patients (≥75 years), which hampers a proper characterisation of the safety profile in this patient population.

3.6. Effects Table

Effects Table for nivo+ipi in first line metastatic MSI-H/dMMR mCRC (DCO: 12 Oct 2023)

Effect	Short description	Unit	Treatment Nivo+Ipi	Control SOC	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS (by BICR per RECIST 1.1)	Time from randomization to first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first	Months (95% CI)	NR (38.44, NA)	5.85 (4.37, 7.79)	HR: 0.21; 95% CI: 0.14,0.32) Final analysis Supported by sensitivity analyses Consistent subgroups High censoring rate (71.9%)/ large range follow-up (6.1-48.4 months) Implausibility of the proportional hazards assumption	
PFS2	Time from randomization to disease progression on the next line of therapy, or death from any cause, whichever occurs first	Months (95% CI)	NR (NA, NA)	29.90 (14.78, NA)	Exploratory analysis	
Unfavourable Effects						
Grade 3-4 AEs		%	48.0	67.0	Improved safety profile based on Grade⩾3 AEs and AEs leading to discontinuation. clinically different from SOC. Safety profile appears in general consistent with the pooled safety dataset, except for a higher incidence of abdominal pain and adrenal insufficiency. No new safety concerns identified.	
SAEs		%	45.5	51.1		
AEs leading to discontinuations		%	20.0	39.8		
Selected/IMAEs	Hypothyroidism/ Thyroiditis	%	17.0	1.1		
	Adrenal insufficiency	%	10.5	0		
	Hyperthyroidism	%	9.0	1.1		
	Diarrhoea/Colitis	%	6.5	1.1		

Abbreviations: PFS: Progression free survival; BICR: Blinded central imaging review; RECIST: Response Evaluation Criteria in Solid Tumours; CI: Confidence interval; NR: Not reached; NA: Not applicable; AE: Adverse event; SAE: Serious adverse event; IMAEs: Immune-mediated adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study CA2098HW demonstrated a statistically significant and clinically meaningful PFS benefit of nivo+ipi over SOC in patients with MSI-H/ dMMR mCRC. The KM-curves start to separate from 3 months onwards and the median PFS was not reached in the nivo+ipi arm at the time of DCO. The difference in KM-curves and the PFS benefit are considered compelling. Given the high censoring rate in the nivo+ipi arm, an efficacy update is expected and it is acceptable to obtain the results post-approval. It needs to be seen whether a plateau can be reached. The lack of OS data is an uncertainty in the current assessment. However, OS data is likely confounded and less informative, due to subsequent IO therapies and crossover. Nevertheless, given the compelling PFS benefit observed and provided that the apparent substantially prolonged effect is maintained based on a longer follow-up, a detrimental effect on OS is highly unlikely and PFS can be viewed as a benefit on its own. Long-term benefit is further supported by PFS2 and results suggest that the PFS of nivo+ipi compares favourably to PFS2 in the SOC arm, in which a substantial percentage received IO in the second line. It is therefore acceptable to obtain OS data post-marketing. The MAH will submit the results of the IA of OS data by Q4 2025 (**REC**). Sensitivity analysis to address the impact of crossover on OS will be performed at the time of IA OS. Another current limitation is the uncertainty on the exact contribution of ipilimumab to the combination treatment, as results on nivolumab monotherapy were not available due to the hierarchical testing strategy. However, results from the 2L setting can be considered sufficient to support an added benefit of ipilimumab and results on the nivolumab monotherapy arm can be submitted post-marketing. The MAH will submit the results of the analysis of nivo+ipi vs nivolumab monotherapy in 1L setting from the Phase III study CA2098HW by Q4 2025 (**REC**).

Safety analyses confirmed the already known safety profiles of nivolumab and ipilimumab, which compared favourably to polychemotherapy regimens. The safety profile of nivo+ipi is characterized by immune-mediated adverse events which are generally manageable. No new safety signals were identified.

3.7.2. Balance of benefits and risks

The PFS benefit of nivo+ipi as shown in study CA2098HW is considered compelling and clinically meaningful. It is acceptable to obtain and submit data on OS and nivolumab monotherapy post-approval, by Q4 2025. The observed efficacy in the first-line treatment of MSI-H/dMMR mCRC outweighs the established risks of treatment.

3.7.3. Additional considerations on the benefit-risk balance

The proposed indication concerns unresectable or metastatic MSI-H/dMMR CRC. Study CA2098HW permitted enrolment of patients with metastatic or recurrent MSI-H/dMMR CRC not amenable to surgery, with patients having local recurrence qualifying for advanced unresectable disease. However, only patients with mCRC were enrolled. The MAH justifies extrapolation to patients with unresectable MSI-H/dMMR CRC based on published data from the use of IO in the neoadjuvant setting in patients with stage II-III disease, and especially NICHE-2 showing a high rate of complete pathologic response and encouraging DFS results were reported after 2 doses of nivo and one dose of ipi followed by surgery. Further, the NCCN guidelines, while acknowledging a lack of data in this setting, recommend IO as options for treatment of unresectable advanced CRC or potentially resectable mCRC with MSI-H/dMMR tumours. The possibility to be treated with curative intent surgeries is considered clinically relevant as this can result in long term survival. Within the current metastatic setting a limited number of patients

underwent curative surgery in both arms. The KEYNOTE-177 study with pembrolizumab also enrolled stage IV disease only. Upon the request of the CHMP to justify extrapolation to unresectable MSI-H/dMMR CRC, the MAH restricted the indication to metastatic CRC without further discussion. Overall, available data in earlier setting provide additional support for efficacy of nivo+ipi in MSI-H/dMMR CRC and given the observed high efficacy in this biomarker defined population in mCRC, extrapolation to the advanced unresectable MSI-H/dMMR CRC population in need of first line systemic treatment is considered acceptable.

3.8. Conclusions

The overall B/R of nivolumab in combination with ipilimumab as first line treatment of unresectable or metastatic MSI-H/dMMR CRC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

A Worksharing application for OPDIVO and YERVOY, as follows:

Extension of indication to include OPDIVO in combination with ipilimumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 37.3 of the RMP has also been submitted.

Extension of indication to include YERVOY in combination with nivolumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.3 of the RMP has also been submitted.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.