Cancer Drugs Fund

Managed Access Agreement

Nivolumab with ipilimumab for untreated advanced renal cell carcinoma [TA581]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Nivolumab with ipilimumab for untreated advanced renal cell carcinoma [TA581]

Company name: Bristol-Myers Squibb Pharmaceuticals Ltd

Primary source of data collection: Ongoing clinical study (CheckMate 214)

Secondary source of data collection: Systemic Anti-Cancer Therapy data set (SACT)

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1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for nivolumab with ipilimumab for untreated advanced renal cell carcinoma [TA581]. A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period is anticipated to conclude by August 2021, when 6-year follow up data from the pivotal CheckMate 214 trial addresses the key uncertainty around long term survival

(see section 5.1). The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

2.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

2.3 Any changes to the terms or duration of any part of the managed access agreement must be approved by NICE and NHS England as co-signatories to the agreement.

2.4 If data collection is anticipated to conclude earlier than the timelines stated in the managed access agreement, for example due to earlier than anticipated reporting of an ongoing clinical trial:

- Where capacity allows NICE will endeavour to reschedule the CDF guidance review date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final SACT or real-world data report (for example if planned outcomes will no longer provide meaningful data).

2.5 If data collection from an ongoing clinical trial is anticipated to be delayed, please note:

- Resource/capacity issues will not be accepted as reasons for delaying the associated CDF guidance review.
- Unless a strong compelling rationale is provided, the CDF guidance review will proceed according to the original timelines outlined in the MAA.
- It may not be possible to amend the date of the final SACT or real world data report, in which case it will be available before the Clinical Study report is completed.

3 Patient eligibility

3.1 Nivolumab with ipilimumab has been recommended for use in the Cancer Drugs Fund for untreated advanced renal cell carcinoma in line with the patient eligibility criteria listed in section 3.2 below.

3.2 Key patient eligibility criteria for the use of Nivolumab in the Cancer Drugs Fund include:

- Patient has unresectable locally advanced or metastatic renal cell adenocarcinoma (RCC) which either has a clear cell component or is a papillary RCC
- No prior systemic therapy for locally advanced/metastatic RCC with the following exception of in the context of clinical trials investigating adjuvant therapies for completely resectable RCC.
- Patient has a prognosis considered either intermediate or poor-risk as per the International Metastatic RCC Database Consortium (IMDC) system, which scores 1 point for each of the following 6 factors. A score of 1-2 indicates intermediate risk and a score of 3-6 denotes poor risk. The IMDC factors are:

  i) Karnofsky performance status of less than 80%

  ii) Less than 1 year from time of initial diagnosis to now

  iii) Heamoglobin less than the lower limit of normal (LLN)

  iv) Corrected calcium concentration greater than >2.5mmol/L

  v) Absolute neutrophil count greater than the upper limit of normal (ULN)

  vi) Platelet count greater than the ULN

- Patient has a Karnofsky performance status of at least 70%.
- no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control
- patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner
- Ipilimumab will be used at the RCC ipilimumab dose of 1mg/Kg every 3 weeks for a maximum of four 3-weekly cycles
- nivolumab will be used at a dose of 3mg/Kg every 3 weeks for the first 4 cycles (ie when in combination with ipilimumab) and then as subsequent monotherapy at a fixed dose of either 240mg every 2 weeks or 480mg every 4 weeks
- a formal medical review to assess the tolerability of treatment with nivolumab and ipilimumab will be scheduled to occur by the start of the 3rd 3-weekly cycle of treatment and thereafter on a regular basis
- treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any toxicities to settle
- Nivolumab and ipilimumab are otherwise to be used as set out in their Summary of Product Characteristics

3.3 The estimate for the total number of eligible patients for untreated advanced renal cell carcinoma is approximately 1559 annually. Not all of these patients will receive nivolumab with ipilimumab. NHS England anticipates that approximately [redacted] of patients eligible for treatment will choose nivolumab with ipilimumab by year 2.

3.4 The SmPC states the recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3

weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks. The mean number of nivolumab doses received within CheckMate 214 is [redacted]. The mean number of ipilimumab doses received within CheckMate 214 is [redacted].

3.5 Nivolumab with ipilimumab reduces the risk of death for patients with untreated advanced RCC by 34% (CheckMate 214, 30 month follow up hazard ratio: 0.66, 95% CI: 0.54, 0.80). Based on log-normal and Kaplan-Meier plus exponential survival extrapolations used in committee's decision-making, the model predicts the life years gained for patients receiving nivolumab with ipilimumab are between 2 and 3 years.

4 Area(s) of clinical uncertainty

4.1 The appraisal committee highlighted the following areas of uncertainty which need to be addressed with further data collection:

- Lack of mature data from the CheckMate 214 clinical trial to demonstrate long-term benefit in overall survival.
- Treatment duration
- Subsequent therapies used in clinical practice
- The proportion of patients with poor-risk or intermediate-risk renal cell carcinoma in clinical practice who would have nivolumab and ipilimumab

5 Source(s) of data collection

CheckMate 214 clinical trial

5.1 The primary source of additional data will be CheckMate 214 which is an open-label, randomised phase III study of nivolumab with ipilimumab versus sunitinib in patients with previous untreated advanced RCC [clinicaltrials.gov: NCT02231749]. 5- and 6-year data cuts are expected to occur in August

2020 and August 2021 respectively. A brief description of the trial is provided below.

Table 1: CheckMate 214 trial description

CheckMate 214 – (Total population, n=1096; Intermediate and poor risk, n= 847)
Description: Multicentre, open-label, randomised phase III study, with nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg solutions IV Q3W for 4 doses then nivolumab 3 mg/kg solutions IV Q2W
Primary Endpoint: IRRC-assessed ORR and PFS, and OS, in intermediate-/poor-risk subjects with previously untreated advanced or metastatic RCC
Secondary Endpoints: IRRC-assessed ORR and PFS, and OS, in any-risk subjects with previously untreated RCC. Incidence of AEs in all treated subjects with previously untreated advanced or metastatic RCC
Exploratory Endpoints: Overall safety and tolerability of NIVO+IPI versus sunitinib. IRRC-assessed ORR and PFS, and OS in favourable-risk subjects with previously untreated advanced or metastatic RCC. Explore potential predictive biomarkers of clinical response by analyzing tumor specimens and blood samples for proteins and genes involved in regulating immune responses. Evaluate HRQoL as assessed by FACT-G. Assess disease related symptoms in each arm based on NCCN FKSI-19. Assess changes in global health status based on EuroQol's EQ-5D.

Abbreviations: AE: adverse event; EQ-5D: EuroQoL 5-Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-19: Functional Assessment of Cancer Therapy-Kidney Symptom Index; HRQoL: health-related quality of life; IRRC: Independent radiological review committee; IV: intravenous; NCCN; National Comprehensive Cancer Network: NIVO+IPI; nivolumab plus ipilimumab; ORR: Overall Response Rate, OS: Overall Survival, PFS: Progression free survival, Q2W: every 2 weeks, Q3W: every 3 weeks, RCC: renal cell carcinoma.

SACT

5.2 NHS England's Blueteq database captures the CDF population. NHS England shares Blueteq data with Public Health England for the CDF evaluation purposes. This sharing is governed by a data sharing agreement between NHS England and Public Health England.

5.3 Public Health England identifies, collects, collates, quality-assures and analyses large population-level datasets for specific diseases and conditions, including cancer. These datasets include the Systemic Anti-cancer Therapy (SACT) dataset, which is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England will use the routinely-captured data collected during the period of the data

collection arrangement to provide analyses as defined in sections 6.3 and 7.3

5.4 Public Health England will collect data, including via the SACT dataset, alongside the primary source of data collection (CheckMate 214).

5.5 Data will be collected on selected baseline demographic and clinical characteristics of patients via Blueteq and SACT. This will include those noted in section 3.2.

6 Outcome data

CheckMate 214 clinical trial

6.1 The key outcome to be collected is long-term overall survival. This data shall become available from the ongoing CheckMate 214 trial and will be provided to NICE when the guidance is reviewed.

6.2 The additional clinical data from CheckMate 214 will resolve clinical uncertainty by providing mature data on:

- time to treatment discontinuation
- duration of response
- number and survival profiles of durable responders
- treatment free intervals
- subsequent treatments

Other data, including SACT

6.3 Data collection via SACT will support data collected from the CheckMate 214 clinical trial. Data will be collected on the use of nivolumab with ipilimumab in clinical practice. Data will not be collected for comparators.

6.4 Data will be collected via Public Health England's routine population-wide datasets, including the SACT dataset. This collection will support data collected in the clinical trial CheckMate 214. During the managed access agreement period, Public Health England will collect data to provide information on selected baseline demographic and clinical characteristics – including prognostic score, overall survival, treatment duration, time to next treatment and the distribution of subsequent therapies given. Notification of applications via Blueteq will be made available by NHS England for the use of nivolumab with ipilimumab. Data collection will continue unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection.

7 Data analysis plan

CheckMate 214 clinical trial

7.1 The data collection would be anticipated to conclude when the 5-year or 6-year follow-up data will be available from the CheckMate 214 trial.

7.2 At the end of the data collection period, the updated data from the ongoing CheckMate 214 trial will be used to update survival extrapolations and other parameters within the cost-effectiveness model.

SACT

7.3 At the end of the data collection period Public Health England will provide a final report for NHS England based on routinely collected population-wide data, including that collected via SACT. The report will present depersonalised summary data, including collected baseline demographic and clinical characteristics, the total number of patients starting treatment and their prognostic score, overall survival, the treatment duration, time to next treatment and the distribution of subsequent therapies given. The necessary controls will be put in place to ensure that patient confidentiality is

not put at risk. The report will be shared with Bristol-Myers Squibb Pharmaceuticals Ltd in advance of the planned review of guidance.

7.4 Completeness of SACT dataset reporting will be shared with NHS England and the Bristol-Myers Squibb Pharmaceuticals Ltd at regular intervals during the data collection period. Public Health England will provide summary results for time to next treatment and distribution of subsequent therapies given to NHS England and the Bristol-Myers Squibb Pharmaceuticals Ltd on an annual basis, to check the continuing validity of the period of the data collection arrangement.

8 Ownership of the data

8.1 For all clinical CheckMate 214 trial data listed above, Bristol-Myers Squibb Pharmaceuticals Ltd will be the owner.

8.2 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data was facilitated by the Public Health England Office for Data Release. Bristol-Myers Squibb Pharmaceuticals Ltd will not have access to the Public Health England patient data, but will receive depersonalised summary data, with appropriate controls in place to cover this. Public Health England will provide a report to NHS England and the Bristol-Myers Squibb Pharmaceuticals Ltd at the end of the managed access period.

8.3 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by Public Health England, have been established with NHS Trusts and NHS England.

8.4 Blueteq's CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and generally for analysis of these data. NHS England, however, shares Blueteq data with Public Health England for CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

9 Publication

9.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results. Interim clinical trial results are anticipated to be presented in scientific conferences.

9.2 Publication of the analysis results of data collected by Public Health England, including through SACT and the data from Blueteq's CDF system, will be planned and implemented by Public Health England.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, as apply between NHS England and Bristol-Myers Squibb Pharmaceuticals Ltd, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

11.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.