Cancer Drugs Fund

Managed Access Agreement

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [TA558]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [TA558]

Company name: Bristol-Myers Squibb Pharmaceuticals Ltd

Primary source of data collection: Ongoing clinical study (CheckMate 238)

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 for adjuvant treatment of resected stage III and IV melanoma [TA558]. 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 in December 2020 when the final overall survival analysis data from the pivotal CheckMate 238 will become available with all subjects having a minimum follow up of 48 months (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 that the data collection period ends as planned in December 2020 and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

3 Patient eligibility

3.1 Nivolumab as a monotherapy has been recommended for use in the Cancer Drugs Fund for the adjuvant treatment of patients with completely resected melanoma with lymph node involvement or metastatic disease who have undergone complete resection 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 newly diagnosed melanoma that has been staged according to the AJCC 8th edition as having stage III disease or completely resected stage IV disease
- The stage III or stage IV disease has been completely resected either via sentinel lymph node biopsy ('sentinel lymphadenectomy') or when indicated via completion lymph node dissection or by resection of distant metastatic disease
- Patient is treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors
- Clinician has discussed with the patient the benefits and toxicities of adjuvant nivolumab in stage III or completely resected stage IV disease and if stage III disease, provided figures (included in Blueteq) related to the risk of disease relapse if a routine surveillance policy is followed

- Patient has an ECOG performance status of either 0 or 1
- Treatment with nivolumab will be continued for a maximum of 12 months (or a maximum of 26 cycles if given 2-weekly) from the start of treatment in the absence of disease recurrence, unacceptable toxicity or withdrawal of patient consent
- a formal medical review as to whether treatment with nivolumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment
- Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle
- Nivolumab is to be otherwise used as set out in its Summary of Product Characteristics

3.3 The estimate for the total number of eligible patients for adjuvant melanoma treatment following surgical resection is approximately 1,365 annually (Company updated Budget Impact model). Not all of these patients will receive nivolumab as adjuvant treatment. NHS England anticipates that approximately 75% of patients eligible for treatment with adjuvant therapy will choose to use a PD-L1 inhibitor.

3.4 The SmPC states nivolumab for adjuvant melanoma is administered at 3mg/kg Q2W as a 60 minute infusion for a maximum treatment duration of 1 year or until disease recurrence or the development of unacceptable toxicity. The mean number of nivolumab doses received within CheckMate 238 is [redacted]. Overall, [redacted] completed the 1 year of nivolumab adjuvant treatment according to the trial protocol.

3.5 Following surgical resection patients are at risk of relapse which is related to the stage of their disease. Nivolumab reduces the risk of relapse following surgical resection. The 24 month Relapse Free Survival (recurrence-free survival) from CheckMate 238 for nivolumab was 62.6% versus ipilimumab at 50.2% (hazard ratio: 0.66, 95% CI: 0.54, 0.81). The model

predicted the life years gained for patients receiving nivolumab as adjuvant treatment are between [redacted] and [redacted] 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 238 clinical trial to demonstrate long-term benefit in overall survival
- Subsequent treatment use in patients relapsing following adjuvant treatment with nivolumab
- Efficacy and safety outcomes for patients re-treated with anti-PD-1 agents for metastatic disease following relapse

5 Source(s) of data collection

CheckMate 238 Clinical trial

5.1 The primary source of additional data will be CheckMate 238 which is a phase III double blind RCT of nivolumab versus ipilimumab in the adjuvant setting [clinicaltrials.gov: NCT02388906].

- The final overall survival analysis will take place when all patients have a minimum follow up of 48 months.
- The final recurrence-free survival analysis will be performed when all subjects have a minimum follow up of 36 months.
- Data on subsequent treatments and outcomes for patients re-treated with nivolumab in the metastatic setting following relapse will be made available when the final overall survival analysis is conducted.

Table 1 CheckMate 238 trial description

CheckMate 238 – Phase III (total n=906; nivolumab n = 453, ipilimumab n= 453)

Description: Randomized, double-blind, phase 3 trial of nivolumab vs ipilimumab for the treatment for resected stage IIIB, IIIC or IV with no evidence of disease (NED) melanoma. Randomization was stratified according to disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c using AJCC 7th edition) and by PD-L1 status at 5% cut-off.
Primary Endpoint: *RFS*
Secondary Endpoints: *OS, Safety*
Exploratory Endpoints: *DMFS, RFS per PD-L1 expression, PROs*
Abbreviations: RFS = recurrence free survival, OS = overall survival, DMFS = distant metastases free survival, PROs = patient reported outcomes, PD-L1 = programmed death ligand 1

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. That 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 238).

5.5 Data will be collected on selected baseline demographic and clinical characteristics of patients via Blueteq and SACT. This will include the performance status of patients, BRAF mutation status, and the proportions of patients with Stage IIIA, Stage IIIB, Stage IIIC, Stage IIID and stage IV disease (according to the AJCC 8th edition) who receive nivolumab in the Cancer Drugs Fund.

6 Outcome data

CheckMate 238 Clinical trial

6.1 The key outcome to be collected is long-term overall survival following adjuvant therapy and subsequent treatments for patients relapsing with metastatic disease. This data shall become available from the ongoing CheckMate 238 trial and will be provided to NICE when the guidance is reviewed.

The additional clinical data from CheckMate 238 will resolve clinical uncertainty by offering mature recurrence-free survival and overall survival data which can be used at a later NICE HTA re-submission. It will also offer more data on subsequent treatments received from patients experiencing relapse which was an area on uncertainty. CheckMate 238 will also provide metastatic treatment outcomes for adjuvant nivolumab treated patients re-treated with anti-PD-1 for metastatic disease following relapse.

Other data, including SACT

6.2 Data collection via SACT will support data collected from the CheckMate 238 clinical trial. Data will be collected on the use of adjuvant nivolumab in clinical practice. Data will not be collected for comparators. .

6.3 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 238. During the managed access agreement period, Public Health England will collect data to provide information on selected baseline demographic and clinical characteristics, 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 adjuvant nivolumab, and for any subsequent stage IV therapies. 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 238 Clinical trial

7.1 The final analysis will follow the analysis plan outlined in the trial protocol for CheckMate 238. The timeframe of data collection is driven by the minimum follow up time required by all patients specified within the statistical analysis plan for the final overall survival analysis to take place.

7.2 At the end of the data collection period overall survival data from the ongoing CheckMate 238 trial will be used to inform the long-term extrapolation in the cost-effectiveness model. Subsequent treatment data will be used to inform the cost-effectiveness model for patients relapsing following adjuvant nivolumab treatment, which was considered an area of uncertainty.

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, the 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 238 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 de-personalised 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.