Cancer Drugs Fund

Managed Access Agreement

Atezolizumab for untreated metastatic urothelial cancer where cisplatin is unsuitable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Atezolizumab for metastatic urothelial carcinoma [TA492]

Company name: Roche Products Ltd

Primary source of data collection: Ongoing phase III clinical study (IMvigor 130)

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

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NHS England Agreement Manager	Prof Peter Clark, CDF Clinical Lead
Roche Products Ltd Agreement Manager	Denzyl Cain
Public Health England Agreement Manager	Martine Bomb, Head of Data Projects

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 atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma (mUC) in patients who are considered cisplatin-ineligible [TA492]. 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 The minimum time frame for data collection is determined by the ongoing phase III, study - IMvigor 130. Analysis for the study is event driven, or on decision by the study sponsor, F. Hoffman-La Roche Ltd. (**the Sponsor**). Full details of study design and analyses are available in sections 5, 6 and 7 of this form.

2.2 Therefore, this agreement shall take effect on publication of the managed access agreement. The data collection is anticipated to conclude December 2020, when it is expected that follow-up data will be available from IMvigor 130 clinical trial.

3 Patient eligibility

The patient eligibility for this Data Collection Arrangement has been updated in July 2018. In July 2018 the European Medicines Agency restricted the use of atezolizumab for untreated urothelial carcinoma. It should now only be used in adults with high levels of PD-L1. For more information, see the summary of product characteristics for atezolizumab.

People who started treatment under the previous patient eligibility criteria may continue without change to the funding arrangements in place for them.

3.1 The patient populations to be treated during the managed access arrangement period are adult patients with locally advanced or mUC who are considered cisplatin ineligible. This constitutes a subgroup of the population covered by the marketing authorisation. Key patient eligibility criteria for atezolizumab use in the Cancer Drugs Fund include:

- Patient has histologically or cytologically documented transitional cell carcinoma of the urothelial tract
- Patient has disease that is either locally advanced (i.e. T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease)
- Patient has not received previous chemotherapy for inoperable locally advanced or metastatic urothelial cancer
- Patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed more than 12 months since completing the platinum-based chemotherapy*

* Patients meeting this criterion are eligible to be considered as treatment naïve for locally advanced/ metastatic disease but must satisfy all other criteria

- Patient has an ECOG performance status of 0 -2

  Note: treatment of patients with performance status 2 with atezolizumab should only proceed with caution as there is limited safety data on PS 2 patients with urothelial carcinoma treated with atezolizumab

- Patient is ineligible for cisplatin based chemotherapy due to one or more of the following:
  - impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60mls/min)
  - hearing loss of 25dB as assessed by formal audiometry
  - NCI CTCAE grade 2 or worse peripheral neuropathy
  - ECOG performance status of 2
- Tumour expresses PD-L1 at a level of 5% or more, as defined by the presence of discernible PD-L1 staining of any intensity in tumour infiltrating immune cells covering ≥5% of tumour area occupied by tumour cells, associated intra-tumoural and contiguous peri-tumoural desmoplastic stroma
- Patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody
- Patient has no symptomatically active brain metastases or leptomeningeal metastases
- Atezolizumab is being given as monotherapy and will commence at a fixed dose of 1200 mg every 3 weeks

- A formal medical review as to whether treatment with atezolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- Patient to be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle
- Atezolizumab to be otherwise used as set out in its Summary of Product Characteristics

3.2 Eligible patients for treatment with atezolizumab are adult patients with locally advanced or metastatic UC with high PD-L1 expression who are considered cisplatin ineligible. Patients with hypersensitivity to atezolizumab or to any of the excipients are contraindicated. It was originally estimated a maximum of [redacted] patients would to receive treatment per annum. Following the updated marketing authorisation, a maximum of [redacted] patients with high PD-L1 expression are estimated to receive treatment per annum.

3.3 Marketing authorisation is for atezolizumab monotherapy administered as 1200mg IV infusion every 3 weeks. Marketing authorisation recommends patients are treated until loss of clinical benefit or unmanageable toxicity (see Table 1 for criteria of study treatment discontinuation as defined in the phase III clinical trials). Extrapolated mean treatment duration from the phase II study, IMvigor 210, is 8.41 months for cisplatin ineligible patients.

4 Area(s) of clinical uncertainty

4.1 The areas of clinical uncertainty include:

- Magnitude of overall survival (OS) and progression-free-survival (PFS) benefit of atezolizumab as compared to the UK standard of care for mUC patients who are cisplatin ineligible (e.g. hazard ratio, duration of effect).

- Health related quality of life (HRQoL) for mUC patients with stable disease and progressive disease, receiving either standard of care or atezolizumab (e.g. EQ5D).

- Atezolizumab treatment duration

5 Source(s) of data collection

Clinical trials

5.1 The primary source of data collection during the managed access arrangement period will be the ongoing phase III study - 1L: IMvigor 130. Outcomes including OS, PFS, treatment duration and HRQoL measured by EQ5D will be available from the study for people with high PD-L1 expression. PD-L1 expression was defined by the proportion of tumour-infiltrating immune cells that expressed PD-L1. The study design is described in brief below, with additional details available in Table 1.

1L: IMvigor 130 study:

5.2 This study was initially implemented with randomisation to two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) in patients who were ineligible for cisplatin-based chemotherapy. In Protocol WO30070, Version 3, a third treatment arm was added (open-label atezolizumab monotherapy), as shown in Figure 1. In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study.

5.3 Chemotherapy choice is specified per patient, prior to randomisation. Patients will be stratified by investigator choice of chemotherapy (gemcitabine +carboplatin, or gemcitabine + cisplatin). As such, clinical uncertainty regarding the incremental benefit of atezolizumab over gemcitabine + carboplatin will be answered via a stratified subgroup of ARM B vs ARM C (see Figure **1**).

5.4 Randomisation was stratified by PD-L1 expression. The high PD-L1 status population (≥5% PD-L1 expression in tumour-infiltrating immune cells) comprises approximately a third of the full trial population.

5.5 Study recruitment is ongoing, with results anticipated in December 2020. It is anticipated 4 months will be required to incorporate these data into an economic model and submission dossier.

Figure 1: IMvigor 130 study design

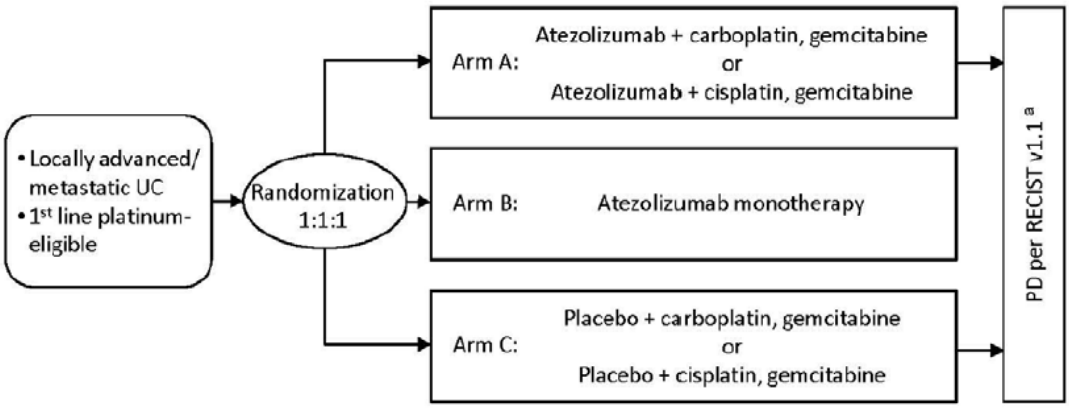

Table 1: Characteristics of atezolizumab phase III study, IMvigor 130

	IMvigor 130 (1L)
Population	Histologically documented, locally advanced (T4b, any N; or any T, N 2−3) or mUC (M1, Stage IV) (also termed TCC or UCC) of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra Eligible to receive platinum-based chemotherapy (either gemcitabine with cisplatin or gemcitabine with carboplatin) with measurable disease, defined by RECIST v1.1.
Study design	1200 patients Phase III, global, multicenter, randomised, three-arm, placebo-controlled, partially blind study Chemotherapy choice made prior to patient randomisation
Study arms	Randomised 1:1:1 (for patients recruited as of protocol version 3) • Arm A (experimental arm): blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine/ with either cisplatin or carboplatin) • Arm B (experimental arm): open-label atezolizumab monotherapy • Arm C (control arm): blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine/ with either cisplatin or carboplatin)

Crossover	No crossover permitted from control arm to either experimental arm
Primary endpoint	Assess atezolizumab + platinum-based chemotherapy compared with placebo +platinum based chemotherapy via the co-primary endpoints of investigator assessed PFS (RECIST v1.1) and OS (time from randomisation to any cause death). Evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy via OS (time from randomisation to any cause death).
Selected Secondary endpoints	Assess atezolizumab monotherapy or in combination with platinum chemotherapy compared with placebo plus platinum chemotherapy via the following outcomes: • ORR • Duration of response • Investigator assessed PFS (For Arm B vs. Arm C only, as this is included as a primary endpoint for Arm A vs. Arm C) • 1 year OS • 1 year PFS • HRQoL (EORTC QLQ-C30)

	• Safety Selected exploratory endpoint • EQ5D-5L
Stratification	• PDL1 expression on tumour-infiltrating immune cells (IC0 [<1% PD-L1 expression in IC] vs. IC1 [≥1% and <5% PD-L1 expression in IC] vs. IC2/3 [≥5% PD-L1 expression in IC] *using SP142 antibody*) • Investigator choice of chemotherapy (gemcitabine + carboplatin, or gemcitabine + cisplatin) • Bajorin risk model/liver metastasis
Key inclusion criteria	• ECOG performance status of ≤ 2 • Considered eligible for platinum based chemotherapy (gemcitabine + carboplatin, or gemcitabine + cisplatin) • No prior chemotherapy for inoperable, locally advanced, or metastatic urothelial carcinoma (patients receiving prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for UC require treatment-free interval >12 months to be considered treatment naive in metastatic UC) Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.) Ineligibility to receive cisplatin-based chemotherapy: Based on criteria published by Galsky et al. (2011) and will be documented.

	• Impaired renal function (GFR > 30 but < 60 mL/min) • NCI CTCAE v4.0 Grade ≥ 2 audiometric hearing loss of 25 decibels at two contiguous frequencies • NCI CTCAE v4.0 Grade ≥ 2 peripheral neuropathy (i.e., sensory alteration or paresthesia, including tingling) • ECOG performance status of 2
Study treatment discontinuation	Patients must discontinue study drug if they experience any of the following: • Intolerable toxicity related to study treatment • Any medical condition that may jeopardize the patient's safety if he or she continues to receive study treatment • Use of another systemic anti-cancer therapy • Pregnancy • Radiographic disease progression per RECIST v1.1* *Exception for atezolizumab if the following are all met: • Patients must have achieved a PR or CR of target lesions.

	• Patients must have ≤ 3 new lesions that are amenable to surgical resection or local ablative therapy (e.g., radiation therapy or radiofrequency ablation). • Patients must have no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per the investigator. • Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator • Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease • Patients must have no decline in ECOG performance status that can be attributed to disease progression. • Patients must have an absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing. • Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of progression.

Other data, including SACT

5.6 NHS England's Blueteq database captures the CDF data. 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.

5.7 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 estimates of:

- Overall survival
- Duration of therapy

6 Outcome data

Clinical trials

6.1 Currently available evidence for atezolizumab in mUC is from a single arm, phase II study (IMvigor 210). This study provides evidence in two cohorts: Cohort 1 - first line patients who are cisplatin ineligible; and Cohort 2 - those having failed prior chemotherapy. Cohort 1 is the population of interest within this DCA. The phase II study is single arm, as such there is significant uncertainty regarding the magnitude of benefit for atezolizumab compared to standard of care, for both OS and PFS.

6.2 The phase III study IMvigor 130, include OS as the primary endpoint. Primary analysis has not yet been conducted, and is anticipated to take place in 2020. This study will provide comparative efficacy data, including HRQoL as measured by EQ5D. OS, PFS and EQ5D data in the IMvigor 130

study will be collected in the same way for comparators as for the intervention. The study compares atezolizumab to the UK standard of care: gemcitabine + carboplatin for patients who are cisplatin ineligible.

Other data

7 Data analysis plan

7.1 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. During the managed access agreement period, Public Health England will collect data so as to provide information on overall survival and duration of therapy.

Clinical trials

7.2 The minimum time frame for data collection is given by the ongoing phase III study. Analyses are event driven, or until such time as the Sponsor decides to terminate the study. The final analysis will follow the analysis plan outlined in the trial protocol.

- [redacted]

7.3 An annual report detailing updated data collection from IMvigor 130 in terms of number of recorded events and anticipated date of final analyses will be provided to NICE by Roche Products Ltd. Roche Products Ltd. will also communicate any updated information on the timing of final analyses of the IMvigor 130 trial if such information becomes available in between update reports.

Other data

7.4 Public Health England will provide a report for NHS England based on routinely collected population wide data, including that collected via SACT, during the data collection period. The report will present de-personalised summary data based on the outcomes identified in section 6. The necessary

controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with Roche prior to the review of the appraisal.

7.5 Completeness of Public Health England dataset reporting will be shared with Roche on a quarterly basis. Public Health England will provide summary results for time on treatment and survival to NHS England annually and at the end of the data collection period, which will be shared with Roche in advance of the planned review of guidance.

8 Ownership of the data

8.1 Data from IMvigor 130 are owned by the Sponsor.

8.2 Data collection will be as per the IMvigor 130 study protocol.

8.3 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. Roche 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 NHSE at the end of the managed access period, which will be shared with Roche.

8.4 Blueteq CDF system data is owned by NHS England. NHS England is responsible for implementing Blueteq data collection and analysis. NHS England 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.

9.2 Publication of the analysis results of data collected by Public Health England, including through SACT, alongside the primary data source will be planned by Public Health England. Roche will be given access to the report produced for the review of the appraisal prior to the planned start of the review.Publication of the analysis results of Blueteq's CDF system data collected alongside the primary data source will be planned by NHS England. Roche will be given access to any report produced for the review of the appraisal and the review of the appraisal prior to the planned start of the review.

Commercial Access Agreement

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