Public Health England

Protecting and improving the nation's health

Pembrolizumab for treating urothelial cancer – data review

Commissioned by NHS England and NHS Improvement

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Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of pembrolizumab for locally advanced or metastatic urothelial cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended commissioning of pembrolizumab through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of pembrolizumab in the CDF population during the managed access period. This report presents the results of the use of pembrolizumab in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 98% of patients and 94% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for pembrolizumab for urothelial cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 27 July 2018 and 26 December 2019, 73 applications for pembrolizumab were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 61 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

61 (98%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration was 5.2 months [95% CI: 3.8, 11.3], (158 days). 47% [95% CI: 34%,60%] of patients were receiving treatment at 6 months and 22% [95% CI: 7%, 42%] of patients were receiving treatment at 12 months.

At data cut off, 57% (N=35) of patients were identified as no longer being on treatment; 34% (N=12) of patients stopped treatment due to progression, 31% (N=11) of patients stopped treatment due to acute toxicity, 6% (N=2) of patients chose to end their treatment, 17% (N=6) of patients died not on treatment, 9% (N=3) of patients died on treatment and 3% (N=1) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median overall survival was 19.5 months (593 days). OS at 6 months was 74% [95% CI: 61%, 83%], OS at 12 months was 66% [95% CI: 52%, 76%].

A sensitivity analysis was conducted for a cohort with at least 6 months data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort.

Conclusion

This report analyses SACT real world data for patients treated with pembrolizumab for urothelial cancer in the CDF. It evaluates treatment duration, overall survival, treatment outcomes for all patients treated with pembrolizumab for this indication.

Introduction

Urothelial cancer (ICD-10: C66) is a rare cancer type and accounts for <1% of all cancer diagnoses in England. In 2017, 596 patients were diagnosed with cancer of the ureter (males 385, females 211)[2].

Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if:

- their tumours express PD-L1 with a combined positive score of 10 or more
- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and
- the conditions of the managed access agreement for pembrolizumab are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in 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 PHE.

NICE Appraisal Committee review of pembrolizumab for urothelial cancer [TA522].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of pembrolizumab (MSD) in treating urothelial cancer [TA522] and published guidance for this indication in June 2018[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of pembrolizumab through the CDF for a period of 25 months, from June 2018 to July 2020.

During the CDF funding period, results from an ongoing clinical trial evaluating pembrolizumab in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of pembrolizumab is KEYNOTE-361[7]. Data collected from the KEYNOTE-361 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for pembrolizumab for urothelial cancer in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the KEYNOTE-361[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Overall survival**
- **Progression free survival**

Overall survival and progression free survival data will be reported in the KEYNOTE-361 trial. PHE will calculate results for overall survival and treatment duration.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (MSD) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of pembrolizumab. It also detailed the eligibility criteria for patient access to pembrolizumab through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for pembrolizumab, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine).

As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Pembrolizumab clinical treatment criteria

- 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
- The patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy for localised urothelial cancer OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy for localised urothelial cancer, 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 (PS) of 0-2
    - Note: treatment of patients with performance status 2 with pembrolizumab should only proceed with caution as there is limited safety data on PS 2 patients with urothelial carcinoma treated with pembrolizumab
- Patient is ineligible for platinum-based chemotherapy for one of the following reasons:
    - impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60 mls/min)
    - hearing loss of 25 dB as assessed by formal audiometry
    - NCI CTCAE grade 2 or worse peripheral neuropathy
- 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 unless it was received as part of the pembrolizumab compassionate access scheme for this indication and the patient meets all other criteria listed here
- Patient has no symptomatically active brain metastases or leptomeningeal metastases
- Pembrolizumab is being given as monotherapy and will commence at a fixed dose of 200 mg per infusion
- A formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- Patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner
- The patient will receive a maximum treatment duration with pembrolizumab of 2 years
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle
- Pembrolizumab will otherwise be used as set out in its Summary of Product Characteristics (SPC)

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for pembrolizumab for the treatment of urothelial cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for pembrolizumab for the treatment of urothelial cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for pembrolizumab for the treatment of urothelial cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

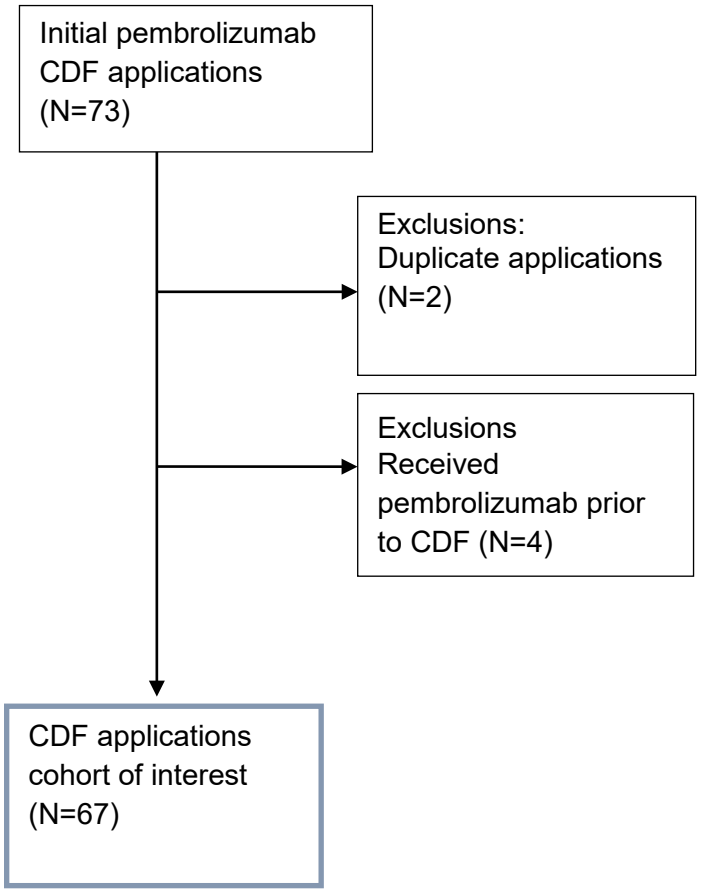
The analysis cohort is limited to the date pembrolizumab entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 27 July 2018 to 26 December 2019. A snapshot of SACT data was taken on 4 April 2020 and made available for analysis on the 14 April 2020. The snapshot includes SACT activity up to the 31 December 2019. Tracing the patients' vital status was carried out on 22 May 2020 using the PDS[1].

There were 73 applications for CDF funding for pembrolizumab for urothelial cancer between 27 June 2018 and 26 December 2019 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 71 unique patients.

Four patients were excluded from these analyses as they appeared to have received pembrolizumab prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for pembrolizumab for treating urothelial cancer between 27 July 2018 and 26 December 2019



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for pembrolizumab in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Pembrolizumab is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. A duration of 20-days has been added to final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Pembrolizumab is a 21-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

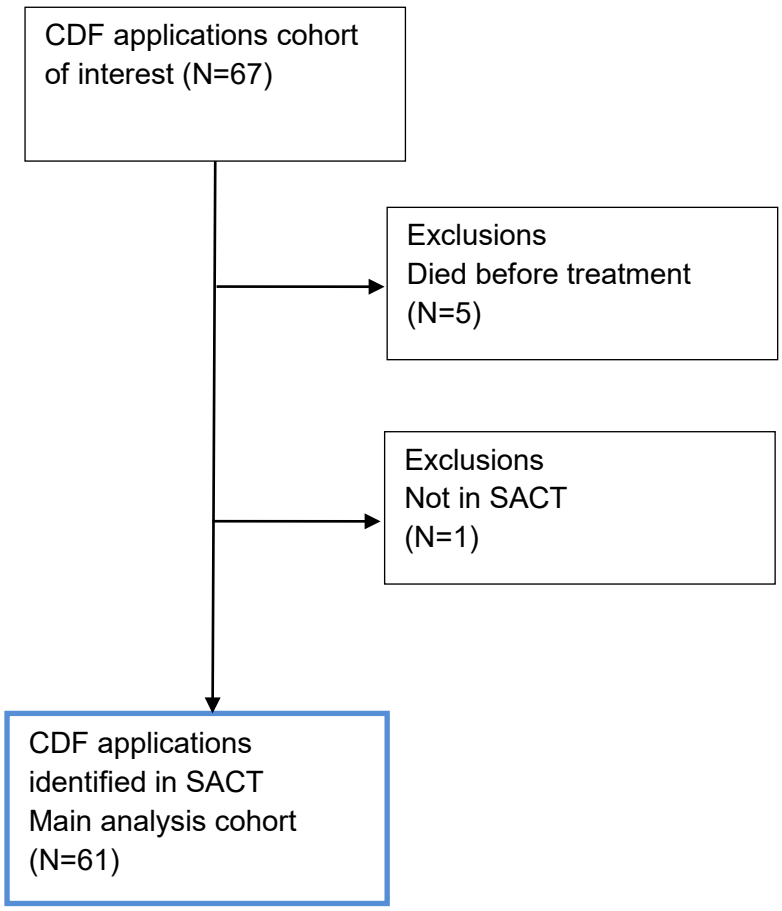
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 67 new applications for CDF funding for pembrolizumab for urothelial cancer, five patients died before treatment and one patient was missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for pembrolizumab for treating urothelial cancer between 27 July 2018 and 26 December 2019



[a] The five patients that died before treatment were confirmed with the relevant trusts by the PHE data liaison team.

A maximum of 62 pembrolizumab records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 98% (61/62) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 85% complete.

Table 1: Completeness of key SACT data items for the pembrolizumab cohort (N=61)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	85%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with pembrolizumab in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 35. Of these, 33 (94%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=35)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	94%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. PD-L1 combination proportion score is 98% complete (60/61).

Table 3: PD-L1 Combined proportion score (CPS) (N=61)

Variable	Completeness (%)
PD-L1 (CPS)	98%

Patient characteristics

The median age of the 61 patients receiving pembrolizumab for urothelial cancer was 74 years; and was consistent for both genders.

Table 4: Patient characteristics (N=61)

Patient characteristics[b]		N	%
Sex	Male	38	62%
	Female	23	38%
Age	<40	0	0%
	40-49	1	2%
	50-59	4	7%
	60-69	14	23%
	70-79	26	43%
	80+	16	26%
Performance status	0	7	11%
	1	28	46%
	2	17	28%
	3	0	0%
	4	0	0%
	Missing	9	15%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

PD-L1 combination proportion score (CPS)

The distribution of CPS in Table 5 shows that 98% (N=60) of patients had a CPS ≥10 and 2% (N=1) had a missing score.

Table 5: Distribution of PD-L1 Combined proportion score in Blueteq (N=61)

PD-L1 (CPS) score	N	%
≥10	60	98%
Not captured	1	2%
Total	**61**	**100%**

Treatment duration

Of the 61 patients with CDF applications, 35 (57%) were identified as having completed treatment by 31 December 2019 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with pembrolizumab in at least three months (see Table 9). The median follow-up time in SACT was 4.2 months (127 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 17 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of 18 months. SACT follow-up ends 31 December 2019.

Table 6: Breakdown by patients' treatment status[c,d,e]

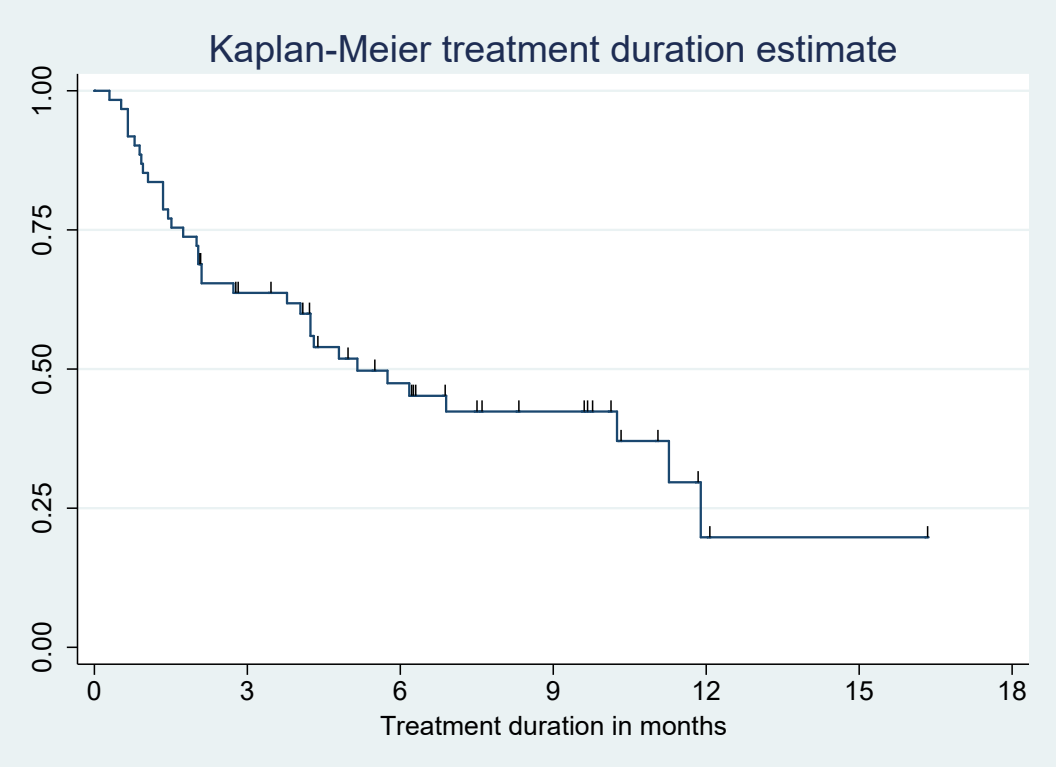
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	22	36%
Patient died – on treatment	3	5%
Treatment stopped	10	16%
Treatment ongoing	26	43%
Total	**61**	**100%**

[c] Figures may not sum to 100% due to rounding.
[d] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[e] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 5.2 months [95% CI: 3.8, 11.3], (158 days) (N=61).

47% of patients were still receiving treatment at 6 months [95% CI: 34%,60%], 22% of patients were still receiving treatment at 12 months [95% CI: 7%, 42%].

Figure 3: Kaplan-Meier treatment duration (N=61)



Tables 7 and 8 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 17 months (517 days).

Table 7: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18
Number at risk	61	35	21	12	2	1

Table 8 shows that for all patients who received treatment, 26 were still on treatment (censored) at the date of follow-up and 35 had ended treatment (events).

Table 8: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18
Censored	26	22	16	9	2	1
Events	35	13	5	3	0	0

Table 9 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 57% (N=35) of patients had ended treatment at 31 December 2019.

Table 9: Treatment outcomes for patients that have ended treatment (N=35)[f,g]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	12	34%
Stopped treatment – acute chemotherapy toxicity	11	31%
Stopped treatment – patient choice	2	6%
Stopped treatment – died not on treatment[h]	6	17%
Stopped treatment – died on treatment	3	9%
Stopped treatment – no treatment in at least 3 months	1	3%
Total	**35**	**100%**

[f] Figures may not sum to 100% due to rounding.
[g] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[h] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=35)

Outcome[i]	Patient died [j] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	11	1	
Stopped treatment – acute chemotherapy toxicity	4	7	
Stopped treatment – patient choice	1	1	
Stopped treatment – died not on treatment	6		
Stopped treatment – died on treatment			3
Stopped treatment – no treatment in at least 3 months		1	
Total	**22**	**10**	**3**

[i] Relates to outcomes submitted by the trust in table 9.

[j] Relates to treatment status in table 6 for those that have ended treatment.

Overall survival

Of the 61 patients with a treatment record in SACT, the minimum follow-up was five months (152 days) from the last CDF application. Patients were traced for their vital status on 22 May 2020. This date was used as the follow-up date (censored date) if a patient is still alive.

The median follow-up time in SACT was 8.8 months (267 days). Figure 5 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was 19.5 months[k] (593 days). Survival at 6 months was 69% [95% CI: 55%, 79%], 12 months survival was 61% [95% CI: 48%, 72%].

Figure 5: Kaplan-Meier survival plot (N=61)

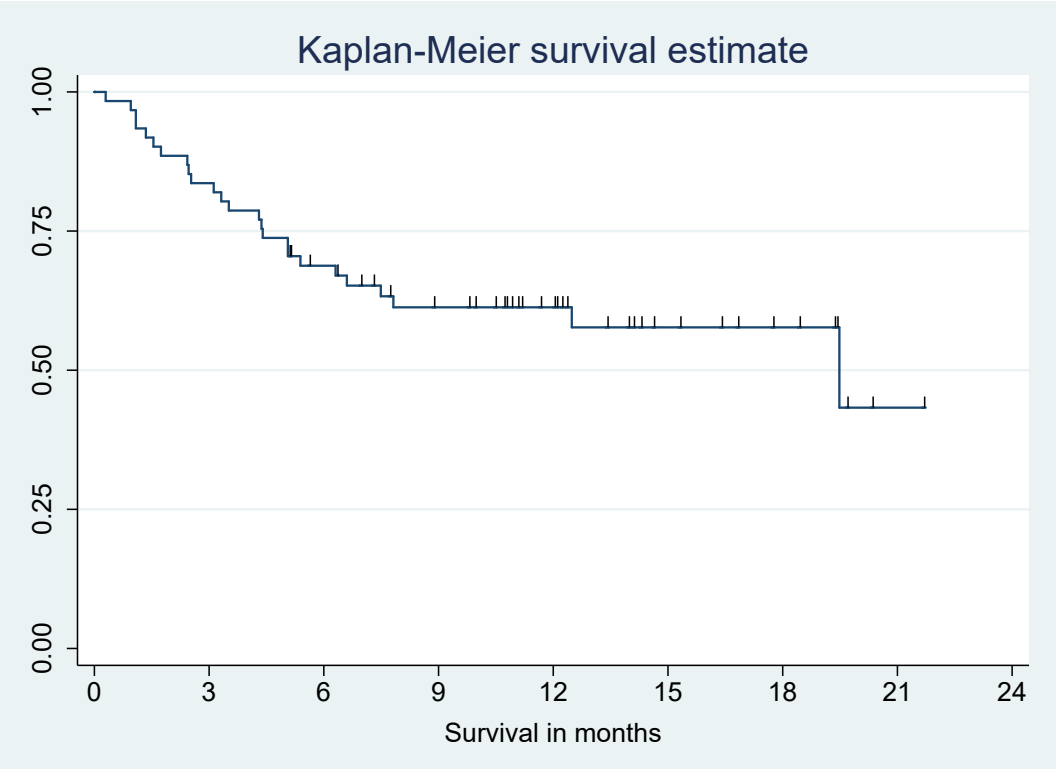


Table 11 and 12 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 22 months (669 days), all patients were traced on 22 May 2020.

Table 11: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	61	51	39	30	19	11	7	1

[k] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Table 12 shows that for all patients who received treatment, 36 were still alive (censored) at the date of follow-up and 25 had died (events).

Table 12: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	36	36	33	28	17	10	6	1
Events	25	15	6	2	2	1	1	0

Sensitivity analyses

Cohort 1: 6-month SACT follow up

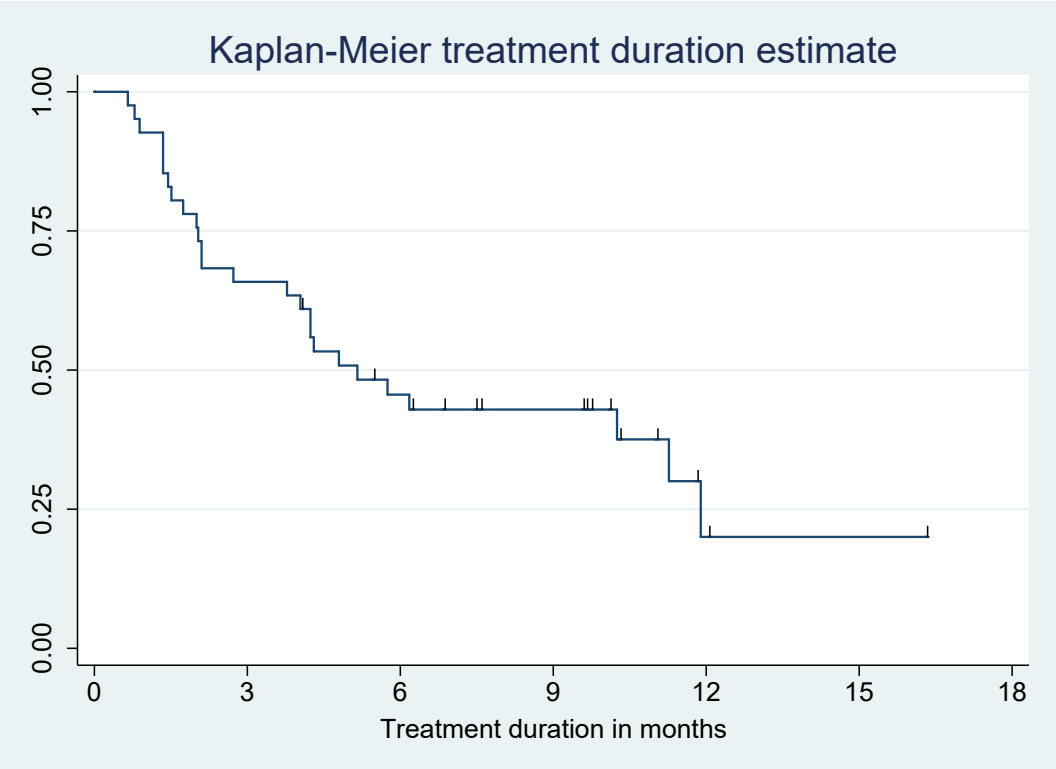
Treatment duration

Sensitivity analyses were carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 27 July 2018 to 30 June 2019 and SACT activity was followed up to the 31 December 2019.

Following the exclusions above, 41 patients (67%) were included in these analyses. The median follow-up time in SACT was 4.8 months (146 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 6. The median treatment duration for patients in this cohort was 5.2 months [95% CI: 2.7, 11.3] (158 days) (N=41).

Figure 6: Kaplan-Meier treatment duration plot (N=41)



Tables 13 and 14 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 17 months (517 days).

Table 13: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18
Number at risk	41	27	17	12	2	1

Table 14 shows that for all patients who received treatment, 15 were still on treatment (censored) at the date of follow-up and 26 had ended treatment (events).

Table 14: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 18	3 - 18	6 - 18	9 - 18	12 - 18	15-18
Censored	15	15	13	9	2	1
Events	26	12	4	3	0	0

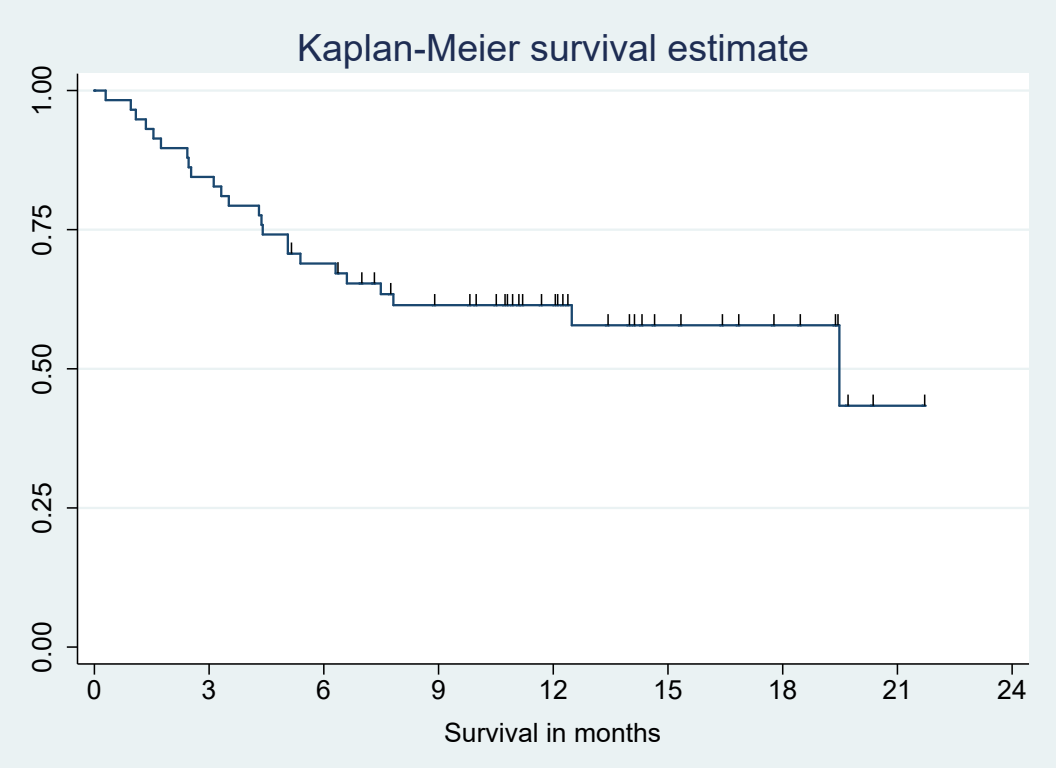
Overall survival

Sensitivity analyses were also carried out for overall survival on a cohort with at least 6 months follow-up in SACT. To identify the cohort, CDF applications were limited from 27 July 2018 to 22 November 2019.

Following the exclusions above, 58 patients (95%) were included in these analyses. The median follow-up time in SACT was 9.8 months (298 days).

Figure 7 provides the Kaplan-Meier curve for overall survival, censored at 22 May 2020. The median survival was 19.5 months[I] (593 days).

Figure 7: Kaplan-Meier survival plot (N=58)



[I] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Tables 15 and 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 22 months (669 days), all patients were traced on 22 May 2020.

Table 15: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	58	49	39	30	19	11	7	1

Table 16 shows that for all patients who received treatment, 34 were still alive (censored) at the date of follow-up and 24 had died (events).

Table 16: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Censored	34	34	33	28	17	10	6	1
Events	24	15	6	2	2	1	1	0

Table 17: Median treatment duration and overall survival, full cohort and sensitivity analysis[m].

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	61	41	58
Median treatment duration	5.2 months (158 days) [95% CI: 3.8, 11.3]	5.2 months (158 days) [95% CI: 2.7, 11.3]	
OS	19.5 months (593 days)		19.5 months (593 days)

[m] Confidence intervals could not be produced for overall survival as there was an insufficient number of events at the time this report was produced

Conclusions

62 patients received pembrolizumab for the treatment of locally advanced or metastatic urothelial cancer [TA522] through the CDF in the reporting period (27 July 2018 and 26 December 2019). 61 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 98%. An additional five patients with a CDF application did not receive treatment. This was confirmed with the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that proportionally more males received pembrolizumab treatment compared to females (61% (N=38) male, 37% (N=23) female). Most of the cohort was aged between 60 and 80+ years (92%, N=56) and 85% (N=52) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 57% (N=35) of patients were identified as no longer being on treatment; 34% (N=12) of patients stopped treatment due to progression, 31% (N=11) of patients stopped treatment due to acute toxicity, 6% (N=2) of patients chose to end their treatment, 17% (N=6) of patients died not on treatment, 9% (N=3) of patients died on treatment and 3% (N=1) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 5.2 months [95% CI: 3.8, 11.3], (158 days). 47% [95% CI: 34%,60%] of patients were receiving treatment at 6 months and 22% [95% CI: 7%, 42%] of patients were receiving treatment at 12 months.

The median overall survival was 19.5 months (593 days). OS at 6 months was 74% [95% CI: 61%, 83%], OS at 12 months was 66% [95% CI: 52%, 76%].

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for this cohort were consistent with the full analysis cohort for both treatment duration (full cohort = 5.2 months; sensitivity analysis cohort = 5.2 months) and overall survival (full cohort = 19.5 months; sensitivity analysis cohort = 19.5 months).

References

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