**The effect of clinical decision-making for starting systemic anti-cancer treatments in response to the coronavirus pandemic in England: A Retrospective Analysis**

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**Abstract**

**Background**
Cancer services worldwide have needed to adapt to the SARS-CoV-2 pandemic to minimise risk to patients and staff. We examined the national impact of COVID-19 on systemic anti-cancer treatment (SACT) immediately after lockdown and after new treatments were introduced to reduce patient risk.

**Methods**
A central database records intention to start all new SACT approved for use in England since 2016 (indications before 2016, notably almost all cytotoxic chemotherapies, are not included). We analysed numbers of monthly treatment registrations after lockdown (April 2020) and after implementation of treatment options with reduced patient risk such as oral or less immunosuppressive drugs (May and June 2020). These were compared with the mean number of registrations and standard deviation (SD) during the prior 6 months of unaffected cancer care (September 2019-February 2020). We calculated the percentage change and absolute difference in SD units.

**Findings**
2969 registrations occurred in April 2020, fewer than in the control period (monthly mean 4386): 32% relative reduction, absolute difference 4.2 SDs. Large reductions occurred across almost all tumour types and intents of cancer therapy (p-values <0.01) with largest falls in non-curative (35%) and neoadjuvant (37%) indications, intravenous drugs (42%) and immunotherapies (39%). In May, total registrations rose to 3950, 10% lower than in the control period (1.3 SDs, p<0.01). There were 5022 registrations in June (15% more than in the control period, 1.9 SDs, p<0.01), with almost universal increases, apart from continued conspicuous reductions in neoadjuvant therapies and low-grade lymphoid malignancies.

**Interpretation**
The initial impact of SARS-CoV-2 on SACT initiation was rapid and substantial. However, following introduction of treatment options to reduce patient risk, registration increases began during May 2020 with above typical levels in June when other clinical and societal risk mitigation factors (such as telephone consultations, facemasks and social distancing) are also likely to have contributed. This pattern reflects an early phase of fewer diagnoses, treatment delay and patient choice to avoid therapy, followed by rapid recovery, particularly stimulated by the provision of new treatment options. However, outcomes of giving less or delayed treatment, particularly for advanced cancers and neoadjuvant therapies, require continued scrutiny.

**Research in context**

**Evidence before this study**

The rapid emergence of the SARS-CoV-2 pandemic in England in 2020 means that there is limited evidence available on the use of systemic anticancer treatments (SACT) during this time. It is known that cancer services have been reduced to minimise viral exposure to both cancer patients (an inherently vulnerable population shown to have poor outcomes following COVID-19 infection) and staff. We searched PubMed (from database inception to August 30, 2020 for articles published in English with search terms ("COVID-19" OR "SARS-CoV-2") AND ("oncology" OR "cancer" OR "malignancy")) and found publications on the impact on cancer patients such as increased risk of hospital admission and higher death rate. More recent data have evaluated the impact of SACT on COVID-19 outcomes; however, there has been limited evidence on the use and provision of SACT during the pandemic.

**Added value of this study**

To our knowledge this is the first attempt to observe how prescribing practice for anticancer treatments had changed at a national level since the pandemic began (based on all drugs approved by the National Institute for Health and Care Excellence since 2016). We demonstrate that a substantial reduction in the number of patients who started newer systemic therapies in April 2020 was followed by an increase in May 2020, and the initial reductions were largely reversed by June 2020 (when the number of treatment registrations was significantly higher than usual). This pattern occurred for all intents of therapy bar neoadjuvant therapy and in most cancer types. These findings can provide some reassurance to patients and clinicians that treatment delays can be minimised or avoided if healthcare providers are able to quickly implement guidance on drug prescribing. This involves giving more treatment options via rapid temporary approval of oral drug alternatives and bringing forward of less immunosuppressive drugs only licensed for later in the treatment pathway. It should be noted that cytotoxic chemotherapies approved before 2016 and hormonal therapies are not included in our findings, so we are unable to comment on their prescribing patterns.

**Implications of all the available evidence**

In England, an example of a high-income country healthcare system, many patients did not start their expected SACT in the early phase of the pandemic although recovery in England was rapid. The impact of not giving or delaying SACT on patient outcomes needs to be monitored in the forthcoming months, especially for non-curative therapies used for advanced disease (some of which only extend survival by a few months), and for neoadjuvant treatment.

## Background

Since the emergence of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), healthcare systems worldwide have adapted to manage the surge in hospital admissions due to Coronavirus Disease 2019 (COVID-19). Additionally, strategies have had to be implemented to reduce transmission of SARS-CoV-2 and protect patients and healthcare workers.

Cancer patients are especially vulnerable to COVID-19 owing to their advanced age and comorbidities as well as to the biologically plausible negative impact of the immunosuppressive nature of both oncology treatment and cancer itself on the host response to SARS CoV-2 infection(1, 2). In addition, the relatively frequent clinic visits required for treatment and assessments may increase the risk of SARS-CoV-2 exposure. Several studies have suggested adverse outcomes in cancer patients with COVID-19 (such as higher mortality or more hospital admissions) (3-11), but others reported no link between recent SACT and increased mortality from COVID-19 (12, 13).

Many cancer services in England and elsewhere have undergone extensive change to minimise COVID-19 exposure to cancer patients and healthcare staff. This has included delayed surgery and radiotherapy, fewer chemotherapy treatment cycles, reduced outpatient visits (often replaced with telephone assessments), and where possible switching from therapies that require intravenous administration to oral drugs. Diagnostic services have also been affected, with a clear reduction in cancer referrals (14, 15).

Guidance from the UK National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE) issued on 20 March 2020 aimed to help clinicians in decision-making by prioritising the need to retain SACT services (16). Clinicians were advised to categorise patients into 6 priority levels based on their cancer stage and treatment: those undergoing highly curative treatment had the top ranking (level 1), and those being treated with non-curative therapies with an intermediate/low chance of palliation had the lowest rank (level 6). Hospitals in England were tasked to rapidly translate this guidance into service provision. Given the global nature of this pandemic and its effect on all healthcare services, similar guidance had also been elsewhere, including by the European Society of Medical Oncology (17).

In our study, we assessed the impact of COVID-19 on the initiation of SACT at a national level, at the height of the pandemic (in April 2020 following societal lockdown on 23 March 2020) and after the NHS implemented additional and specific treatment options in April and May 2020 to mitigate the risk of COVID 19 to patients requiring SACT. We used direct observable evidence based on the actual number of patients initiating SACT.

## Methods

*Database*

NHS England, the commissioner of all SACT except for hormone therapies, has required clinicians to register all patients commencing SACT for all drug indications recommended by NICE since April 2016, via a central web database, the NHS England Prior Approval system. For each patient, the clinician selects the appropriate indication, which includes cancer type, drug name and specific line of therapy in the treatment pathway; the mode of administration is obvious (oral or intravenous). The indication description allowed accurate categorisation of intent of therapy (curative/non-curative intent for advanced disease, and neoadjuvant/adjuvant intent for early stage disease) by one author JJC, which was confirmed by a second clinician PC (both are oncologists). A list of currently approved indications with all the treatment criteria which have to be satisfied for each indication and including the new COVID-19-specific measures is available via the Cancer Drug Fund Website (https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-ver1.169.pdf).

For sake of simplicity, all immunotherapies for solid tumours were classified as being non-curative in intent unless given in the specific indications of maintenance therapy (the potentially curative treatment of durvalumab following radical chemo-radiotherapy in lung cancer) or as adjuvant therapy in melanoma. The system captures all immunotherapies, all monoclonal antibodies (excluding rituximab and trastuzumab), all antibody-drug conjugates and nearly all approved tyrosine kinase inhibitors. Most

cytotoxic chemotherapies are not included, having been approved prior to 2016. We obtained data from April 2019 to June 2020.

*Data Analysis*

The study outcome was the number of SACT registrations seen per month. Societal lockdown was formalised on March 23rd 2020 in England, so registrations during March reflect both normal usage and the start of the impact of the pandemic. We focussed on the number of registrations seen per calendar month in April, May and June 2020. The control period against which April to June 2020 were compared was chosen to be 1 September 2019 to 29 February 2020 (i.e. the 6 pandemic-unaffected months before April) because these months were the closest in chronological time. Using April to June 2019 (whole months) as the control period would have been inappropriate because the number of SACT registrations is influenced by the total number of newly approved drug indications which differs for a particular month, from year to year (many new indications were recommended between 1 April and 29 August 2019). However, we also provide data from April-June 2019 as a secondary comparison.

The average (mean) number of monthly registrations was calculated for the control period, along with the standard deviation (SD). The mean value was an appropriate comparator because the observed monthly number was stable between 1 September 2019 and 29 February 2020 (see figures below). This mean value was compared to the number of registrations seen per calendar month in April, May and June 2020, using both relative and absolute changes. The relative reduction was calculated as the ratio of these two numbers. The absolute reduction was calculated as the difference expressed as the number of SDs away from the monthly average for the control period, to reflect the usual variability between the control months and to provide a standardized parameter given that the number of registrations varies by tumour type, and line and type of therapy. Being greater than two SDs from the control value is considered a large absolute reduction. A chi-square test for comparing two counts was used to make comparisons with the control period ($p<0.05$ denoting statistical significance). The data used to produce the results are provided in Supplementary Appendix pages 10-11. Analyses were performed in GraphPad/Prism version6. We analysed the months of April to June 2020 separately as we had no prior expectation of any patterns and wanted to examine each month, and not fit trends.

*Role of the Funding source*

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and the final responsibility to submit for publication. JJC, DD, PC and AH had access to the raw data

**Findings**

159 separate indications were recorded in the registration system by the last day of March 2020, and 204, 211 and 211 indications by the last day of April, May and June 2020, respectively. These latter three indication numbers included the new COVID-19 specific measures introduced by NHS England. NICE recommendations added two new indications in April 2020 (larotrectinib and lorlatinib, both indications for very small numbers of patients) and three new indications in May 2020 (atezolizumab in advanced triple negative breast cancer, atezolizumab in small cell lung cancer and trastuzumab emtansine as adjuvant breast cancer therapy, all for potentially larger patient populations). Other new treatment options in response to the pandemic were introduced on 12th, 14th, and 28th April and 4th, 5th and 22nd May (Supplementary Appendix pages 8-9). These included oral drug alternatives and bringing forward of less immunosuppressive drugs only licensed for later in the treatment pathway.

In April 2020 there were 2969 registrations, lower than in any month during the control period (4177, 4669, 4493, 3922, 4819 and 4235 for September 2019 to February 2020 respectively). The figure for April was 1417 fewer than the mean number per month of 4386 from the control period (SD 335). This represents a 32% relative reduction (2969/4386=0.68); and an absolute difference of 4.2 SDs from 4386 (1417/335); Figure 1A. These were large relative and absolute reductions, which were highly statistically significant. During May the total number of registrations increased to 3950, and was 10% (436/4386) lower than the control period (1.3 SD difference, fewer registrations; $p<0.0001$). In June there were more registrations than in the control period (5022 vs 4386); a 15% increase (1.9 SD difference, $p<0.0001$).

Figure 1 shows the relative reductions in the number of registrations according to therapy and tumour type, in April to June 2020, each compared with the control period. Figures 2-3 and Supplementary Appendix pages 2-6 show the observed number of registrations per month (September 2019 to June 2020), along with the absolute differences seen in April. Supplementary Appendix pages 10-11 provides all of the relative and absolute differences for each of April to June 2020 with p-values.

The reductions in registrations in April were consistently seen across all groups, including intent of therapy, tumour type, line of non-curative therapy, and mode of administration (the results and categories below are not necessarily mutually exclusive). All were large effects. The reduction was least for oral drugs (18% fewer [1453/1762], or 2.0 SDs); p<0.0001. The reduction was 42% (1515/2621, 6.0 SDs) for intravenous drugs, and 39% (500/821, 5.4 SDs) for immunotherapies (all of which are intravenous). The relative reductions during April for the four most common solid tumour registrations were 33% (663/985) breast, 57% (154/360) prostate, 36% (404/62) lung, and 32% (280/413) skin.

During April 2020, the relative reduction in registrations were 37% (119/190) for neoadjuvant therapy and 35% (2449/3739) for non-curative treatment indications (the absolute reductions were also large 4 to 5 SDs), with a smaller reduction for curative therapies (16%, 144/172). Cytotoxic chemotherapy experienced more significant reductions in registrations (51% reduction, 533/1089). There were also large reductions for each line of non-curative therapy: 30% (1265/1797) first-line, 36% (774/1201) second-line, and 45% (410/742) third-line; all with substantial absolute differences (3.3-4.8 SDs).

In May, continued relative and absolute reductions compared to the control period were seen for: neoadjuvant therapies (30%, 133/190), non-curative second and third or more lines (25% [896/1201] or 30% [520/742] respectively), cytotoxic chemotherapies (29%, 770/1089), and intravenous drugs (18%, 2137/2621); all with p<0.0001. Reductions (compared to the control period) were less marked than in April for cancers of the breast (10%, 891/985), lung (4%, 603/627), and skin (17%, 342/413).

However, the numbers of new registrations in May were higher than the control period (having increased from April to May) for curative and adjuvant therapies. Immunotherapies had also increased (from April to May) but were still 10% (736/821) lower than in the control period. The most substantial increases in tumour-specific registrations were seen for prostate cancer (37%, 493/360), urothelial cancer (24%, 72/58) and acute leukaemia (54%, 145/94) compared to the control period.

In June, the situation was largely reversed from April. The number of registrations was higher than in the control period, and in many cases the increases were clinically large (and p<0.0001), for example non-curative first line therapies (27%, 2291/1797), oral drugs (28%, 2263/1762); and for prostate cancer (83%, 660/360) nearly all of which was the provision of enzalutamide as an alternative to chemotherapy for metastatic hormone-sensitive disease) and urothelial cancer (56%, 91/58). However, the number of registrations continued to be lower than in the control period for neoadjuvant therapies (45% [104/190] reduction), CLL (29% [96/135]), and follicular lymphoma and Waldenstrom's macroglobulinaemia (31% [108/157]); all p<0.0001.

The NHS England COVID-19 specific drug indications introduced in April and May 2020 contributed substantially to the rise in the May and June total registration figures: 81% (795 of the additional 981 registrations compared to April) in May and 44% (896 of a rise of 2053 registrations compared to April) in June.

Finally, we examined the total number of monthly registrations as far back as April 2019 (Supplementary Appendix page 7). Even with the usual variability (when there may be more or fewer new drug approvals from month to month) and also with the expected seasonal drop in December (which is only modest), the decreases between adjacent months were never as large as the one seen in April 2020; and the increase from April to June 2020 is much larger than seen across any two-month period in the previous year. Even if we had used April to June 2019 as the comparison period (mean number of registrations 3868), the number seen in April 2020 (2969) and June 2020 (5022) are still substantially different to an extent beyond usual variation (p<0.0001).

**Discussion**

Our study provides a national assessment of the effect of SARS-CoV-2 on patients starting their SACT, likely to be seen in other countries, particularly those with similar healthcare structures. We show the negative initial impact on prescribing patterns followed by a quick recovery in most clinical scenarios two months later.

The initial substantial reduction in April 2020 in patients starting recently approved SACT drugs was due to several factors, including patient choice, clinical advice on the benefit and risks of starting treatment, and a reduction in referrals and subsequent diagnoses (as a result of fewer patient presentations or reduced service capacity). However delayed diagnosis could only have affected patients having curative, adjuvant, neoadjuvant and non-curative first-line treatments which together comprised 56% of the population commencing these registered SACTs in the control period. In addition, we do not consider the changes observed in April to June 2020 to reflect seasonal variation as the only significant seasonal fall seen in the NHS has been in December of each year, which is modest.

There was a significant reduction in registrations overall towards the start of the pandemic (32% in April, 10% in May), and the effect was greater for non-curative indications particularly for later lines of therapy. During May 2020, there were noticeable increases in prescribing from April, particularly for curative and adjuvant treatments, immunotherapies and first-line non-curative therapies, but reductions persisted by comparison to the control period, particularly for neoadjuvant therapies. By June the number of registrations was higher than the control period, which was seen for most intents of therapy and tumour types, apart from neoadjuvant treatments and in low-grade lymphoid malignancies.

The increases in registrations seen in May and particularly in June are likely to reflect both delayed starts of treatment and an increase in referrals and diagnoses following the pandemic peak. Treatments given temporary approval by the NHS to reduce the risk to patients also contributed substantially to the increase in May and June: 81% of the increase in May and 44% of the rise in June came from these measures. By June, more of the increment was in routinely available treatments, signifying a substantial shift towards ‘business as usual’ with hospital systems making adjustments using social distancing, telephone consultations, face masks, and routine SARS-CoV-2 testing with designated “clean” treatment areas. These changes in prescribing reflect a healthcare system that can adapt quickly to the provision of new treatment options, many of which only became available in late April and early May.

Tumour subtypes such as prostate cancer and chronic lymphocytic leukaemia had a large reduction in registrations in April. The typically higher age of such patients, linked to COVID-19 risk, and the less aggressive biology of these more indolent cancers, were likely factors when considering treatment delays. The availability of new oral treatment options with much reduced immunosuppressive risk proved beneficial; introduction of first line enzalutamide instead of chemotherapy for metastatic hormone-sensitive prostate cancer contributed substantially to registrations increasing to 37% above pre-pandemic levels in May and 83% higher than the control period in June. By contrast, initiation of treatments for CLL in May and June remained much lower than the control period. A reluctance to initiate therapy in lymphoid malignancy probably reflects the additional immunosuppression imposed by the disease itself and the reported high mortality among such patients with COVID-19 infection (18, 19).

There was a reduction in immunotherapy registrations in April. Although immunotherapy is not generally considered to be immunosuppressive for most patients, it is likely that clinicians were reluctant to expose patients to multiple hospital visits and sought to avert treatment toxicity. There is also a potential risk of additive toxicity from immunotherapies that induce inflammation, especially pneumonitis. Such concerns have not however been borne out in recent reports showing no association between PD-1 blockade and COVID-19 severity (20).

The greater reduction in intravenous treatment registrations (42% in April) as opposed to oral therapies (18%) reflects a desire to maintain treatment where possible, especially given that many oral treatments (e.g. tyrosine kinase inhibitors) are not strongly immunosuppressive and these drugs could be delivered to patients’ homes. Nevertheless, the increase in June is striking for oral drugs (28% increase compared to the control period).

Some of the smallest reductions in registrations in April were seen for those treatments deemed curative and adjuvant, reflecting the higher benefit-risk ratio. Notable examples of curative therapies

that were used less include durvalumab after chemoradiotherapy for non-small cell lung cancer, and recently approved additions to chemotherapy in acute leukaemia such as gemtuzumab ozogamicin. The rises in curative treatments observed in May and June were mainly related to the provision of venetoclax combinations and gilteritinib for acute myeloid leukaemia. The adjuvant treatment registrations were confined to HER-2 positive breast cancer and melanoma, although the decrease in adjuvant therapies during April was largely seen in melanoma due to a fall in adjuvant immunotherapy. One explanation for this reduction could be more aggressive risk stratification, with less adjuvant treatment for those deemed at lower risk of relapse, combined with a desire to avoid potentially toxic treatment and/or hospital visits. Nevertheless, use of these adjuvant therapies rose quickly in May and June to above the level in the control period.

The reduced number of registrations for neo-adjuvant treatment is likely to reflect patients proceeding straight to the treatment option of surgery rather than risking chemotherapy complications and subsequent delays, and this conspicuous trend clearly continued into May and June.

This study has some limitations. First, the NHS registration system records an intention to treat that may not necessarily result in treatment itself, though previous audits have demonstrated that 92-95% of registrations result in actual treatment (Personal Communication, Jose Dominguez-Lezcano, Internal Audit, NHS England Specialised Commissioning Finance Department). Second, this analysis only covers drugs approved for use since 2016 and does not include hormone therapies or free-of-charge drugs from companies. The majority of adjuvant and neoadjuvant treatment across solid malignancies is with conventional cytotoxic chemotherapy, which is not captured by the national registration system. Similarly, many curative treatments were established before 2016, including those for germ cell tumours, lymphoma, and acute leukaemia, so data on these treatments are not recorded. The NHS SACT registration data therefore does not represent the total change in prescribing practice for all treatments that occurred during the pandemic. Because most standard cytotoxic chemotherapies are delivered intravenously, we expect there to have been a corresponding reduction in use of these as well but we cannot quantify this. Third, the registration system does not indicate whether patients who started SACT had reduced or delayed doses in order to minimise clinic visits. Future patient-level analyses may also show how age, sex, geographical location, tumour factors and intent of therapy together influenced the start of SACT.

The therapies listed on the national SACT registration system have proven benefits for patients in terms of longer survival, and/or reduced risk of cancer progression or recurrence. Not giving or delaying these treatments by 1-2 months, particularly for advanced cancers where approved drugs may improve survival by only a few months, could have consequences for patients. Clinical outcomes such as survival need to be carefully examined in these patients over at least the next year to quantify such effects. Delays in treatment have been shown to lead to worse outcomes in some (21-23) but not all malignancies (24). Similarly, the reduction in use of neoadjuvant therapies also requires assessment as to any impact on longer term outcomes

Our study shows the consequences of NHS England offering clinicians and patients a wide range of treatment options including drugs not yet appraised by NICE or which are off-label but which are likely to result in less risk to patients from the pandemic. Early evidence shows that these additional options contributed to the greater number of registrations for new patients starting SACT in May and June 2020.

In conclusion, our study has four key messages. First, we show that at the height of the pandemic significantly fewer cancer patients started SACT than expected, but services had recovered in a short space of time (two months). Second, clinicians and healthcare providers can act quickly to provide treatment options considered to be less risky to patients but are still effective. Third, while it is important to consider a risk-benefit balance for each patient when determining the start of anti-cancer therapies, the emerging data on outcomes for patients receiving SACT who contract COVID-19 highlight the need for continued scrutiny and discussion as to the overall gains of systemic anti-cancer treatment. Fourth, it will be important to audit the outcomes of SACT on patients during the pandemic including those given the newly permitted treatment options. Many of these options were off-label and the impact of these will provide important data to healthcare providers.

**Contributors**

JJC, AH, and PC created the initial concept and study design; DD and NP were responsible for the data collection and verification of the raw data; AH and JJC performed the analyses; JJC, AH, PC and PJ interpreted the data; and JJC, DD, NP, PC, PJ and AH were involved in the manuscript writing, and decision to submit. All authors had access to the data.

**Declaration of interests**

JJC has received personal fees from Pfizer outside the submitted work. PJ reports grants from Epizyme and Janssen, personal fees from Takeda, Bristol-Myers Squibb, Novartis, Celgene, Boeringher Ingelheim, Kite Pharmaceuticals, Genmab and Incyte, outside the submitted work.

**Funding**
The work was partly supported by the Cancer Research UK trials centre core grant to University College London (reference C444/A15953).

**Data sharing**
The summated data used in the analyses are provided in the supplementary appendix. The original source data comes from the NHS England central database, which was accessed by DD and NP in their role within the Commercial Medicines Directorate, NHS England & NHS Improvement. Total numbers of registrations for the initiation of systemic anti-cancer therapies approved for use since July 2016 and funded by the Cancer Drugs Fund are published by drug, indication and month on the NHE England website (Cancer Drugs Fund page). This is done quarterly and 1 quarter in arrears. To protect patient anonymity, any registration number per month of less than 10 patients/month is shown as being "<10". Such data provision has an open government license and hence can be used for any type of analysis. Currently NHS England does not routinely publish registration data for drug indications that are routinely commissioned. Registration data for drugs funded by the Cancer Drugs Fund and by routine commissioning are subject to the rules governing Freedom of Information requests and NHS England provides such data.

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**Figures**

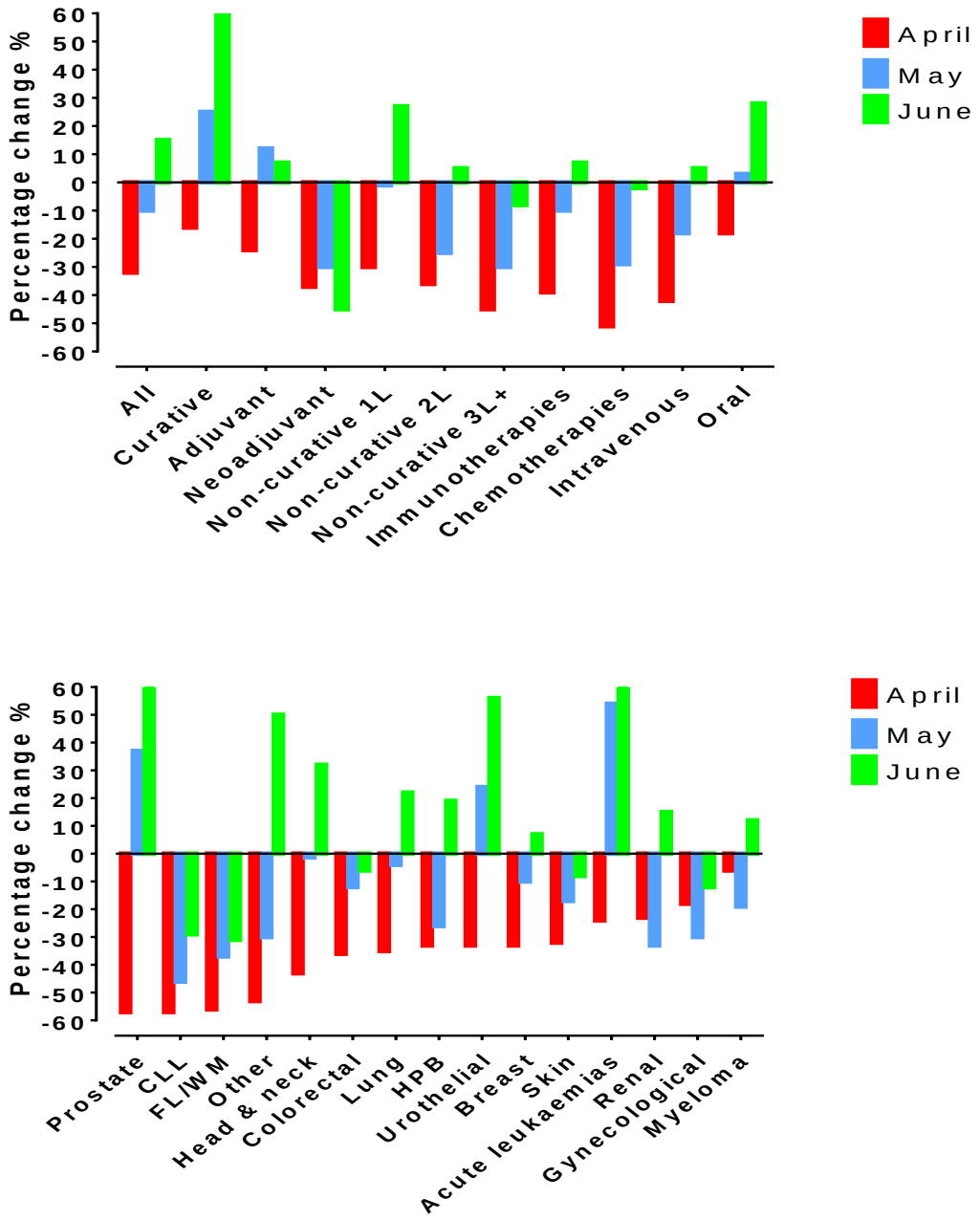


Figure 1. The relative (percentage) reductions in SACT registrations in April, May and June 2020, each compared to the mean monthly number between September 2019 and February 2020 (values in Supplementary Table 2). Figure 1A (top): according to type and line of therapy; Figure 1B (bottom) according to tumour type.

Abbreviations: 1L first line, 2L second line, 3L+ third or more line, CLL: chronic lymphocytic leukaemia, FL/WM: follicular lymphoma/Waldenstrom's macroglobulinaemia; Other: neuroendocrine tumours, thyroid, sarcoma, gastrointestinal stromal tumours, gestational trophoblastic disease and central nervous system tumours; HPB: Hepato-, pancreas and biliary tract.

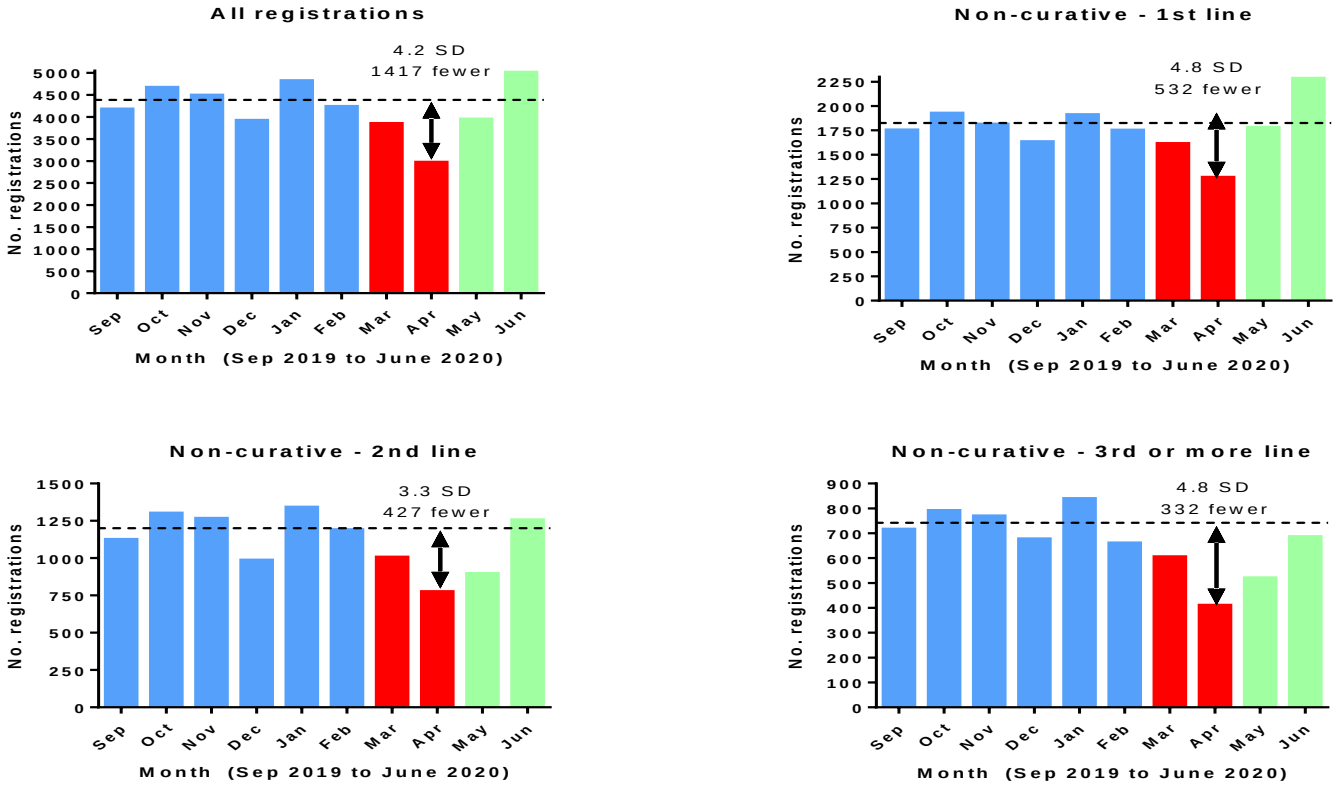


Figure 2. The number of SACT registrations observed per month, for all registrations and by line of non-curative therapy. The number seen in April 2020 is compared with the mean number between September 2019 and February 2020 (dashed horizontal line). The arrow shows the difference between April 2020 and the mean value, and also expressed as number of standard deviations (SD) from the mean. All reductions in April had $p \leq 0.0001$ (all differences and p-values for May and June are in Supplementary Table 2).

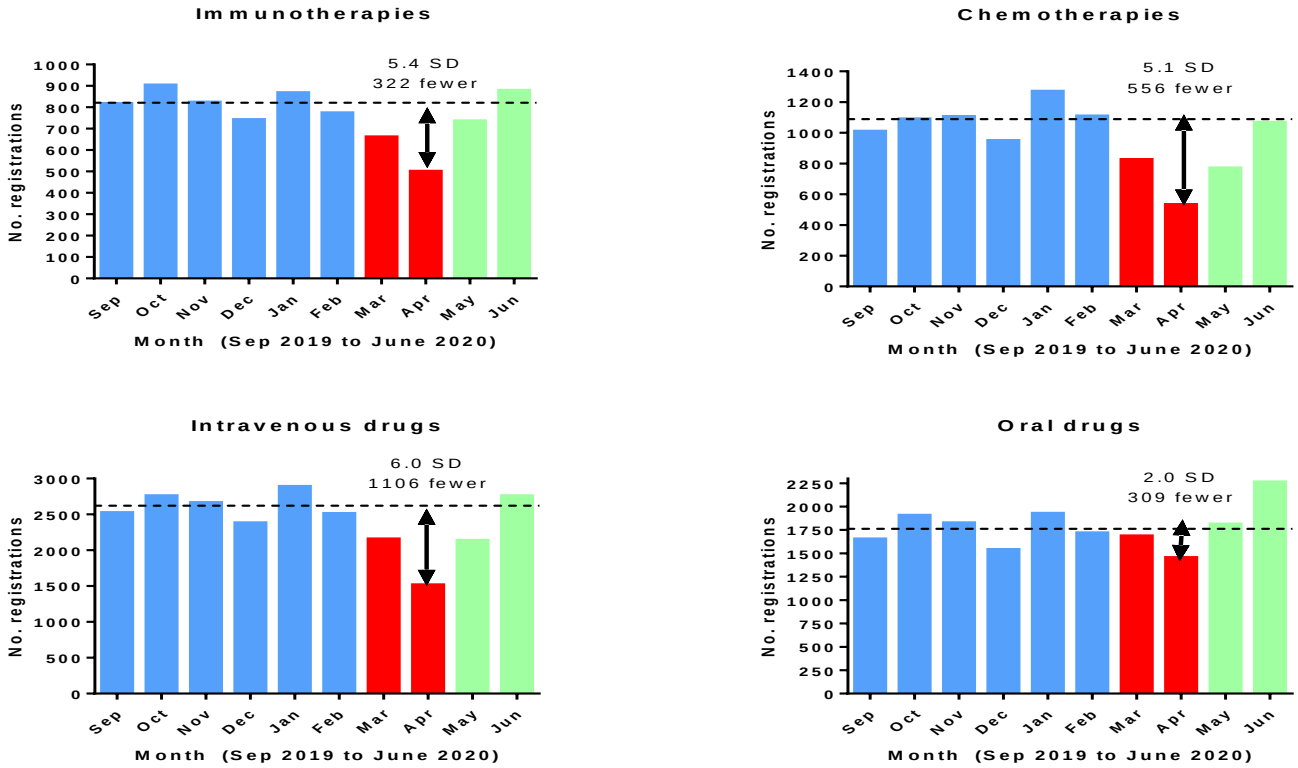


Figure 3. The number of SACT registrations observed per month, according to type of therapy. The number seen in April 2020 is compared with the mean number between September 2019 and February 2020 (dashed horizontal line). The arrow shows the difference between April 2020 and the mean value, and also expressed as number of standard deviations (SD) from the mean. All reductions in April had $p \leq 0.0001$ (all differences and p-values for May and June are in Supplementary Table 2).