**Title: Abiraterone in "High" and "Low-risk" Metastatic Hormone Sensitive Prostate Cancer.**

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**Abstract**

**Background**

Abiraterone acetate received licencing only for use in “high-risk” metastatic hormone-naïve prostate cancer (mHNPC) following the LATITUDE trial findings. However, a “risk” related effect was not seen in the STAMPEDE trial. There remains uncertainty as to whether men with LATITUDE “low-risk” M1 disease benefit from androgen deprivation therapy (ADT) combined with abiraterone acetate and prednisolone (AAP).

**Objectives**

Evaluation of heterogeneity of effect between LATITUDE “high” and “low” risk M1 prostate cancer receiving ADT+AAP in the STAMPEDE trial.

**Design, Setting and Participants**

A post-hoc subgroup analysis of the 2017 STAMPEDE “abiraterone comparison.” Staging scans for M1 patients contemporaneously randomised to ADT or ADT+AAP within the STAMPEDE trial were evaluated centrally and blind to treatment assignment. Stratification was by risk according to the criteria set out in the LATITUDE trial. An exploratory subgroup stratification incorporated the CHAARTED criteria.

**Outcome measurements**

The primary outcome measure was overall survival (OS), the secondary outcome measure failure-free survival (FFS). Further exploratory analysis evaluated clinical skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer-specific death (PCSD). Standard Cox-regression and Kaplan-Meier survival estimates were employed for analysis.

**Results and Limitations**

901 M1 STAMPEDE patients were evaluated after exclusions. 428 (48%) patients were identified as low-risk and 473 (52%) high-risk. Patients receiving ADT+AAP had significantly improved OS (low-risk HR: 0.66, 95% CI [0.44-0.98]) and FFS (low-risk HR: 0.24, 95% CI [0.17-0.33]) compared to ADT alone. Heterogeneity of effect was not seen between low and high-risk groups for OS or FFS. For OS benefit in low risk the number needed to treat was four times greater than for high risk. However, this was not observed for the other measured endpoints.

**Conclusion**

Men with mHNPC gain treatment benefit from ADT+AAP irrespective of risk stratification for “risk” or “volume”.

**Patient summary**

Co-administration of abiraterone acetate and prednisolone with androgen deprivation therapy is associated with prolonged overall survival and disease control compared to ADT alone in all men with metastatic disease starting hormone therapy for the first time.

## 1 Introduction

Two randomised controlled trials have reported survival gains for men with metastatic hormone-naïve prostate cancer (mHNPC) treated with androgen deprivation therapy (ADT) plus abiraterone acetate and prednisolone/prednisone (AAP) compared to ADT alone.[1,2] These results have established ADT+AAP as an alternative standard-of-care to ADT + docetaxel in the treatment of men with mHNPC. However, there are important differences in the design of the two trials regarding inclusion of patients based on their disease burden: LATITUDE recruited only newly-diagnosed metastatic (M1) patients with "high-risk" disease starting long term ADT for the first time, whereas STAMPEDE recruited non-metastatic (M0) and M1 patients without risk stratification. The LATITUDE trial defined high-risk disease according to a combination of poor prognostic radiological and/or pathological features. In 2018, the EMA and FDA licensed AAP for the treatment of M1 patients with "high-risk" disease only.[3,4] Uncertainty now exists regarding the treatment benefit for patients with "low-risk" M1 disease. To address this, patients in the "abiraterone comparison" of STAMPEDE underwent image-based post-hoc subset analysis, stratified retrospectively by baseline staging risk to assess whether ADT+AAP is effective in "low" as well as "high-risk" M1 disease.

## 2 Patients and methods

### 2.1 Trial design

STAMPEDE uses a multi-arm multi-stage platform (MAMS)[5] design to test multiple treatment approaches against control.[6–9] All patients relevant to this comparison were randomised to ADT+AAP (Trial arm G) or ADT alone (Trial arm A). Patients underwent baseline imaging prior to randomisation, including computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis/abdomen, and a technetium-99 bone scan before 1:1 randomisation to ADT+AAP or ADT alone.

### 2.2 Cohort selection and imaging review

Patients from the "abiraterone comparison" were excluded from this analysis only if they had incomplete information precluding classification into low or high risk. Baseline bone scintigraphic images from patients with bone metastases were reviewed centrally for risk stratification by a Urologist (AH). Quality control was by independent random sample reporting by an independent Consultant Radiologist (HD) blinded to both treatment assignment and the findings of the first investigator. A random sample of 85 patients underwent such a review. The primary and secondary scan readers were blinded to treatment allocation and outcome during all scan assessments. Providing there was sufficient concordance (>90%), the primary reader's assessments would be used.

The radiological criteria for classification into low/high-risk were based upon the LATITUDE trial because of its current influence in treatment registration in mHNPC.[1,2] This defined high-risk disease as having any 2 of: (i) ≥3 bone metastases on bone scan, (ii) Gleason sum ≥8, and (iii) any visceral metastases. The analysis was also applied to the same population stratified by volume criteria used in the CHAARTED trial, [10] defining high-volume disease as: (i) ≥4 bone metastases on bone scan, including ≥1 outside the vertebral bodies or pelvis, and/or (ii) visceral metastases.[10] The number and location of

bone metastases was recorded, then combined with documented diagnostic biopsy Gleason score and the presence of visceral metastases on CT/MRI, permitting stratification by LATITUDE and CHAARTED criteria.

### 2.3 **Statistical analyses**

The primary outcome measure was overall survival (OS), with secondary outcome, failure-free survival (FFS): this was defined as radiological, clinical or PSA progression, or death from prostate cancer as per pre-defined STAMPEDE criteria.[2] Other outcome measures evaluated were clinical skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer specific death (PCSD), defined previously.[11] Data from the published "abiraterone comparison", frozen from the trial database on 10-Feb-2017, was used for survival analyses.[2] Data lock for the retrospective scan data was 01-Aug-2018.

Prior to analysis, we pre-specified the hypothesis that there would be no difference in the treatment effect from adding AAP across the subgroups.

Kaplan-Meier (KM) methods were used to plot survival curves and Cox proportional hazard models to estimate relative treatment effects. Cox models were adjusted for randomisation stratification factors (except for randomising centre, presence or absence of metastases, type of ADT, and planned use of prostate radiotherapy) and stratified according to time periods defined by co-recruiting trial arms. Proportional-hazards assumptions were checked. A hazard ratio (HR) <1 represents evidence for ADT+AAP and HR>1 represents benefit of ADT alone. Confidence intervals (CI) are reported at 95% levels. Heterogeneity of treatment effects among M1 risk subgroups were evaluated using interaction terms in the adjusted Cox regression models. Time-to-event analyses used time from randomisation to the outcome of interest, with those not reporting the event censored at the time of last contact. Median follow-up was determined from reverse censoring from death. All analyses were performed using Stata v15 (StataCorp LP, College Station, TX, USA).

# 3 Results

## 3.1 Study cohort

Between 15-Nov-2011, and 17-Jan-2014, 990 mHNPC M1 patients were randomised to receive ADT alone or with AAP. Patients with incomplete information precluding radiological risk-based classification were excluded as follows: absent Gleason score (n=34), unobtainable bone scintigraphy (n=41), bone metastases diagnosed using non-conventional imaging (n=14). 901 mHNPC patients underwent stratification using LATITUDE risk criteria (**Figure 1**) and thereafter, CHAARTED volume criteria. Baseline characteristics by LATITUDE- and CHAARTED-defined risk/volume subgroups were balanced between the two treatment arms (**Table 1**). 428 (48%) patients were classified as low-risk by LATITUDE criteria, 402 (45%) using CHAARTED criteria. High-risk disease using LATITUDE and CHAARTED criteria was seen in 473 (52%) and 499 (55%) patients, respectively. Median follow-up of the cohort was 42 months.

## 3.2 Quality control

759 patients had bone metastases. A random sample of 85 (11%) patients from this population was included in the quality control process. Concordance between the primary and independent reviewer for the volume subgroup classification was 92% (78/85).

## 3.3 Overall survival

330/901 patients (195 ADT, 135 ADT+AAP) had died. When stratified according to LATITUDE criteria for low-risk, the ADT+AAP combination therapy demonstrated a survival advantage: (HR=0.66; 95% CI [0.44-0.98]); Absolute 3-year survival 83% ADT+AAP, 78% ADT alone (**Figure 2A).** Improvement was also seen in the high-risk disease subgroup: (HR=0.54; 95% CI [0.41-0.70]); Absolute 3-year survival 65% ADT+AAP, 45% ADT **(Figure 2B**). The heterogeneity of treatment effect between high and low-risk groups was not statistically significant (p-interaction=0.39, Figure 4), although for overall survival in low-risk, four times

more patients needed treatment (20 vs 5) to prevent one death after 3 years, compared with the high-risk group.

### 3.4 **Failure-free survival**

This population included 191 failure-free survival events with ADT+AAP and 354 with ADT-alone. An absolute improvement of 44% in 3-year FFS was observed in "low-risk" patients treated with ADT+AAP (76% ADT+AAP vs 32% ADT), (HR: 0.25; 95% CI [0.17-0.33]) (**Figure 2C**). A 33% absolute improvement in 3-year FFS was also observed in high-risk patients (45% AAP vs 12% ADT), (HR: 0.31; 95% CI [0.25-0.39]) (**Figure 2D**). There was no evidence of heterogeneity for ADT+AAP between the high and low-risk subgroups (p-interaction = 0.29) (**Figure 4**).

### 3.5 **Additional efficacy end points**

Additional efficacy measures evaluated the impact of ADT+AAP on SRE, PFS and PCSD within high and low-risk subgroups. In low-risk, a 12% absolute improvement in SRE free survival at 3-years favoured ADT+AAP treatment (91%) compared to the ADT-alone group (79%) (HR: 0.31; 95% CI [0.18-0.54]) (**Supplementary figure 1A**). A further 25% absolute improvement in low-risk 3-year PFS favoured ADT+AAP (81%) compared to ADT-alone (56%), (HR:0.33; 95%CI [0.23-0.48]) (**Supplementary figure 2A**). Furthermore, a 7% absolute reduction in PCSD at 3-years favoured ADT+AAP (89%) compared to ADT-alone (82%). The competing-risks sub-hazard ratio for PCSD in the low-risk subgroup was 0.51 (95% CI [0.31-0.84]). Similar results were found across all these three additional end points in the high-risk subgroup. (**Supplementary figures 1 to 3**). There was no evidence of heterogeneity in benefit afforded by the ADT+AAP combination between low and high-risk subgroups for SRE, PFS and PCSD (**Figure 4**).

### 3.6 **CHAARTED "volume" stratification**

An exploratory analysis was undertaken stratifying patients by disease volume on bone scan according to CHAARTED trial criteria (**Figure 5**). ADT+AAP conferred a significant improvement in survival at 3-years of 6% (83% vs 77%) compared to ADT-alone in low-volume disease (HR: 0.64; 95% CI [0.42-0.97]) **(Figure 3)**. A 42% absolute gain was also seen in 3-year FFS with ADT+AAP (74%) compared to ADT (32%) in low-volume (HR: 0.26; 95% CI [0.19-0.36]) **(Figure 3)**. No evidence of heterogeneity of effect for ADT+AAP was observed for OS (p-interaction=0.77) or FFS (p-interaction=0.47). ADT+AAP treatment advantages were consistent throughout all additional efficacy end points irrespective of volume subgroup stratification **(Figure 5).**

### 3.7 **Exploratory analysis in LATITUDE low-risk and CHAARTED low-volume**

LATITUDE and CHAARTED definitions differ, such that 18% (n=164/901) of patients identified as low-risk/volume according to one definition were stratified as high-risk/volume by the other (**Figure 1**). We therefore evaluated the efficacy of ADT+AAP in patients from lower risk/volume categories using both LATITUDE and CHAARTED definitions. In the "double-low" subgroup of 333 patients, ADT+AAP again demonstrated significant improvements in survival over ADT-alone (HR: 0.56; 95%CI [0.34-0.94]) and FFS (HR: 0.21; 95%CI [0.14-0.30]) (**Supplementary Table 1** and **Supplementary Figure 4 and Figure 5**).

### 3.8 **Sensitivity analysis of patients with de-novo metastatic disease**

The analysis of STAMPEDE patients by metastatic burden may be influenced by patients with recurrent disease following previous radical treatment. Exclusion of patients receiving prior radical therapy provided a de-novo cohort of 859 patients. The cohort was stratified according to LATITUDE risk criteria (**Supplementary Figure 6**) and secondarily by CHAARTED volume criteria (**Supplementary Figure 7**). Benefit of ADT+AAP over ADT alone was observed for all subgroups, irrespective of risk or volume

stratification throughout all endpoints. The relative hazard for survival in de-novo low-risk patients was slightly superior to the original cohort analysis (section 3.3), (HR: 0.64, 95% CI [0.42-0.97]). A similar result was seen for low-volume subgroup survival analysis, (HR: 0.60. 95% CI [0.39-0.92]).

## 4 Discussion

The results from this STAMPEDE analysis support the use of ADT+AAP in men with mHNPC irrespective of “risk” or “volume” stratifications. The ADT+AAP benefit extended throughout all measured efficacy endpoints with a clear survival advantage in the de-novo metastatic setting (HR: 0.59, 95% CI [0.47-0.74]). The survival benefit with ADT+AAP extends to the entire M1 cohort, irrespective of subgroup classification as defined by LATITUDE or CHAARTED criteria, on each of the efficacy outcome measures. There was no evidence of subgroup interaction to support preferential subgroup ADT+AAP treatment selection. However, four times the number of low-risk patients required treatment to match the OS observed in high-risk patients. The high-risk de-novo group in STAMPEDE showed a 48% relative reduction in the risk of death and a 69% relative risk reduction in treatment failure, complementing the conclusions from the LATITUDE trial.[1] However, the outcome in low-risk M1 patients had not been directly scrutinised, because such patients were not recruited in LATITUDE and “risk”/”volume” categorisation was not applied prospectively in STAMPEDE. Image analysis subsequent to the primary report of the STAMPEDE “abiraterone comparison" demonstrates a 34% lower relative risk of death and 76% lower relative risk of treatment failure in the “low-risk” subgroup. The improvement in outcome in this subgroup is comparable to that in the “high-risk” patients evaluated in the LATITUDE trial, which reported a 38% lower relative risk of death in the ADT+AAP group compared to those allocated ADT and a 53% lower relative risk of radiological progression or death respectively.[1] The advantages of ADT+AAP treatment in “low” and “high-risk” disease extend throughout all exploratory outcome measures, including reductions in SREs, PFS and PCSD. The results also show that 37% of M1 patients are identified with low-volume and low-risk mHNPC. This subgroup may potentially benefit from ADT+AAP combination therapy, yet are presently denied treatment based on the current risk-based license indications for AAP.[3,4]

There are inherent limitations to a post-hoc subgroup analysis of this type, primarily the retrospective nature of its design. Despite this, the proportion of patients with evaluable scans was large, with the additional benefit of comprehensive follow-up. The metastatic burden was evaluated using conventional, as opposed to newer imaging modalities, in concordance with previously-defined volume criteria. This radiological limitation was balanced by an understanding that the true utility of novel imaging modalities such as PSMA PET scanning remains to be determined. Consequently, such imaging modalities are not currently used widely in clinical decision making in mHNPC. The interpretation of all conventional imaging is subject to inter-observer variation. We endeavoured to minimise this by centralisation and re-analysis of all imaging independently of the main trial team. Objectivity of results was maintained using a standardised approach to radiological interpretation, blinding reviewers to the outcome of treatment and using pre-defined subgroup criteria for low-risk/low-volume as defined by other groups. The incorporation of an imaging quality control process within the study design added confidence to this centralised imaging reporting methodology. A further study limitation is reflected in the patient cohort itself. The majority of patients in our study had de-novo M1 disease. The application of our results to patients who develop M1 disease after prior local therapy will require further evaluation.

Within current international practice there is an incomplete understanding and consensus for what constitutes an optimal definition of "disease burden"[12] ; the current definitions of risk stratification are cited.[1,10,13–17] Variations in the prevalence of "low-burden" disease across these definitions can vary between 23-44%, potentially influencing volume-based treatment decisions.[18] Current definitions also fail to acknowledge the poor prognostic implication of combined bone and metastatic nodal disease.[19] Emerging exploratory analysis within oligometastatic HNPC patients treated with prostatic radiotherapy suggests that nodal and/or <4 bone metastases stratifies patients with the greatest accuracy.[20]

Accepting these limitations, we incorporated subgroup radiological stratification according to LATITUDE and CHAARTED trial definitions because of their current clinical influence in guiding ADT+AAP and docetaxel treatment in mHNPC. The consistency of ADT+AAP benefit between the two stratified subgroup criteria limits bias associated with conclusions drawn from a single stratified definition. Scrutinising the magnitude of stratified subgroup discrepancy between the LATITUDE and CHAARTED criteria revealed stratification mismatch in 18% of the trial cohort. Despite this, even when only patients with low-risk and low-volume criteria using both definitions were considered, there was significant evidence of improved OS and FFS in patients treated with ADT+AAP. International guidance should now be re-evaluated to consider altering the licenced indications to include the use of ADT+AAP in M1 patients irrespective of radiological disease burden as an alternative to ADT+docetaxel. [21–23]

The treatment landscape for "low-burden" (oligometastatic) mHNPC is undergoing rapid evolution following presentation of this data and that presented in the STAMPEDE M1 radiotherapy comparison. [24] The latter demonstrated a 32% relative reduction in risk of death (HR: 0.68, 95% CI [0.52-0.90]) in oligometastatic patients. Current speculation relating to the low-burden benefit of docetaxel in this setting will be addressed following release of the STAMPEDE docetaxel long term data analysis in 2019. In future, the benefit of combining focal and systemic therapy for low-burden mHNPC requires clarity and will be addressed by the PEACE 1 trial (NCT01957436) and future STAMPEDE-based study. Metastasis directed therapy (MDT) may also provide further disease control benefits as recently demonstrated, but this requires clarification in light of developments in adjuvant therapies and novel imaging. [25]

## 5 Conclusions

Men with mHNPC benefit from ADT+AAP whether they have LATITUDE low/high risk or CHAARTED low/high volume categorisation. The license indications for the use of this combination treatment irrespective of “risk” or “volume” classification should now be reconsidered.

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**Table and figure legends**

**Table 1 –** Baseline patient characteristics of 901 M1 patients included and defined for LATITUDE risk and CHAARTED volume criteria

**Figure 1 –** Consort diagram showing the UK M1 study cohort selection for metastatic volume stratification using CHAARTED and LATITUDE definitions. Two by two table shows matched and unmatched proportions of high and low-volume/risk patients using the LATITUDE and CHAARTED definitions. Percentages in brackets are based on the whole study population (n=901).

**Figure 2** – Kaplan-Meier curves according to M1 risk stratification using LATITUDE criteria for overall survival (OS) (A: Low-risk, B: High-risk) and failure free survival (FFS) (C: Low-risk, D: High-risk).

**Figure 3 –** Kaplan-Meier curves according to M1 volume stratification using CHAARTED criteria for overall survival (OS) (A: Low-volume, B: High-volume) and failure free survival (FFS) (C: Low-volume, D: High-volume).

**Figure 4 –** Forest plot of hazard ratios (HR) for AAP from adjusted Cox models on overall survival (OS), failure-free survival (FFS), skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer specific death (PCSD) within LATITUDE low and high-risk subgroups.

**Figure 5** – Forest plot of hazard ratios (HR) for AAP from adjusted Cox models on overall survival (OS), failure-free survival (FFS), skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer specific death (PCSD) within CHAARTED low and high-volume subgroups.

**Supplementary figures and tables**

**Supp Figure 1 –**Kaplan-Meier curves of skeletal-related events (SRE) according to M1 risk/volume stratification using the LATITUDE (A: Low-risk, B: High-risk) and the CHAARTED (C: Low-volume, D: High-volume) definitions.

**Supp Figure 2 –** Kaplan-Meier curves of progression-free survival (PFS) according to M1 risk/volume stratification using the LATITUDE (A: Low-risk, B: High-risk) and the CHAARTED (C: Low-volume, D: High-volume) definitions.

**Supp Figure 3 –** Kaplan-Meier curves for prostate cancer specific death (PCSD) according to M1 risk/volume stratification using the LATITUDE (A: Low-risk, B: High-risk) and the CHAARTED (C: Low-volume, D: High-volume) definitions.

**Supp Figure 4 –** Kaplan-Meier curves of overall survival (OS) for patients classified as (A) LATITUDE low-risk and CHAARTED low-volume, (B) LATITUDE low-risk and CHAARTED high-volume, (C) LATITUDE high-risk and CHAARTED low-volume, and (D) LATITUDE high-risk and CHAARTED high-volume.

**Supp Figure 5 –** Kaplan-Meier curves of failure-free survival (FFS) for patients classified as (A) LATITUDE low-risk and CHAARTED low-volume, (B) LATITUDE low-risk and CHAARTED high-volume, (C) LATITUDE high-risk and CHAARTED low-volume, and (D) LATITUDE high-risk and CHAARTED high-volume.

**Supp Figure 6 – "Sensitivity Analysis"** Forest plot of hazard ratios (HR) for "de-novo" AAP from adjusted Cox models on overall survival (OS), failure-free survival (FFS), skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer specific death (PCSD) within LATITUDE stratified low and high-risk subgroups.

**Supp Figure 7 – "Sensitivity Analysis"** Forest plot of hazard ratios (HR) for de-novo AAP from adjusted Cox models on overall survival (OS), failure-free survival (FFS), skeletal-related events (SRE), progression-free survival (PFS) and prostate cancer specific death (PCSD) within Chaarted low and high-risk subgroups.

**Supp Table 1 -** Overall and failure-free survival outcomes of LATITUDE and CHAARTED high and low-risk or volume matched and mismatched patients.

**The STAMPEDE Investigators include the following:**

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**Trial Steering Committee:** James Larkin (chair), Jan Erik Damber, Alan Horwich, Tim Clayton; *Previous* --- Jonathan Ledermann, John Fitzpatrick, David Kirk, Jim Paul, Richard Emsley

***:: Participating Site List***

**Structure: City, Hospital** (M patients during recruitment window: Recruiting investigators)

**United Kingdom**

- **Addenbrookes Hospital** (D Mazhar)
- **Ashford William Harvey Hospital** (C Thomas; N Mithal; A Edwards)
- **Aylesbury, Stoke Mandeville Hospital** (T Pwint; P Camilleri)
- **Ayr Hospital** (H Glen; J Ansari)
- **Barnet General Hospital** (U McGovern; A Eichholz)
- **Basingstoke & N Hampshire Hospital** (R Shaffer)
- **Bath, Royal united Hospital** (O Frim; M Beresford, P Kehagioglou)
- **Belfast City** (J O'Sullivan; D Mitchell, S Jain, PL Shum)
- **Birmingham, City Hospital** (D Ford)
- **Birmingham, Good Hope Hospital** (D Ford)
- **Birmingham, Heartlands Hospital** (A Zarkar)
- **Birmingham, QE** (N James)
- **Blackburn East Lancashire Trust** (O Parikh; N Charnley)

- **Bolton, Royal Bolton Hospital** (T Elliott)
- **Boston, Pilgrim Hospital** (M Panades; D Ballesteros-Quintail)
- **Bournemouth, Royal Bournemouth Hospital** (S Brock)
- **Bradford Royal Infirmary** (S Brown)
- **Brighton, Royal Sussex County Hospital** (A Robinson; G Plantaniotis)
- **Bristol H & O Centre** (A Bahl; C Herbert; S Masson)
- **Burton, Queen's Hospital** (M Smith-Howell; S Chetiyawardana; P Pattu)
- **Bury St Edmunds, West Suffolk Hospital** (C Woodward; Y Rimmer)
- **Cardiff, Velindre** (J Lester; J Staffurth, J Barber, S Kumar, N Palaniappan, M Button, J Tanguay)
- **Chelmsford, Broomfield Hospital** (A Hamid)
- **Cheltenham General Hospital** (J Bowen; S Jonnada, P Jenkins)
- **Chester, Countess of Chester Hospital** (A Ibrahim)
- **Coventry & Warwickshire, University Hospital** (J Worlding; A Stockdale)
- **Crewe, Leighton Hospital** (J Wylie)
- **Cumbria, Cumberland Infirmary** (A Kumar)
- **Darlington Memorial Hospital** (M Kagzi; J Hardman, C Peedell)
- **Derby, Royal Derby Hospital** (P Chakraborti)
- **Devon, North Devon District Hospital** (D Sheehan; P Stephens)
- **Doncaster Royal Infirmary** (V Sivoglo; C Ferguson, M Alzouebi)
- **Dorset County Hospital** (P Crellin)
- **Dudley, Russells Hall Hospital** (P Keng-Koh; S Tirmazy)
- **Eastbourne District General Hospital** (F McKinna)
- **Edinburgh, Western General** (D McLaren)
- **Essex County Hospital** (D Muthukumar; B Sizer, M Kumar)

- **Exeter, RD&E** (D Sheehan; R Srinivasan, V Ford)
- **Gillingham, Medway Hospital** (H Taylor)
- **Glangwili General Hospital** (MD Phan)
- **Glasgow, BOC** (B Venugopal; J Wallace, R Jones, C Lamb)
- **Guildford, Royal Surrey County Hospital** (R Laing; S Khaksar, K Wood, J Money-Kyrle)
- **Harlow, Princess Alexandra Hospital** (N Gupta; L Melcher)
- **Hereford County Hospital** (W Grant; A Cook)
- **Huddersfield Royal Infirmary** (U Hofmann)
- **Hull, Castle Hill Hospital** (M Simms; J Hetherington)
- **Inverness, Raigmore Hospital** (N McPhail; C MacGregor)
- **Ipswich Hospital** (R Venkitaraman; C Scrase)
- **Keighley, Airedale Hospital** (S Brown)
- **Kent and Canterbury Hospital** (C Thomas; R Raman, N Mithal)
- **Kent, QE Q Mother Hospital** (R Raman)
- **Kidderminster General Hospital** (L Capaldi; M Churn)
- **Larbert, Forth Valley Royal Hospital** (N Sidek)
- **Leeds, St James University Hospital** (W Cross; C Loughrey, S Jagdev, A Henry, D Bottomley, S Prescott, A Paul)
- **Lincoln County Hospital** (T Sreenivasan; D Ballesteros-Quintail, M Panades)
- **Liverpool, Royal Liv University Hospital** (Z Malik; C Eswar)
- **Liverpool, UH Aintree** (P Robson)
- **London, Charing Cross Hospital** (A Falconer; S Mangar)
- **London, Guy's Hospital** (S Chowdhury; S Morris)
- **London, N Middlesex Hospital** (J Newby; A Thompson, L Melcher, M Singhera)

- **London, Royal Free Hospital** (M Vilarino-Varela; K Pigott; N Rosenfelder)
- **London, St Bartholomew's Hospital** (P Wells; K Tipples)
- **London, St Georges Hospital** (L Pickering)
- **London, UCH** (U McGovern; H Payne)
- **Maidstone, Kent Oncology Centre** (H Taylor; K Lees, A Clarke, S Beesley)
- **Manchester Christie Hospital** (N Clarke; T Elliott, J Livsey, J Wylie, R Conroy, A Choudhury, A Tran, J Logue)
- **Manchester, Royal Oldham Hospital** (J Livsey; A Choudhury)
- **Manchester, Salford Royal Hospital** (N Clarke; T Elliot)
- **Middlesbrough, James Cook UH** (C Peedell; H Van der Voet, J Hardman)
- **Newcastle, Freeman Hospital** (A Azzabi; R McMenemin, J Frew)
- **North Staffordshire UH** (F Adab; S Vengalil, R Bhana)
- **Northwood, Mount Vernon Hospital** (P Hoskin; P Ostler, R Alonzi, C Westbury, R Hughes, N Anyamene)
- **Nottingham University Hospitals** (City Campus) (S Sundar; J Mills, G Walker, E Chadwick)
- **Nuneaton, George Eliot Hospital** (A Chan)
- **Oxford, Churchill Hospital** (A Protheroe; D Cole, A Sabharwal, M Tuthill)
- **Poole Hospital** (J Davies)
- **Portsmouth, Q Alexandra Hospital** (J Gale)
- **Preston, Royal Preston Hospital** (A Birtle; O Parikh, M Wise, N Charnley)
- **Reading, Royal Berkshire Hospital** (P Rogers; H O'Donnell)
- **Redditch, Alexandra Hospital** (B Kurec; J Hamilton)
- **Romford, Queen's Hospital** (S Gibbs; K Tarver)
- **Royal Hampshire Hospital** (S Paisey)

- **Scarborough General Hospital** (M Hingorani)
- **Sheffield, Weston Park** (C Ferguson; O Din, M Alzouebi, L Evans, T Das)
- **Shrewsbury, Royal Shrewsbury Hospital** (N Srihari; R Prashant)
- **Somerset, Weston General Hospital** (S Hilman)
- **Southampton General Hospital** (C Heath; M Wheater, S Crabb)
- **Southend University Hospital** (D Tsang; I Ahmed, O Chan)
- **Southport and Formby District GH** (N Bhalla)
- **St Leonards-on-Sea, Conquest Hospital** (F McKinna; K Lees)
- **Stevenage, Lister Hospital** (R Hughes)
- **Stockport, Stepping Hill Hospital** (J Logue; C Coyle)
- **Stockton-on-Tees, UH North Tees** (D Leaning; D Shakespeare)
- **Sunderland Royal Hospital** (A Azzabi; I Pedley, S Iqbal)
- **Sutton-in-Ashford, King's Mill Hospital** (D Saunders; G Walker)
- **Sutton-London, RMH** (D Dearnaley; N Van As, C Parker, V Khoo)
- **Swansea, Singleton** (D Pudney; J Wagstaff, MD Phan)
- **Swindon, Great Western Hospital** (O Khan; D Cole)
- **Taunton, Musgrove Park Hospital** (E Gray; J Graham, M Varughese)
- **Torbay District General Hospital** (A Lydon; R Srinivasan)
- **Tyne & Wear, S Tyneside District Hospital** (A Azzabi)
- **Warrington Hospital** (I Syndikus; S Tolan)
- **Warwick Hospital** (A Stockdale)
- **Wigan, Royal Albert Edward Infirmary** (A Tran)
- **Wirral, Clatterbridge Centre for Oncology** (S Tolan; I Syndikus, N Bhalla, A Ibrahim, A Montazeri, J Littler)

- **Wolverhampton, New Cross Hospital** (S Tirmazy; I Sayers)
- **Woolwich, QE Hospital** (S Hughes)
- **Worcestershire Royal Hospital** (L Capaldi; J Bowen)
- **Worthing Hospital** (A Nikapota; G Plataniotis)
- **Wycombe Hospital** (P Camilleri; A Sabharwal, T Pwint, G Andrade)
- **Yeovil District Hospital** (E Gray; G Sparrow)
- **York Teaching Hospital** (J Joseph; D Bottomley)

**Switzerland**

- **Basel Universitatsspital** (C Rentsch)
- **Berne University Hospital** (Inselspital) (G Thalmann)
- **Chur Kantonsspital Graubunden** (R Strebel; R Cathomas)
- **Istituto Oncologico della Svizzera Italiana** (E Roggero)
- **Kantonsspital St Gallen** (D Engeler)
- **Lausanne,Centre Hospital Univ Vaudois** (3: D Berthold)

Plus more than 3,000 local site team staff across these hospitals.

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