haematologica
Journal of The Ferrata Storti Foundation

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Received: April 28, 2022.
Accepted: August 17, 2022.

Citation: Samir Asher, Aikaterini Kazantzi, Fatjon Dekaj, Luke Steventon, Aisha Khatun, Louise Ainley, Annabel McMillan, Neil Rabin, Ashu Wechalekar, Jonathan Sive, Charalampia Kyriakou, Xenofon Papanikolaou, Ke Xu, Shameem Mahmood, Brendan Wisniowski, Lydia Lee, Kwee Yong, and Rakesh Popat. Under-representation of ethnic minorities in early phase clinical trials for multiple myeloma.
Haematologica. 2022 Aug 25. doi: 10.3324/haematol.2022.281322 [Epub ahead of print]

Under-representation of ethnic minorities in early phase clinical trials for multiple myeloma

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Disclosures: No authors disclose any conflicts of interest

Acknowledgements: RP and KY are supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Contributions: SA, AK, FD, LS and AK performed research. SA performed data analysis. SA and RP wrote the manuscript.

Data sharing statement: Original data can be made available through direct contact with the corresponding author.

Differences in outcomes and access to clinical trials for patients with multiple myeloma (MM) from ethnic minorities have been previously reported predominantly from the United States of America (US). [1-5] This study investigated if disparities by ethnicity existed for MM patients enrolled onto clinical trials at a state-funded UK National Health Service (NHS) haematology specialist-centre. Retrospective data compared clinical trial enrolment to standard of care (SOC) outpatient clinic cohorts and the expected incidence of MM. Overall, non-White groups had lower representation in early phase clinical trials than expected by overall incidence and distribution within SOC clinics.

MM is an incurable haematological malignancy with approximately 6000 new UK cases per year and a projected rise in incidence of 11% by 2035.[1,2] Black patients have a higher prevalence of MM than White and Asian patients (per 100,000: White males: 6.1-6.5; Asian males: 3.6-6.4; Black males: 10.9-18.2).[3,4]

Population-based studies have reported that disease-specific survival outcomes for Black compared to White MM patients in the US can be equivalent or potentially better with equivalent availability of healthcare. [5,6] Biological differences including genetic events between ethnicity have been identified; however whilst they maybe associated with differences in survival, this has not been conclusively determined. [7,8] The odds ratio in the US for receiving an autologous stem cell transplant (SCT) was higher for White than Black MM patients despite SCTs being beneficial for both groups.[9,10] When controlling for overall health and potential access barriers including socioeconomic status, Black patients were 37% less likely to undergo an SCT.[11] Lower enrolment of ethnic minority patients have also been demonstrated across clinical trials in the US, likely due to socioeconomic and cultural reasons.[12,13] Given the increased incidence of MM in the Black population and underlying biological differences, such disparities may limit the applicability of trial results to real-world populations and limit survival gains for the communities not enrolled.

To investigate if disparities in trial enrolment and SCT existed in the UK, we conducted a retrospective study from electronic health records at University College Hospital, London. MM patients enrolled into sequential clinical trials between 2014-2021 were grouped as early (phase I, phase I/II) or late phase (phase II, phase III). Trial enrolment was compared with patients attending SOC MM clinics from May-August 2019 and November-December 2020, and the prevalence of MM in England and London according to the National Cancer Registration and Analysis Service (NCRAS) between 2006-2015[14]. Self-reported ethnicity was categorised to White, Black, Asian and Mixed/other according to the Office for National Statistics *(supplementary data 1)*.[15] Analysis of "Non-White" included Black, Asian and Mixed/other groups. High risk (HR) fluorescence in situ hybridization (FISH) was defined as having one or more of 17p deletion, t(4;14), t(14;16), t(14;20).

ANOVA, Mann-Whitney, Fisher's exact test, Kaplan Meier analysis were performed (GraphPad Prism v9.0).

The clinical trial cohort included 197 MM patients enrolled from 25 trials (57 (28.9%) early phase, 140 (71.1%) late phase). Median age was 62 years (range 38-85) with a median of 5 prior lines of therapy (range 0-13; early phase, 4 (2-13); late phase, 2 (0-8)). Ethnic grouping was: White, 143 (72.6%); Black 23 (11.7%); Asian, 8 (4.1%); Mixed/other 7 (3.6%); unknown 15 (7.6%) giving a Black:White ratio of 0.16. This skewing was more marked for early (Black:White 0.10) than late phase trials (Black:White 0.19) (*Table 1*). Ethnic distribution was variable across age (p=0.027) with Black patients having a lower median age compared to White patients at trial enrolment (59 vs 66 years; p=0.015). This was not significant for Asian (61.5 years; p=0.13) or Mixed/other groups (71 years; p=0.97). There was no difference between ethnicity and number of prior lines (p=0.51). Of the 173 patients with FISH results, 20.8% were HR. This was not significant between early and late phase sub-groups (p=0.68). No significant difference was seen in HR FISH between White and Black patients (p=0.41) and White and non-White patients (p=0.64). When analysing each individual HR lesion, no difference was identified between White and Black (del(17p) 18 vs 2, p=0.74; t(4;14) 11 vs 2, p>0.99) and White and non-White patients (del(17p) 18 vs 6, p>0.99; t(4;14) 11 vs 2, p=0.52). As with other studies, there were increased numbers of t(11;14) in Black compared to White patients (29.2% vs 14.2%) although not statistically significant (p=0.079).[7] There was no significant difference in median overall survival (OS) between ethnic groups (p=0.93); White, 10.9 years; Black 11.8 years; Asian 15.1 years; Mixed/other 13.5 years with a median follow-up of 7.6 years.

The SOC cohort comprised of 362 patients with a median age of 65 years (range 33-90) and had received a median of 2 prior lines (range 0-10). Ethnic grouping was: White, 243 (67.1%); Black, 54 (14.9%); Asian, 31 (8.6%); Mixed/other 27 (7.5%); unknown 7 (2.9%) giving a Black:White ratio of 0.22. White patients were older compared to other ethnic groups (White, 66.5 years; Black, 61.0 years; Asian 60.0 years, Mixed/other, 60.0 years; p=0.008). Ethnicity did not vary by prior lines of therapy (p=0.20). OS was similar across all ethnic groups (median OS: White, not reached; Black not reached; Asian 11.8 years; Mixed/other not reached).

MM prevalence by ethnicity was reported by NCRAS from 17,618 patients across England and 2,618 patients within London. In London ethnicity was: White 1510 (57.7%); Black 618 (23.6%); Asian 318 (12.1%); Mixed/other 172 (6.57%). The Black:White ratio in England and London was 0.06 and 0.41 respectively.[14]

Non-White patients were underrepresented in the trials cohort compared to SOC (p=0.01). This difference was more significant when comparing early phase trials to SOC (p=0.003). No difference

however was seen between White and non-White patients in late phase trials compared to SOC (p=0.17) (*Figure 1).* Comparing the prevalence of MM in London to trial enrolment, lower proportions of non-White to White patients were enrolled into early phase trials (p<0.0001). This was not significant for late phase trials (p=0.24) *(Figure 2).* Black patients were underrepresented in early phase trials compared to non-Black patients (p=0.012), not reflected in late phase trials (p=0.064), *(Figure 3).* No significant differences were seen in enrolment of White and Asian or Mixed/other groups vs MM prevalence in London.

365 patients in both the trial and SOC clinic cohorts received prior SCT. Ethnic grouping was: White 270 (74.0%); Black 36 (9.9%); Asian 32 (8.8%); Mixed/other 16 (4.4%); unknown 11 (3.0%). White patients were more likely to have received a SCT compared to non-White (p<0.03), Black (p=0.01) and Mixed/Other (p=0.01) patients. There was no significant difference between White vs Asian (p=0.14) patients receiving a SCT. Black and Asian patients who underwent ASCT were younger than White patients (median age 59 years; p=0.0002 and 59 years; p=0.001 vs 65 years respectively).

Whilst there is evidence discrepancies in clinical trial enrolment exist within the US, limited data exists from other countries, particularly those with state-funded healthcare systems. This UK dataset demonstrates that ethnic disparity in clinical trial participation persists despite equal healthcare availability particularly for early phase trials, where there were differences compared to the expected prevalence of MM and the population seen in SOC clinics. These differences were predominantly observed for Black patients rather than the other minorities. Several reasons have been proposed for this including socio-economic class, mistrust/previous negative experiences with healthcare professionals (HCP) or healthcare systems, lack of culturally appropriate communication and a discrepancy between the ethnicity of HCPs compared to patients. Co-morbidities may vary between ethnicities although not assessed in this analysis. There may be biological factors such as a higher burden of comorbidities preventing trial eligibility [5,6,8-11,13]. These factors may be more apparent when experimental early phase trials with an intense treatment schedule are offered compared to a phase 3 trial that may more closely resemble SOC. In addition, patients for early phase trials were referred from a wider geography to those entering late phase trials, indicating potential selection bias at local centres. Despite differences in enrolment, there were no differences in OS observed by ethnicity in either the trial or SOC cohorts suggesting that different ethnic groups can do equally well. The lower proportion of Black patients undergoing SCT requires further investigation.

Whilst this study provides insight to the ethnic distribution of patients at an academic MM centre, there may be selection bias of the population treated due to its location versus other geographies.

Given London is one of the most ethnically diverse cities in the UK, higher proportions of minorities were expected to be enrolled. Data reported from the trial, SOC and NCRAS cohorts have been collected at different timepoints and should be considered when comparing population groups. The numbers of Asian and Mixed/other were small which limits further analysis and national or multi-national datasets are required to fully understand these.

Further studies are required to understand and mitigate financial, cultural and religious barriers influencing trial recruitment. Additionally, study design and eligibility criteria e.g., taking into consideration racial neutropenia should also be reassessed to be more inclusive of the wider population.

In conclusion, this data highlights disparities in trial enrolment of ethnic minorities exist in state funded healthcare systems and recommends further work to resolve this.

References

1. Cancer Research UK. 2018. *Myeloma statistics*. [online] Available at: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero> [Accessed 12 October 2021].

2. Becker N. Epidemiology of multiple myeloma. Recent Results Cancer Res. 2011;183:25-35.

3. Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. Leukemia. 2012;26(4):609-614.

4. National Cancer Intelligence Network and Cancer Research UK. Cancer Incidence and Survival by Major Ethnic Group, England, 2002-2006. [online] Available at: <www.ncin.org.uk/piblications/reports> [Accessed 12 October 2021]

5. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood. 2010;116(25):5501-5506.

6. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. 2017;1(4):282-287.

7. Baker A, Braggio E, Jacobus S, et al. Uncovering the biology of multiple myeloma among African Americans: a comprehensive genomics approach. Blood. 2013;121(16):3147-3152.

8. Manojlovic Z, Christofferson A, Liang WS, et al. Comprehensive molecular profiling of 718 Multiple Myelomas reveals significant differences in mutation frequencies between African and European descent cases. PLoS Genet. 2017;13(11):e1007087.

9. Joshua TV, Rizzo JD, Zhang MJ, et al. Access to hematopoietic stem cell transplantation. Cancer. 2010;116(14):3469-3476.

10. Hari PN, Majhail NS, Zhang MJ, et al. Race and outcomes of autologous hematopoietic cell trans-plantation for multiple myeloma. Biol Blood Marrow Transplant. 2010;16(3):395-402.

11. Fiala, M.A., Wildes, T.M. Racial disparities in treatment use for multiple myeloma. Cancer. 2017;123(9):1590-1596.

12. Duma N, Azam T, Riaz IB, Gonzalez-Velez M, Ailawadhi S, Go R. Representation of Minorities and Elderly Patients in Multiple Myeloma Clinical Trials. Oncologist. 2018;23(9):1076-1078.

13. Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. Leuk Lymphoma. 2016;57(12):2827-2832.

14. National cancer registration and analysis service (ncras). Haematological Cancers . [Online]. Available from: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/haematological_cancers/ [Accessed 27 May 2021]

15. Ethnic group, national identity and religion. Ethnic group, national identity and religion - Office for National Statistics. [Online]. Available from: https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion [Accessed 24 January 2022]

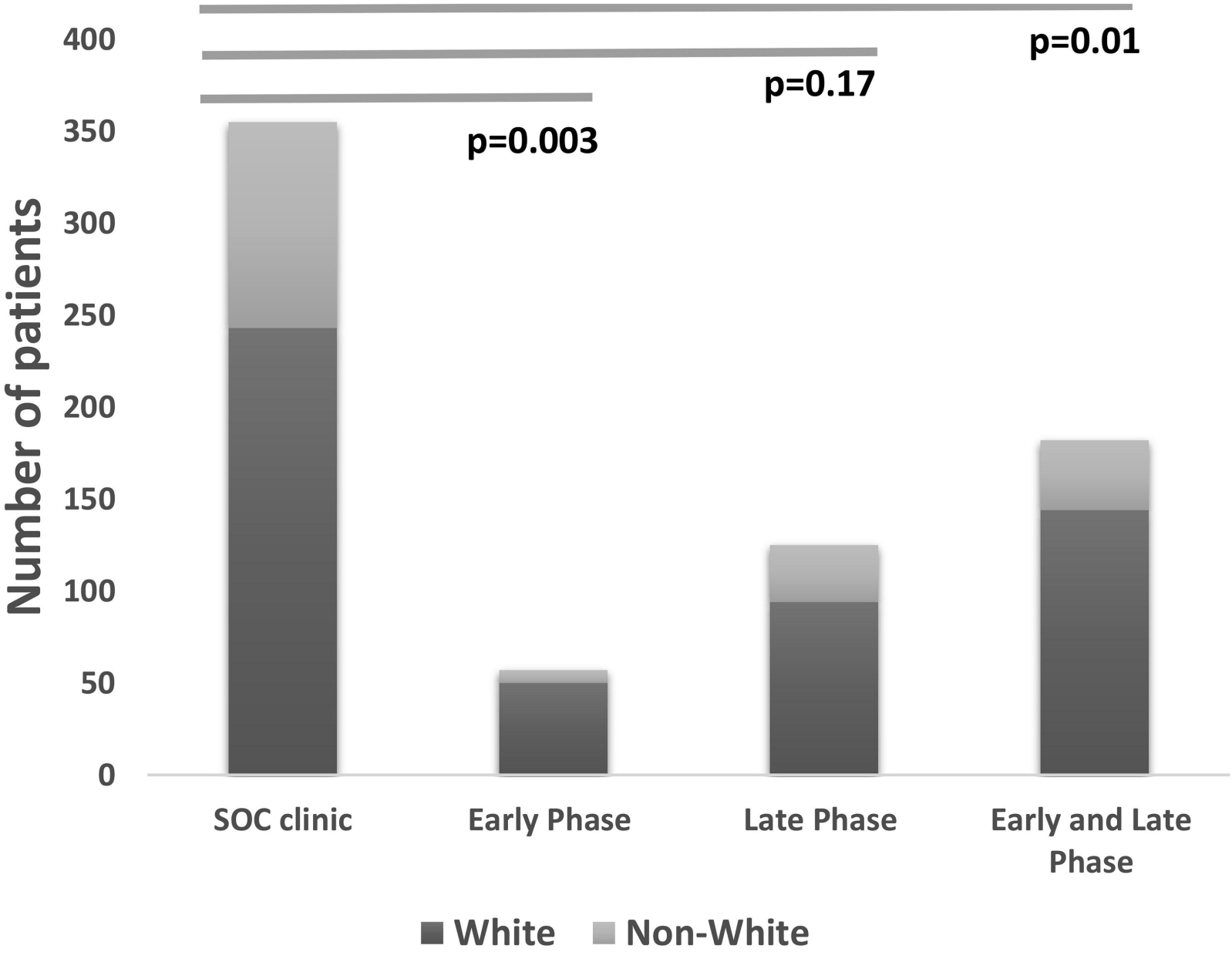
Table 1: Patient characteristics

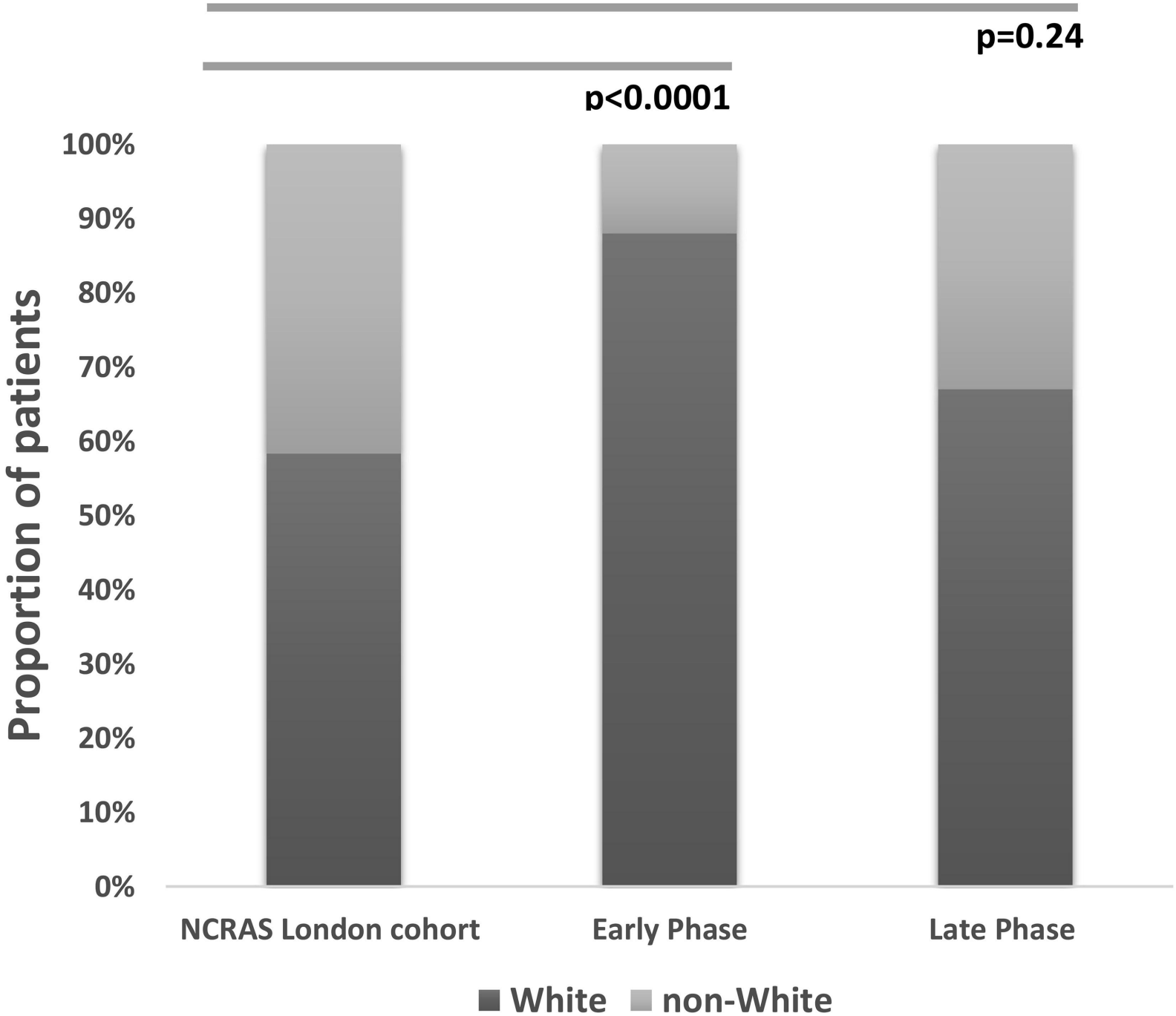
	Trial	EP Trial	LP Trial	SOC clinic
Characteristics				
Patients				
All	197	57	140	362
Sex				
Male	105	34	79	201
Female	77	23	61	161
Ethnicity				
White	144	50	94	243
Black	23	5	18	54
Asian	8	<5	6	31
Mixed/Other	7	<5	7	27
Unknown	15	<5	15	7
Median age				
All	67.5	59.5	65	65
White	66	65	66	66.5
Black	59	65	59	61
Asian	61.5	65.5	59	60
Mixed/Other	71	N/A	71	60
Unknown	61.5	N/A	61.5	65.5
Median lines of Rx				
All	4	3	1	2
White	4	7	3	2
Black	4	8	2	2
Asian	2	7	1	3
Mixed/Other	1	N/A	1	2
Unknown	1	N/A	1	1
Cytogenetics available				
All	173	51	122	
White	125	44	81	
Black	23	5	18	
Asian	6	<5	<5	
Mixed/Other	7	N/A	7	
Unknown	12	N/A	12	
HR cytogenetics				
All	36	12	47	
White	28	11	17	
Black	<5	<5	<5	
Asian	<5	<5	<5	
Mixed/Other	<5	N/A	<5	
Unknown	<5	N/A	<5	

Trial: Refers to all patients enrolled onto trials; EP: early phase; LP: late phase; SOC: standard of care; HR: high risk

Figure 1: Lower proportions of non-White patients enrolled into clinical trials, and more significant for early phase trials, compared to standard of care (SOC) clinic cohort

Figure 2: Lower proportions of non-White patients enrolled into early phase clinical trials compared to NCRAS London cohort


p=0.01
p=0.17
p=0.003
400
350
300
250
200
150
100
50
0
Number of patients
SOC clinic
Early Phase
Late Phase
Early and Late Phase
White
Non-White


p=0.24
p<0.0001
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Proportion of patients
NCRAS London cohort
Early Phase
Late Phase
White
non-White

Supplementary Data 1:

Ethnicity classification

Recorded ethnicity	**Sub-classification**
White British	White
White Irish	
Other White Background	
Black African	Black
Black Caribbean	
Other Black Background	
Asian Indian	Asian
Asian Pakistani	
Asian Bangladeshi	
Chinese	
Other Asian Background	
Mixed White and Asian	Mixed/Other
Mixed White and Black African	
Mixed White and Black Caribbean	
Other Mixed Background	
Other Ethnic Background	
Not stated/Unknown	Unknown
Not yet asked	
Refused to give	