

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

Differences in outcomes and access to clinical trials for patients with multiple myeloma (MM) from ethnic minorities have been previously reported predominantly from the 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) hematology specialist-center. Retrospective data compared clinical trial enrollment 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 hematological malignancy with approximately 6,000 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 may be 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 SCT 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 enrollment 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.

In order to investigate if disparities in trial enrollment 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 enrollment 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 categorized to White, Black, Asian and Mixed/other according to the Office for National Statistics (*Online Supplementary Table S1*).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 five 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 seven (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 analyzing 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 two 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 seven (2.9%) giving a Black:White ratio of 0.22. White patients were older com-

Table 1. Patient characteristics.

Characteristics	Trial	EP Trial	LP Trial	SOC clinic
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; Rx: race.

pared 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 1,510 (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 enrollment, 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 ($P=0.064$). No significant differences were seen in enrollment of White and Asian or Mixed/other groups *versus* MM prevalence in London.

Three hundred and sixty-five patients in both the trial and

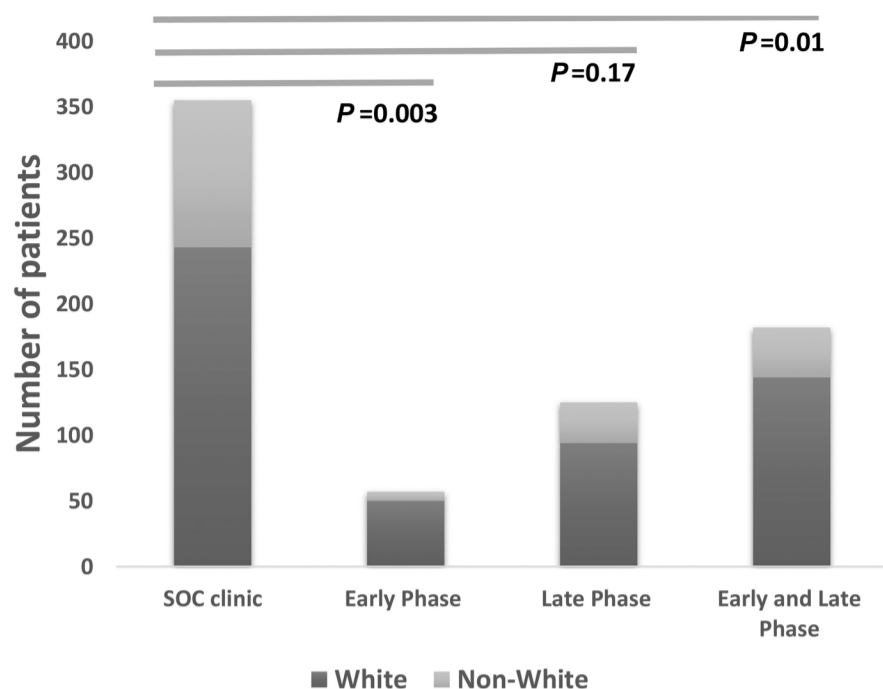


Figure 1. Lower proportions of non-White patients enrolled into clinical trials, and more significant for early phase trials, compared to standard of care clinic cohort. SOC: standard of care.

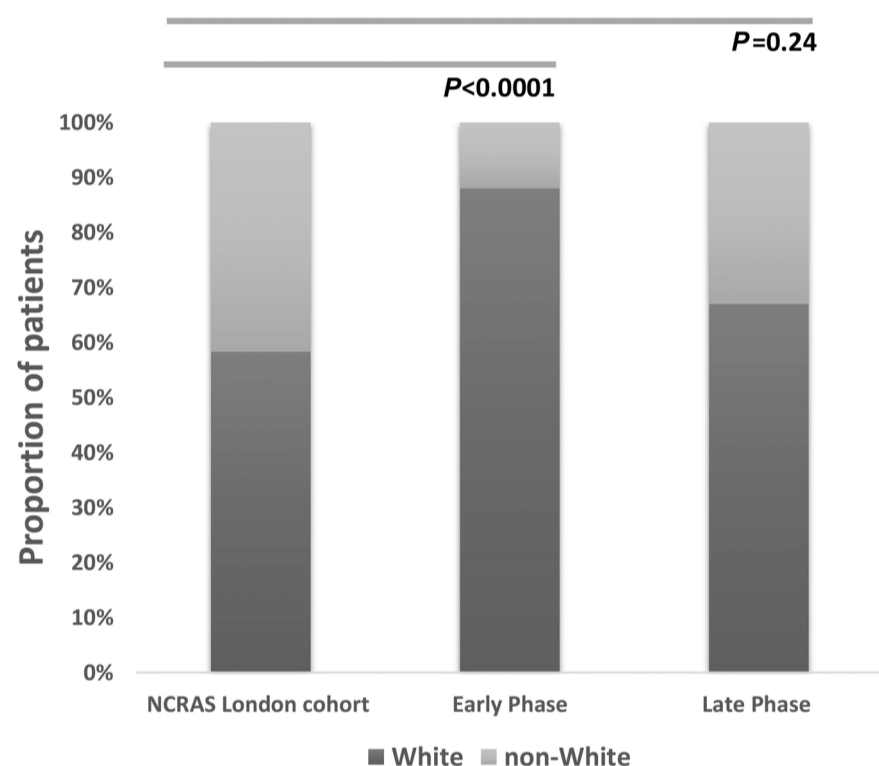


Figure 2. Lower proportions of non-White patients enrolled into early phase clinical trials compared to NCRAS London cohort.

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 versus 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 enrollment 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 HCP 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 III 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, indi-

cating potential selection bias at local centers. Despite differences in enrollment, 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 center, 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 time points 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 enrollment of ethnic minorities exist in state funded health-care systems and recommends further work to resolve this.

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Data-sharing statement

Original data can be made available through direct contact with the corresponding author.

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