Impact of East Asian Ancestry on Response to First-Line Osimertinib: A Real-World Canadian Cohort

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Background

Mutations within the EGFR tyrosine kinase promotes the growth and survival of lung tumour cells, but can be effectively targeted by EGFR-inhibiting drugs which interrupt this oncogenic cycle and dramatically improve the prognosis of patients with this type of lung cancer. EGFR mutations are common driver mutations in adenocarcinoma of the lung, but are well recognized vary in prevalence among different genetic populations, where patients of East Asian ancestry have a much higher incidence of EGFR mutations than is found among Caucasian populations. [1]

Osimertinib is a third generation EGFR-inhibitor with the duel ability to irreversibly bind both EGFR activating mutations as well as the T790M mutation, the latter which confers resistance to earlier generation EGFR-inhibitors, [2] and is now the preferred first-line treatment option for EGFR-mutant non-small cell lung cancer. [3] This recommendation is based on the findings of the phase-III FLAURA clinical trial which demonstrated benefit and effectiveness of osimertinib as a first-line treatment for EGFR-mutant NSCLC patients; however, subgroup analysis suggest the magnitude of benefit may differ between Asian and non-Asian patients. [4,5]

Prior real-world data from our institution also suggests EGFR-mutant NSCLC patients of Asian racial ancestry are the most likely to derive benefit from earlier generation EGFR-inhibitors. [6]

In response, this study examined real-world clinical population of EGFR-mutant patients treated with first-line osimertinib to compare and contrast the demographic and clinical characteristics and response to osimertinib among Asian and non-Asian patients.

Methods

The institutional Glans-Look Lung Cancer Research Database contains demographic, clinical, pathological, treatment and outcome data from patients diagnosed with NSCLC living in the Canadian province of Alberta. This data repository was used to identify all patients with advanced or metastatic non-small cell lung cancer receiving osimertinib in the first line setting between 2018 and 2021. Patients were stratified according to the presence or absence of Southeast Asian racial ancestry.

Racial ancestry was determined using previously validated techniques which rely on patient country of birth and surname. [7,8] Patients identified as having Asian ancestry in electronic medical record chart notes, or those with both southeast Asian country of birth and surname were classified as 'Asian' for the purpose of this study.

Univariate and multivariate methods were used to compare groups and identify factors predictive of time to progression (PFS) on osimertinib.

Results & Interpretation

77 patients were identified:

Demographic and Clinical Characteristics of Cohort

Table 1: Comparison of Demographic and Clinical Characteristics of Asian and non-Asian cohorts

Characteristic	Entire Cohort n = 77 n (%)	Asian Cohort n = 25 n (%)	Non-Asian Cohort n = 52 n (%)	Statistical Test p-value
Age at Diagnosis (years)				
Median (IQR)	68 (61-78)	70 (59-85)	67 (61-75.5)	$X^2(1)$, p=0.76
< 65	32 (42)	11 (44)	21 (40)	
≥ 65	45 (58)	14 (56)	31 (60)	
Sex				
Male	31 (40)	12 (48)	33 (63)	$X^2(1)$, p=0.3
Female	46 (60)	13 (52)	19 (37)	
Smoking History				
Ever Smoker	36 (47)	9 (36)	27 (52)	$X^2(1)$, p=0.2
Never Smoker	39 (51)	15 (60)	24 (46)	
Unknown	2 (2)	1 (4)	1 (2)	
ECOG at Osimertinib Initiation				
Good (< 2)	51 (66)	15 (60)	36 (69)	$X^2(1)$, p=0.4
Poor (≥ 2)	25 (44)	10 (40)	16 (31)	
EGFR Mutation				
Common (Exon19del; L858R)	72 (94)	24 (96)	47 (90)	$X^2(2)$, p=0.5
Uncommon	1 (1)	0 (0)	1 (2)	
Complex (duel common and uncommon mutation)	4 (5)	1 (4)	4 (8)	
M-stage at Osimertinib Initiation				
M0 (advanced, unresectable)	9 (11)	2 (8)	7 (13)	
M1a	19 (25)	9 (36)	10 (20)	$X^2(3)$, p=0.4
M1b	17 (22)	6 (24)	11 (21)	
M1c	32 (42)	8 (32)	24 (46)	
Brain Metastases at Osimertinib Initiation				
Yes	15 (19)	3 (12)	12 (23)	$X^2(1)$, p=0.3
No	62 (81)	22 (88)	40 (77)	
Metastatic Disease Onset				
After relapse	14 (18)	5 (20)	9 (17)	$X^2(1)$, p=0.8
At diagnosis	66 (82)	20 (80)	43 (83)	
Meets FLAURA Inclusion Criteria				
(based on ECOG and type of EGFR mutation)				
Yes	50 (65)	15 (60)	35 (67)	$X^2(1)$, p=0.5
No	27 (35)	10 (40)	17 (33)	
Treatment Post Osimertinib				
Yes	22 (29)	4 (16)	18 (23)	$X^2(1)$, p=0.08
No	55 (71)	21 (84)	34 (67)	

IQR: inter-quartile range; * denotes significance, determined *a priori* at p<0.05

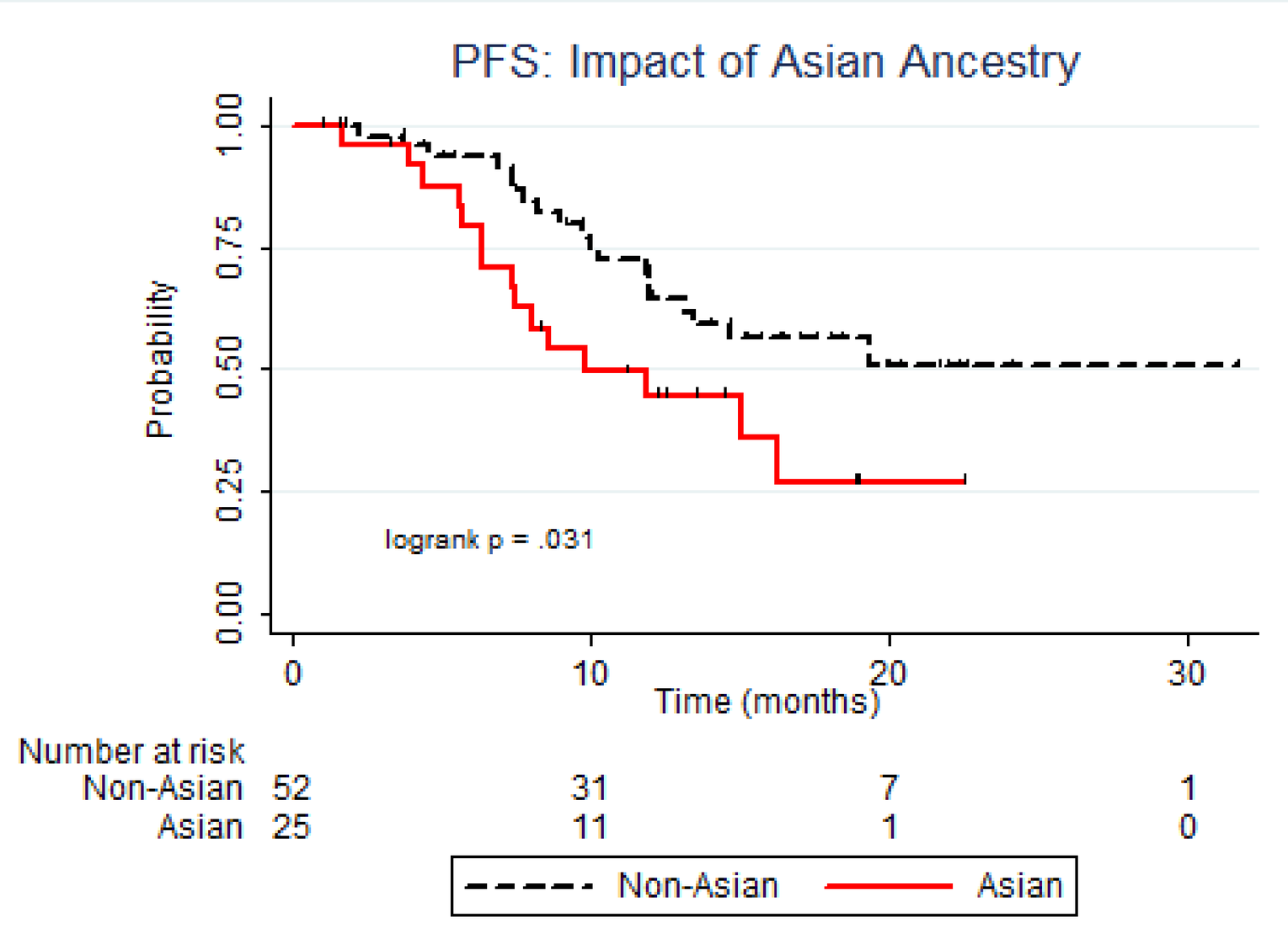
In terms of demographics, overall, the cohort was predominantly females (60%), never-smokers (51%) over the age of 65 at diagnosis (58%).

In terms of clinical characteristics, overall, the cohort possessed a common EGFR-mutation (94%), distant metastatic disease (64%) had good performance status at treatment initiation (66%). Brain metastases were present in 19% of the cohort at Osimertinib initiation.

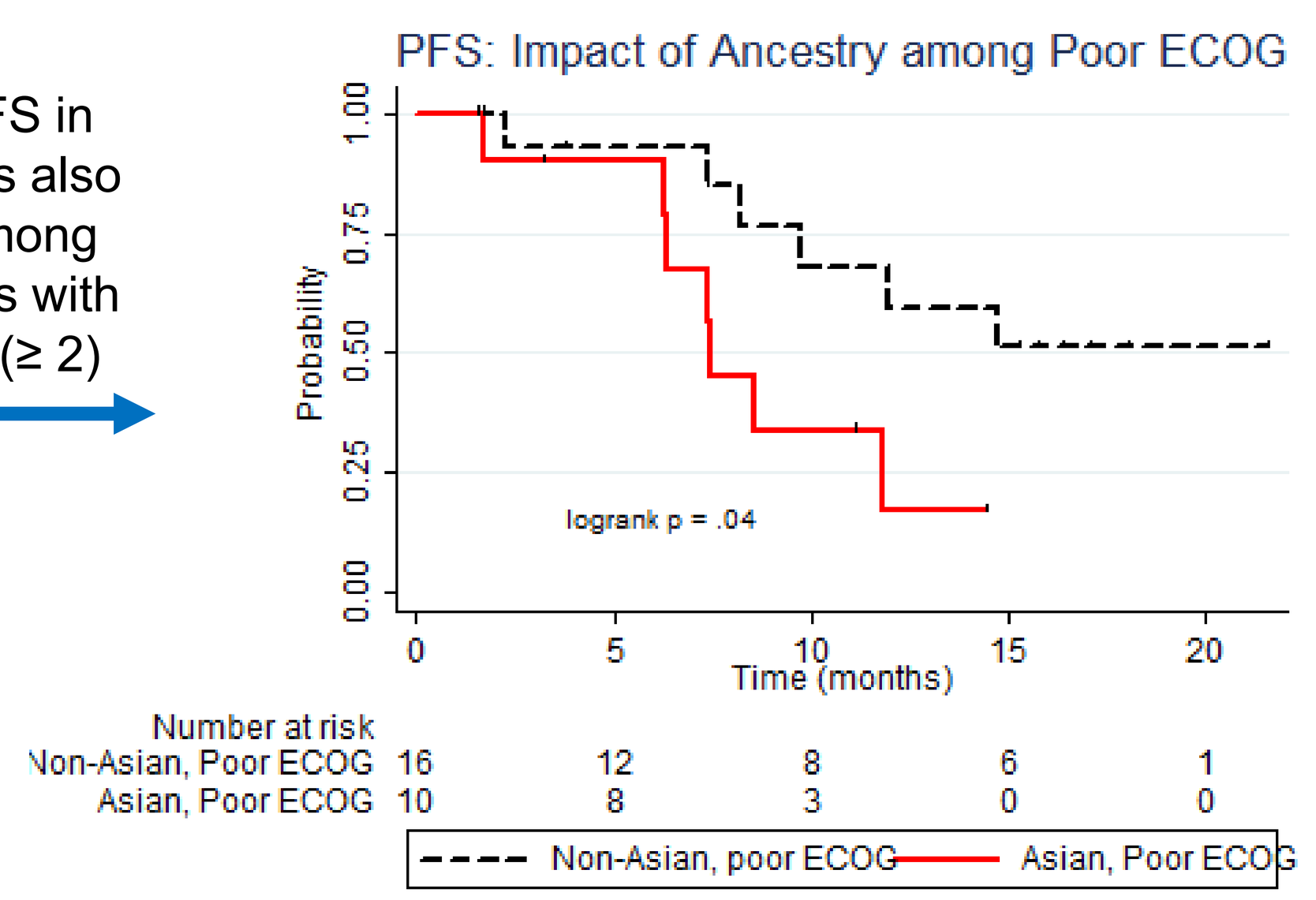
Based on ECOG and EGFR-mutation type, 65% of the cohort would have met basic eligibility criteria for the Phase III FLAURA trial.

There were no statistically significant differences in demographic or clinical characteristics observed between Asian and non-Asian cohorts.

Progression-Free Survival on Osimertinib



Reduced PFS in Asian patients also observed among Asian patients with poor ECOG (≥ 2)



	Progression-Free Survival (months)	Log-rank p-value
Overall: *15.0 months* Asian vs. Non-Asian	9.8 vs not reached	0.03*
Good ECOG: Asian vs. Non-Asian	15.0 vs. not reached	0.27
Poor ECOG: Asian vs. Non-Asian	7.5 vs. not reached	0.04*

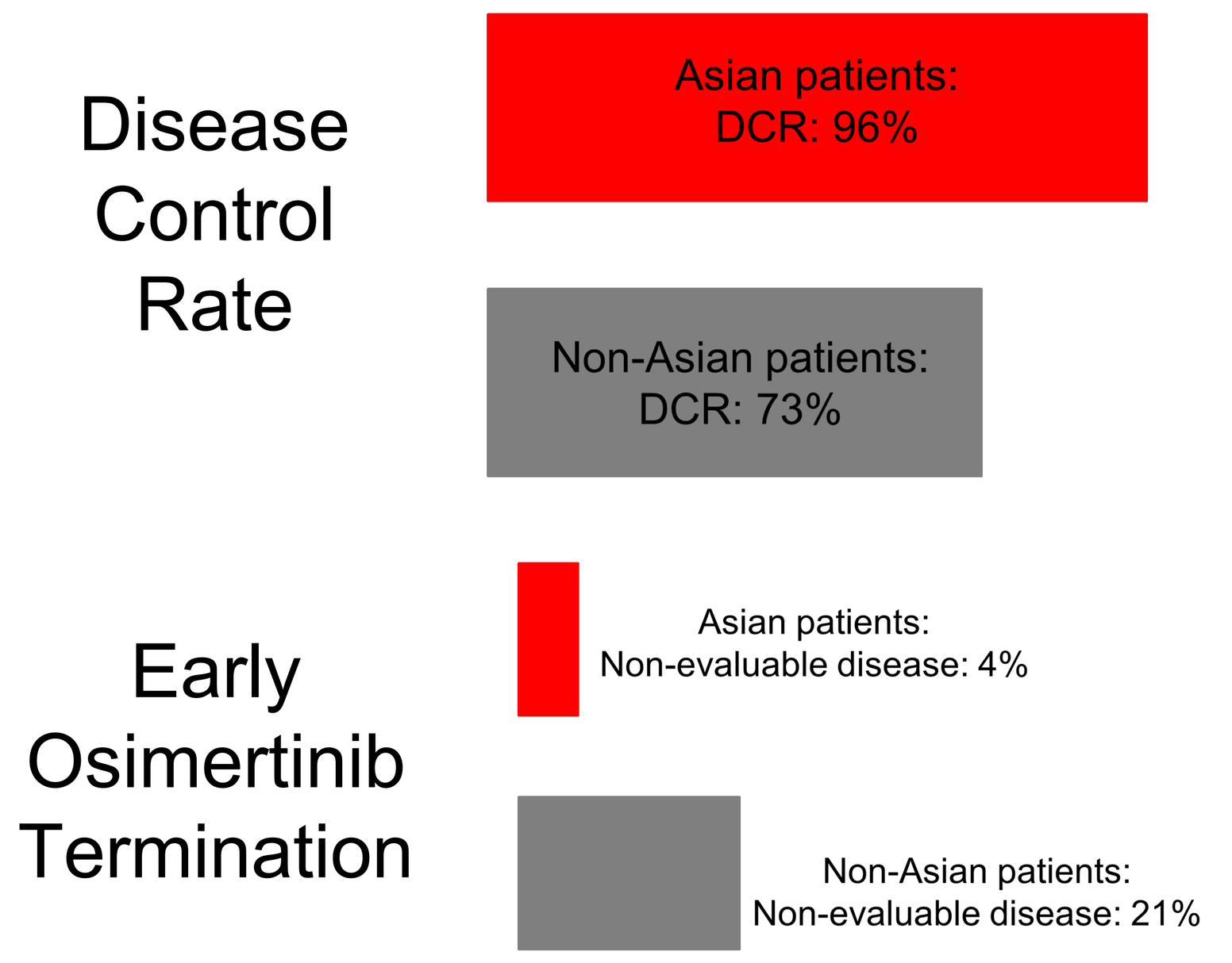
Patients of Asian racial ancestry had significantly shorter time to progression than non-Asian patients. This seems to be based in poor ECOG patients.

Results & Interpretation

Clinical Response to Osimertinib

Despite a shorter time to progression, patients of southeast Asian racial ancestry were observed to have a significantly better clinical response to osimertinib.

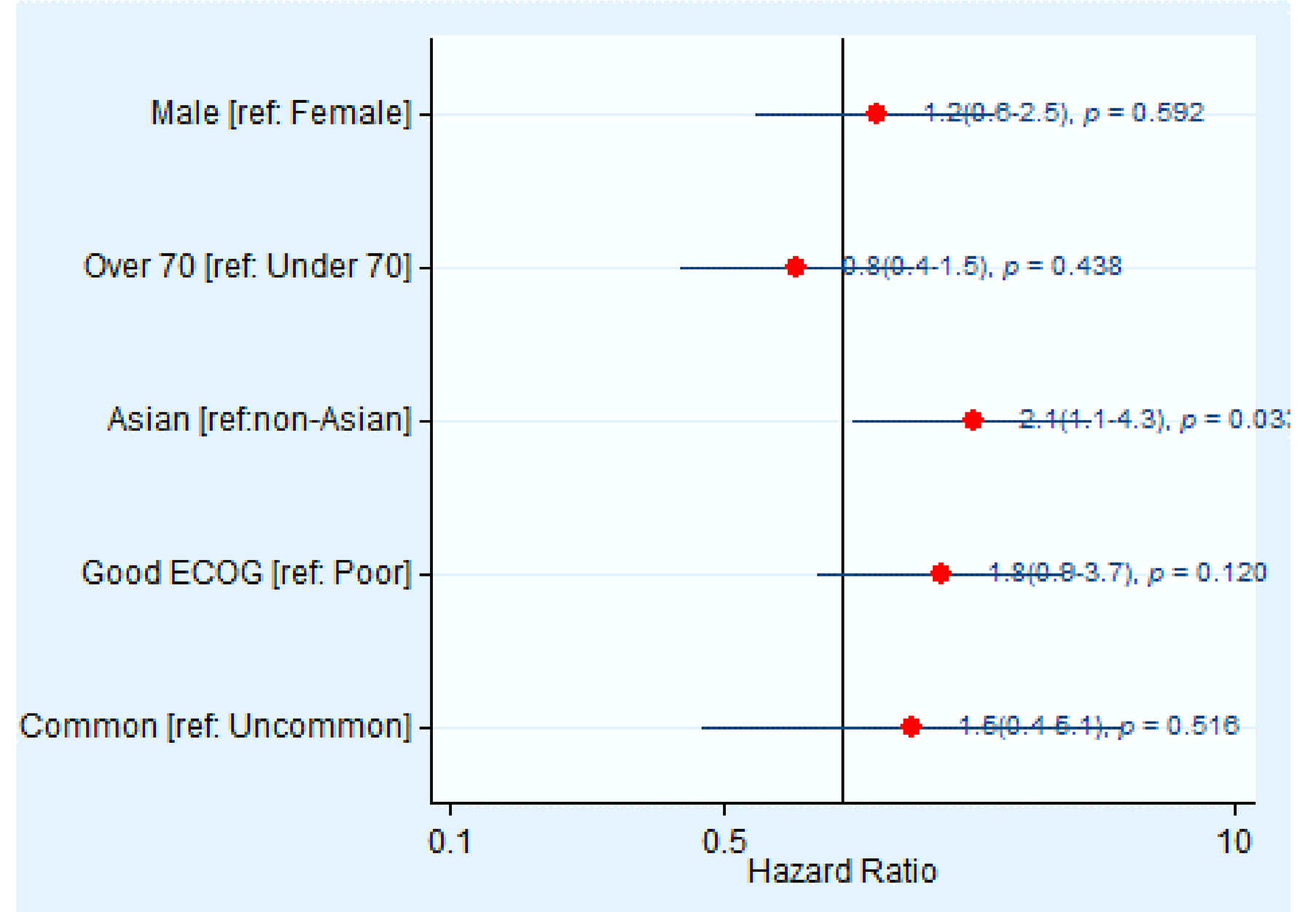
This may be driven by a significantly higher rate of early osimertinib termination prior to disease response evaluation in non-Asian patients due to adverse events



Features Associated with Reduced PFS on Osimertinib (Multivariate)

In controlling for multiple known confounders, Asian ancestry was found to be independently prognostic of shorter PFS on osimertinib:

HR: 2.1 [95% CI: 1.1 – 4.3], p=0.03



Conclusions

This racially heterogenous cohort demonstrates that among these real-world patients:

- Most achieve disease stability (or better) with first-line osimertinib.
- An overall median PFS comparable to that from the FLAURA clinical trial (15.0 vs. 14.4 months) is achieved. [1]
- Patient of Asian ancestry, despite achieving a period of osimertinib-mediated disease control, experienced reduced PFS.

Further investigations focused on understanding potential differential response to osimertinib by racial ancestry is warranted.

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