Tumor proliferation associates with greater sensitivity to androgen receptor pathway inhibition in metastatic prostate cancer

To the Editor: Proliferation is a hallmark of cancer (1). Androgens increase proliferation of prostate cancer cells in vitro and inhibition of androgens markedly reduces proliferation. Observational cohorts have suggested that increased proliferation associates with a poor response to hormone therapy, including the androgen receptor pathway inhibitors (ARPI) abiraterone or enzalutamide (2). To better understand the relationship between tumor proliferation and the effect of ARPI when added to androgen deprivation therapy (ADT), we analyzed prostate cancer biopsies from patients on ADT randomized to abiraterone in the STAMPEDE platform.

Between November 2011 and January 2014, 914 nonmetastatic and 1,003 metastatic patients enrolled into the STAMPEDE abiraterone trial (3). To enhance statistical power in nonmetastatic disease given a lower event rate, 1,060 nonmetastatic patients enrolled between July 2014 and March 2016 in the abiraterone and enzalutamide trial were combined in this analysis, similar to the primary report (4). Of the 2,977 patients, 2,963 were recruited in the United Kingdom (115 centers) with consent for tissue collection from 2,912. Ki-67 was scored for 1,605 cases (Figure 1A and Supplemental Figure 1A; supplemental material available online with this article; https://doi.org/10.1172/JCI203201DS1). Tumors biopsied after ADT were excluded in a sensitivity analysis restricted to 1,413 ADT-naive cancers (88%).

Baseline characteristics for the analytical cohort were consistent with the full trial cohorts reported previously (3, 4) (Supplemental Table 1). By February 2024, 34% (n = 364) of the nonmetastatic and 75% (n = 397) of the metastatic cohort had died.

Ki-67 was higher in the presence of lymph node involvement in nonmetastatic disease ($F_{1,1074}$=28, P < 0.001) but there was no difference between low- and high-volume metastatic disease ($F_{1,510}$=0.45, P = 0.504, Figure 1B). Ki-67 was positively associated with Gleason score ($F_{7,1593}$=9, P < 0.001, Figure 1C) and tumor stage ($F_{5,1599}$=4, P < 0.001 Figure 1D), but not pre-ADT serum PSA (Spearman's ρ = –0.02, Supplemental Figure 1C). ADT-exposed tumors had lower Ki-67 scores (Supplemental Figure 1D).

Ki-67 score was linearly associated with shorter survival. In nonmetastatic disease, adjusted for baseline characteristics, a 10-percentage point increment in Ki-67 was associated with a 23% increase in hazards of death (95% CI: 12%–37%; P < 0.001) with ADT and 25% (95% CI: 8%–45%; P = 0.004) with ADT and abiraterone (Figure 1E). In metastatic disease, every 10-percentage point increased hazards of death by 31% (95% CI: 19%–44%; P < 0.001) with ADT, but only 6% (95% CI: −2%–16%, P = 0.172) with ADT and abiraterone (Figure 1F and Supplemental Table 2).

Given this strong attenuation, we identified that abiraterone effectiveness was significantly greater in metastatic cancers with higher Ki-67 scores (interaction P < 0.001, Figure 1G, Supplemental Table 3).

In contrast, and despite a similar number of events, we did not identify treatment effect heterogeneity in nonmetastatic patients (HR=0.97; 95% CI: 0.85–1.11; Figure 1H). This interaction was unchanged when using metastasis progression-free survival as the endpoint or when excluding patients biopsied after ADT (Supplemental Table 3).

The Statistical Analysis Plan prespecified dichotomizing Ki-67 around the median value in metastatic patients (<15%, ≥15%, Figure 1, I and J). There was attenuation of the interaction effect with dichotomization, suggesting that linear modelling may better capture the biological gradient of response.

Our study has some limitations. Tumor collection started after completion of accrual, but the large patient numbers reduce the risk of confounding factors from retrieval. Tumors could have been biopsied after treatment started, affecting Ki-67 expression: sensitivity analyses excluding these cases confirmed the same clinical associations. Scores in our study were independently reviewed by uropathologists using a standardized validated scoring methodology (5), but may not fully capture intratumoral heterogeneity. This could be addressed in future work that could also incorporate additional morphological information.

In conclusion, highly proliferating tumors are more aggressive and more sensitive to ARPI. In contrast, our recent study on an overlapping set of patients identified no interaction of proliferation with docetaxel sensitivity (6). While all patients with metastatic disease derived a meaningful survival benefit from abiraterone, the greater benefit in highly proliferative disease identifies a potential cancer vulnerability that could be exploited to further increase the anticancer effect of ARPI.

Conflict of interest

Conflicts of interest are included in the Supplemental Data.

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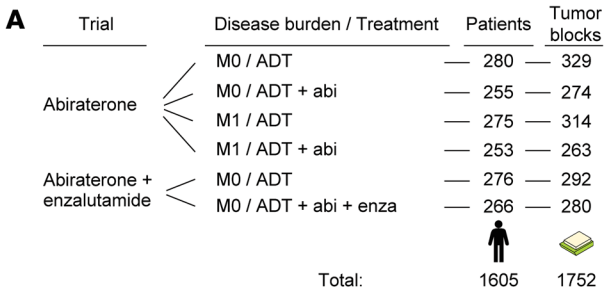
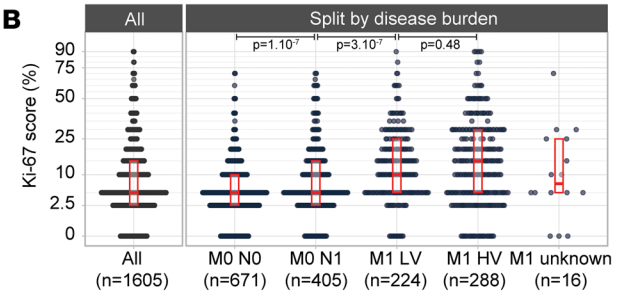
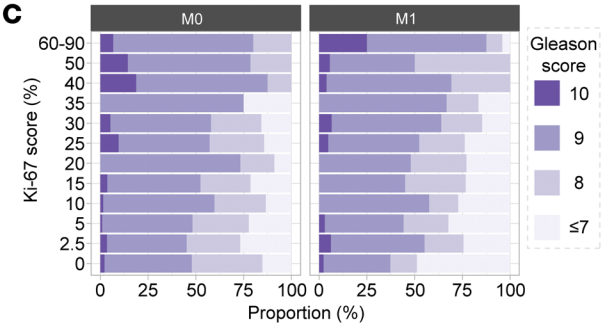
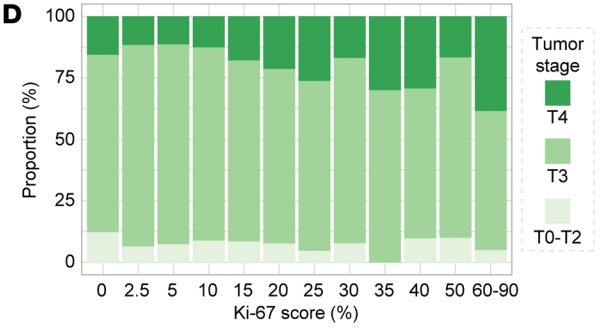
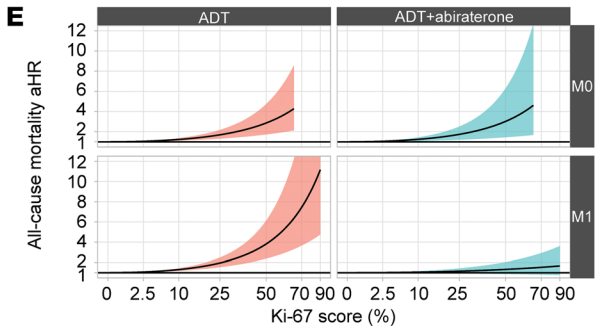
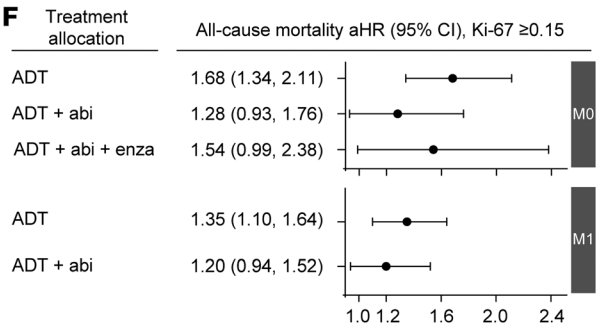

A
Trial
Disease burden / Treatment
Patients
Tumor blocks
Abiraterone
M0 / ADT
280
329
M0 / ADT + abi
255
274
M1 / ADT
275
314
M1 / ADT + abi
253
263
Abiraterone + enzalutamide
M0 / ADT
276
292
M0 / ADT + abi + enza
266
280
Total:
1605
1752

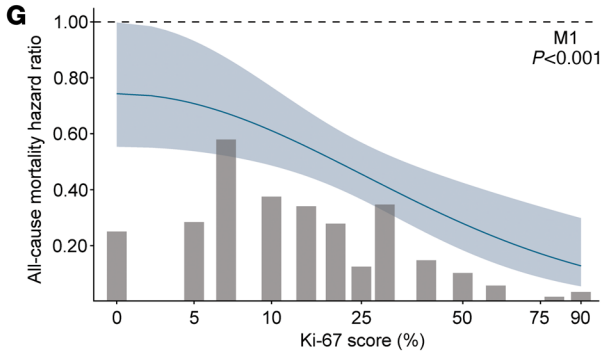

B
All
Split by disease burden
p=1.10-7
p=3.10-7
p=0.48
Ki-67 score (%)
All (n=1605)
M0 N0 (n=671)
M0 N1 (n=405)
M1 LV (n=224)
M1 HV (n=288)
M1 unknown (n=16)

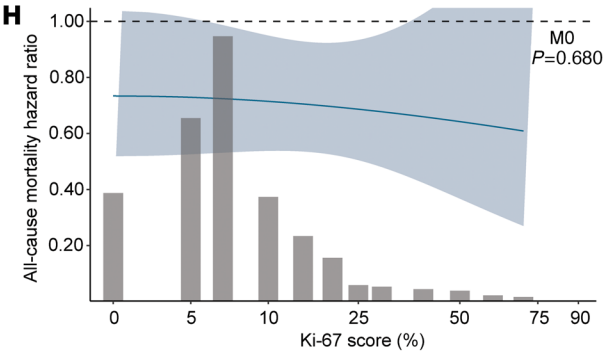

C
M0
M1
Ki-67 score (%)
Gleason score
10
9
8
≤7
Proportion (%)

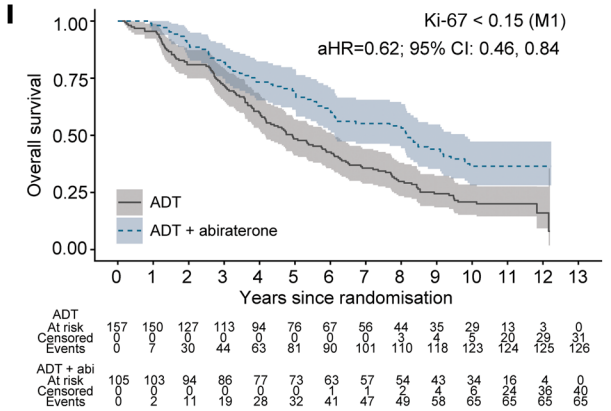

D
Proportion (%)
Tumor stage
T4
T3
T0-T2
Ki-67 score (%)


E
ADT
ADT+abiraterone
M0
M1
All-cause mortality aHR
Ki-67 score (%)


F
Treatment allocation
All-cause mortality aHR (95% CI), Ki-67 ≥0.15
ADT
1.68 (1.34, 2.11)
ADT + abi
1.28 (0.93, 1.76)
ADT + abi + enza
1.54 (0.99, 2.38)
M0
ADT
1.35 (1.10, 1.64)
ADT + abi
1.20 (0.94, 1.52)
M1


G
M1
P<0.001
All-cause mortality hazard ratio
Ki-67 score (%)


H
M0
P=0.680
All-cause mortality hazard ratio
Ki-67 score (%)


I
Ki-67 < 0.15 (M1)
aHR=0.62; 95% CI: 0.46, 0.84
Overall survival
ADT
ADT + abiraterone
Years since randomisation
ADT
At risk 157 150 127 113 94 76 67 56 44 35 29 13 3 0
Censored 0 0 0 0 0 0 0 0 3 4 5 20 29 31
Events 0 7 30 44 63 81 90 101 110 118 123 124 125 126
ADT + abi
At risk 105 103 94 86 77 73 63 57 54 43 34 16 4 0
Censored 0 0 0 0 0 0 1 2 4 6 24 36 40
Events 0 2 11 19 28 32 41 47 49 58 65 65 65 65

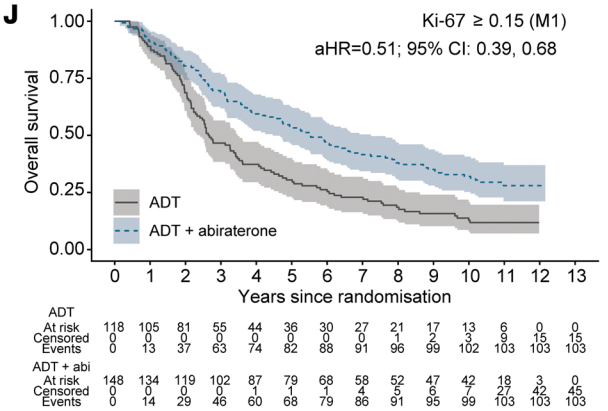

J
Ki-67 ≥ 0.15 (M1)
aHR=0.51; 95% CI: 0.39, 0.68
Overall survival
ADT
ADT + abiraterone
Years since randomisation
ADT
At risk 118 105 81 55 44 36 30 27 21 17 13 6 0 0
Censored 0 0 0 0 0 0 0 0 1 2 3 9 15 15
Events 0 13 37 63 74 82 88 91 96 99 102 103 103 103
ADT + abi
At risk 148 134 119 102 87 79 68 58 52 47 42 18 3 0
Censored 0 0 0 0 1 1 1 4 5 6 7 27 42 45
Events 0 14 29 46 60 68 79 86 91 95 99 103 103 103

Figure 1. Ki-67 proliferation score in advanced prostate cancer. (**A**) Sample flow (see Supplemental Figure 1A for more information). (**B**) Bee swarm probability mass density plot of Ki-67 score; pairwise 1-way ANOVA significance test *P*-values are reported. (**C**) Gleason score by Ki-67 score and metastatic stage (M0, non-metastatic, M1LV: low-volume metastatic, M1HV: high-volume metastatic). (**D**) Tumor stage distribution by Ki-67 score. (**E**) Multivariable mortality adjusted treatment effect hazard ratio (aHR) conditional on semiquantitative Ki-67 score (reference: Ki-67=0). (**F**) Forest plot of multivariable mortality hazard ratios. (**G** and **H**). Multivariable model-based conditional average treatment effect point across Ki-67 scores, with Ki-67 frequency bars: *P* values for partial deviance tests of interaction between Ki-67 score and addition of abiraterone. (**I** and **J**) Kaplan-Meier curves (overall survival) by allocated treatment and Ki-67 subgroup in metastatic disease, with subgroup aHR.

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