Basal tumour subtype was associated with poor clinical responses to neoadjuvant apalutamide prior to prostatectomy in intermediate- to high-risk localised prostate cancer

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INTRODUCTION

Our Phase II clinical trial (NCT03124433) using neoadjuvant apalutamide 3 months prior to radical prostatectomy in patients with intermediate- to high-risk localised prostate cancer demonstrated a favourable clinical outcome. Twenty-one patients (84%) achieved a pathological response rate by means of tumour volume reduction. In addition, 21 patients (84%) achieved a biochemical response with nadir PSA at the end of the study. Here, we are reporting the results of the androgen receptor (AR) signalling and molecular landscape in these patients as part of the exploratory outcome of our study.

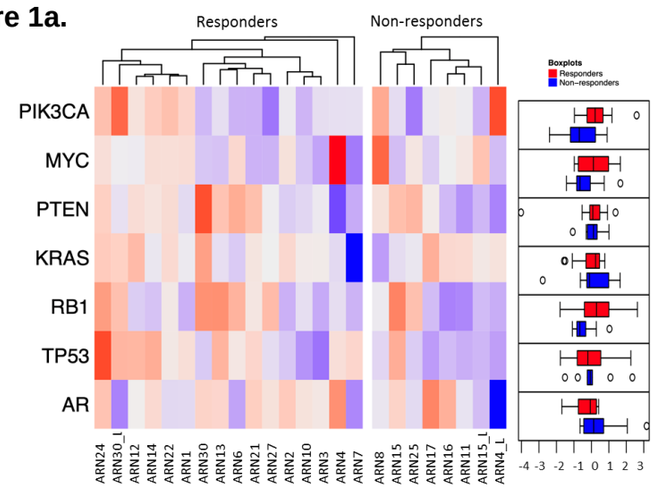
METHODS

Tumours were retrieved from prostatectomy specimens using laser capture microdissection (LCM) technology. RNA expression in tumours prior to apalutamide treatment (prostate core needle biopsy specimens) and post-apalutamide treatment (LCM tumours from prostatectomy specimens) were analysed using reverse-transcription polymerase chain reaction (RT-PCR). Sequencing and data analyses were conducted using a conventional sequencer and RNA module. 'Responders' group was determined by the attainment of a nadir serum prostate-specific antigen (PSA) level post-operatively within the study period. 'Non-responders' group was determined by patients who failed to achieve a nadir PSA or had a PSA recurrence detected early beyond the study period. Treatment response grade groups were determined by a validated grading system based on microscopic features (Grade A:most favourable, Grade B:intermediate, Grade C:poorest treatment response)[1].

RESULTS

Targetted sequencing were performed in tumours obtained from a total of 21 post-apalutamide (post-ARN) patients, in which 15 were matched with available pre-treatment (pre-ARN) needle biopsy specimens. There were no significant mutational differences in the gene expression between Responders (n=15) and Non-responders (n=6). However, a significant correlation between downregulation of TP53 and AR signalling pathways was observed. Non-responders were found to have a lower expression of TP53 and a higher AR expression **[Figure 1a&b]**. In the Responders group, we found a significant higher expression of AR and lower expression of RB1, KRAS and PTEN prior to treatment (pre-ARN) **[Figure 2a&b]**. On the other hand, the Non-responders showed a lower expression of RB1 and KRAS prior to treatment (pre-ARN)**[Figure 3a&b]**. Expression of AR-related genes such as KLK2, KLK3, RAB3B, STEAP1 and STEAP2 were significantly lower in Responders **[Figure 4a&b]**. However, Non-responders showed a significantly higher expression of STEAP1 and FKBP5 prior to treatment (pre-ARN) compared to post-treatment (post-ARN) **[Figure 5a&b]**. Overexpression of FKBP has been associated with recurrent disease *in vivo*[2] and it may correspond to early resistance to apalutamide in the Non-responders in our study. Furthermore, as we segregated tumour into different subtypes using the PAM50 signatures[3], we showed that luminal B subtypes were associated with a more favourable response, whereas basal tumours were linked to adverse tissue outcomes and poorer biochemical response rates **[Figure 6]**.

Figure 1a.



1b.

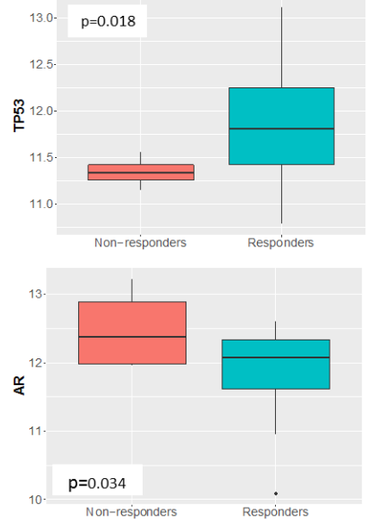
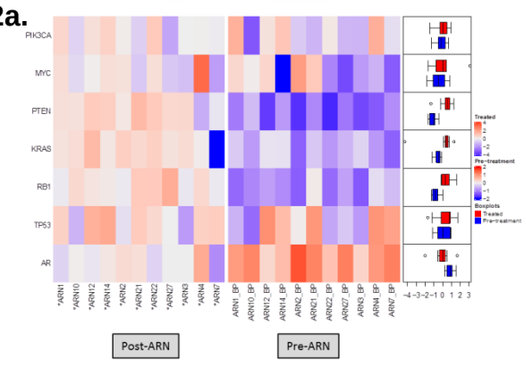


Figure 2a.



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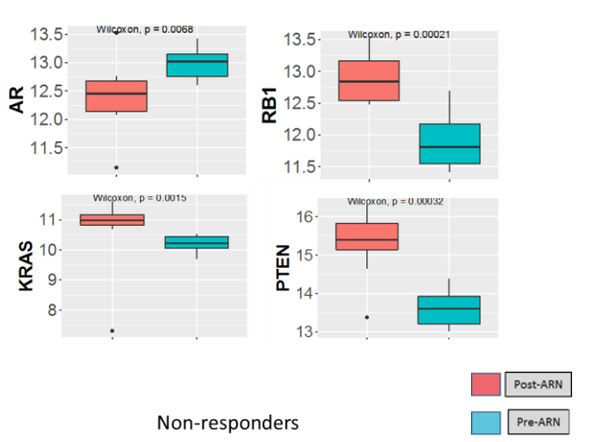
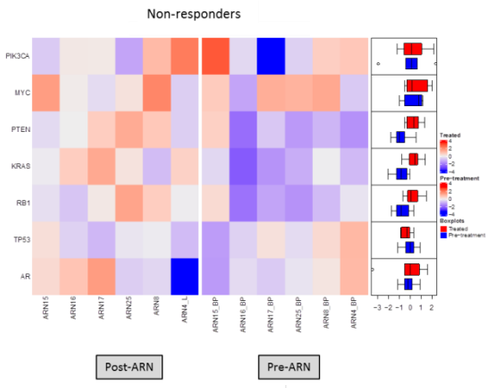


Figure 3a.



3b.

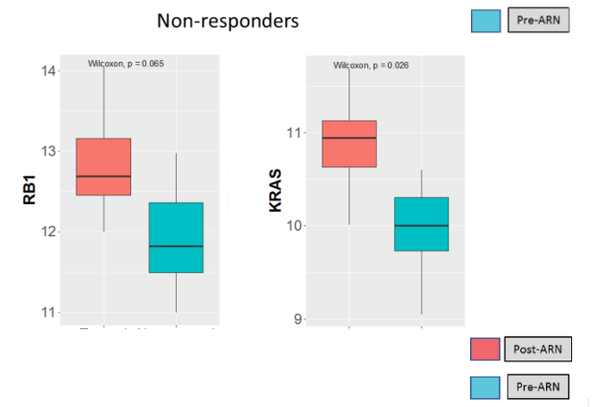
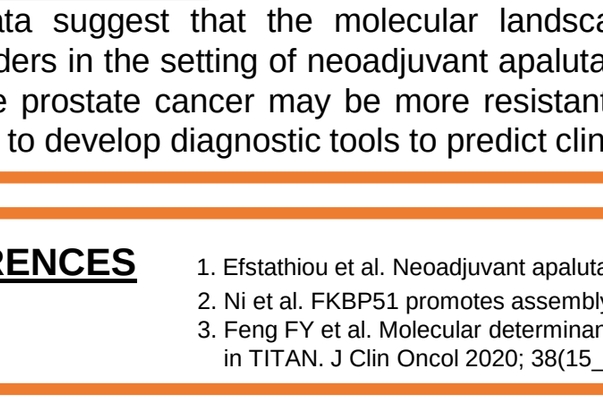


Figure 4a.



4b.

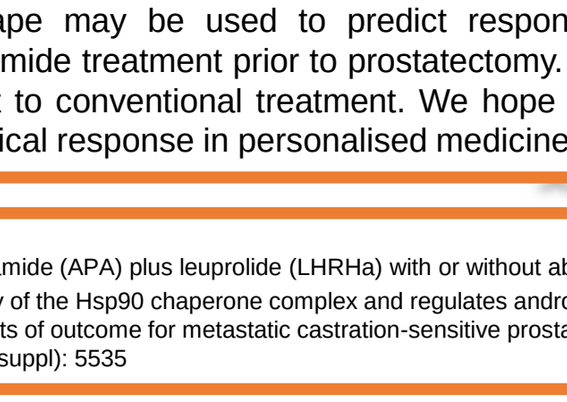


Figure 5a.

5b.

Figure 6.

CONCLUSIONS

Our data suggest that the molecular landscape may be used to predict responders versus non-responders in the setting of neoadjuvant apalutamide treatment prior to prostatectomy. Moreover, a basal subtype prostate cancer may be more resistant to conventional treatment. We hope that our data may lead us to develop diagnostic tools to predict clinical response in personalised medicine.

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