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# REAL-WORLD USE OF FIRST-GENERATION ANTI-ANDROGENS (FGAS): IMPACT ON PATIENT OUTCOMES AND SUBSEQUENT THERAPIES IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCPRC)



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## DECLARATIONS

### Ethics approval and consent to participate

The ePAD project was granted multisite ethics approval by the Royal Melbourne Hospital Human Research Ethics Committee on 01/05/2018, prior to commencement of data collection. The approval included a waiver of the requirement for individual patient consent given the retrospective, non-interventional and de-identified nature of the research and the patient group (advanced cancer) HREC/15/MH/352.

This study was conducted in accordance with the Australian National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and was carried out according to the principles of the Declaration of Helsinki.

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## CONFLICTS OF INTEREST

**Arun Azad**

Consultant — Astellas, Janssen, Novartis; Speakers Bureau — Astellas, Janssen, Novartis, Amgen, Ipsen, Bristol Myers Squibb; Honoraria — Astellas, Janssen, Novartis, Tolmar, Amgen, Pfizer, Telix;

Scientific Advisory Board — Astellas, Novartis, Sanofi, AstraZeneca, Tolmar, Pfizer, Telix; Travel & Accommodation - Astellas, Merck Serono, Amgen, Novartis, Janssen; Research Funding —Astellas (investigator), Merck Serono (investigator), Astra Zeneca (investigator), Bristol Myers Squibb (institutional), Astra Zeneca (institutional), Aptevo Therapeutics (institutional), Glaxo Smith Kline (institutional), Pfizer (institutional), MedImmune (institutional), Astellas (institutional), SYNthorx (institutional), Bionomics (institutional), Sanofi Aventis (institutional), Novartis (institutional)

**Edmond M Kwan**

Honoraria – Janssen, Ipsen; Travel & Accommodation – Astellas Pharma, Pfizer and Ipsen; Research Funding – Astellas Pharma (institutional), AstraZeneca (institutional), Bristol Myers Squibb (institutional), Pfizer (institutional), Merck Serono (institutional).

**Jeffrey Goh**

Scientific Advisory Board – AstraZeneca, Bristol Myers Squibb; Travel & Accommodation – AstraZeneca, Astellas

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**ABSTRACT**

*Objectives*: To investigate the recent real-world use of FGAs in mCRPC using a retrospective multi-centre cohort study.

*Materials and Methods*: The electronic CRPC Australian Database (ePAD) was interrogated to identify patients with mCRPC. Clinicopathological features, treatment and outcome data, stratified by FGA use, were retrieved and reported through descriptive statistics. Survival analyses were calculated using the Kaplan-Meier method and groups compared using log-rank tests. Factors influencing overall survival were analysed using Cox proportional hazards regression models.

*Results*: We identified 634 mCRPC patients, enrolled in ePAD between January 2016 and March 2019, including 322 (51%) who received FGAs. Median follow-up time was 21.9 months. Patients treated with FGAs were more likely to have lower International Society of Urological Pathologists (ISUP) grade group (p=0.04), longer median time to CRPC (25.6 versus 16.0 months, p<0.0001) and were less likely to have visceral metastases (5.0% v 11.2%, p=0.005) or to have received upfront docetaxel (p<0.0001). PSA50 response to FGA occurred in 119 (37%) patients and was independently associated with

improved overall survival (HR=0.233, p<0.001). Prior FGA treatment did not significantly influence the selection of subsequent life-prolonging treatments for mCRPC or their PSA50 response rates.

*Conclusion*: In our cohort, FGAs were commonly used in lower-risk mCRPC and their use did not significantly influence the choice or duration of subsequent systemic therapy. A PSA50 response to FGA therapy was an independent favourable prognostic marker, associated with improved overall survival.



## INTRODUCTION

Prostate cancer represents the second most common cause of cancer death among men in the western world (1), with significant symptom burden, high rates of hospitalisation and intervention (2, 3). Androgen deprivation therapy (ADT) is an effective treatment in advanced prostate cancer. However, until the recent development of novel therapeutics, patients with castration-resistant prostate cancer (CRPC) typically had limited effective treatment options (4). Appreciation of the critical role of androgen receptor signalling (5) has led to the development of first generation anti-androgens (FGAs) including bicalutamide and nilutamide (6). Before the introduction of novel therapeutics such as taxane chemotherapy, abiraterone acetate and enzalutamide, FGAs were the only treatment options for CRPC and historically demonstrated modest PSA50 response rates (≥ 50% reduction from pre-treatment PSA) of approximately 20-30% in CRPC (7-9). Since the development of novel androgen receptor signalling inhibitors (ARSIs), abiraterone acetate and enzalutamide, which are more efficacious than FGAs, maintaining higher PSA50 rates and significantly improving overall survival (OS)(8-10), the role of FGAs in the treatment of mCRPC has become less clear (11).

This retrospective, multi-centre Australian cohort study evaluated the real-world use of FGAs in the treatment of mCRPC. We aimed to examine patient and disease characteristics of those treated with FGAs, to define their efficacy in modern-day, and to investigate their influence on subsequent systemic therapy choice and treatment outcomes.

## METHODS

The electronic CRPC Australian Database (ePAD) was interrogated to identify patients with mCRPC from 11 healthcare sites. ePAD is a multi-centre clinical registry that prospectively collects clinicopathologic information, treatment and outcome data regarding men with CRPC. Data is collected from rural and metropolitan settings within several states in Australia, including academic centres, community hospitals and private practice settings. Patients with CRPC who had received no more than one line of systemic therapy were eligible for inclusion. CRPC is defined by Prostate Cancer Working Group 3 (PCWG3) criteria; progression despite androgen deprivation therapy (ADT) with suppressed testosterone, as defined by a rise in serum prostate-specific antigen (PSA), radiological progression of pre-existing disease, and/or the appearance of new metastases (12). Data is entered into ePAD and updated at regular intervals by treating clinicians or trained data abstractors through review of all relevant medical records.

Clinicopathologic features, PSA50 response rates and subsequent systemic therapy including treatment choice, duration and response data were extracted. Patients were stratified into two groups; those who had received prior FGA treatment, following castration-resistance, and those who had not. Prior FGA was defined as an FGA administered between development of castration-resistance and administration of subsequent first-line systemic therapy. First-line systemic therapy was defined as the first additional systemic therapy administered following the development of CRPC and progression on FGA therapy, where applicable. This excludes upfront chemohormonal therapy with docetaxel chemotherapy prescribed in combination with ADT in the hormone-sensitive setting. Treatment with FGAs was discontinued at the time of progression, and prior to commencement of first-line systemic therapy. Patients were also stratified according to the date of development of castration resistance, relative to the date of first availability of any ARSI through the pharmaceutical Benefits Scheme (PBS) in Australia, defined as 01 August 2013.

Clinicopathological differences between patient groups were compared using T-tests for continuous variables and Chi-Square analyses or Fisher's exact tests for categorical variables. Duration of systemic therapy and survival analyses were performed using the Kaplan Meier method and differences compared using log-rank tests. Overall survival was defined as time from development of castration resistance to death from any cause. Univariate and multivariate Cox proportional hazard regression modelling was performed to analyse the effect on overall survival. Variables with a p-value <0.2 identified by univariate analyses were included in the multivariate analysis, in addition to age at CRPC diagnosis, to ensure all variables with potential impact on overall survival were incorporated. Hazard ratios (HR) and 95% confidence interval (CI) were reported for each factor. Prism software (version

8.3.1, GraphPad Software LLC, La Jolla California, USA) was utilised for all analyses except Cox proportional hazard regression models, which were performed using Stata/SE software (version 16.1, StataCorp LLC, Texas, USA). Results were considered statistically significant with p-values of <0.05.

Rates of PSA50 response to both FGAs and additional systemic therapies were calculated, as defined by the proportion of patients with ≥ 50% reduction in serum PSA compared to baseline pre-treatment PSA levels. Time to treatment failure (TTF) was defined as the duration of therapy, when treatment was ceased due to progression (biochemical, radiological or clinical). If treatment was ceased for reasons other than progression, TTF was defined as time to commencement of second-line therapy. Patients who had not commenced second-line therapy were censored at date of last follow-up.

## RESULTS

We identified 634 patients with mCRPC within the ePAD registry, who were enrolled in ePAD between January 2016 and March 2019. The majority (88%) of patients developed CRPC after 01 August 2013. During a median follow-up time of 21.9 months, 322 patients (51%) had received FGAs, given as initial therapy following diagnosis of castration resistance. The median duration of treatment with FGAs was 7.6 months. A minority of patients received more than one FGA, with 22 patients (7%) administered two FGAs, and 3 patients (1%) receiving three FGAs. Among 557 patients who developed CRPC after 01 August 2013, 257 (46%) received FGAs prior to any further systemic therapy.

### *Baseline Characteristics*

Clinicopathological characteristics are reported in Table 1, recorded at the time of CRPC, stratified according to prior treatment with FGAs. Patients treated with FGAs were more likely to have lower International Society of Urological Pathologists (ISUP) grade group ≤ 3 at diagnosis (p=0.04), increased time to development of CRPC (median 25.6 months versus 16.0 months, p<0.0001) and were less likely to have visceral metastases (5.0% versus 11.2%, p=0.005) or have received upfront chemohormonal therapy (22.4% versus 3.4%, p<0.0001). There were no significant differences between groups with respect to median age, ECOG performance status, or PSA doubling time. Patients treated with FGAs were more likely to have a higher cardiovascular risk profile, with a significantly greater proportion having hypertension (61% versus 49%, p<0.003) and hypercholesterolaemia (43% versus 33%, p<0.01).

*Efficacy of FGAs*

Of 322 patients treated with FGAs, 119 (37%) achieved a PSA50 response, 63 (20%) had a PSA response of less than 50% compared to baseline levels and 139 (43%) had no PSA response. A total of 147 patients had died during the follow up period. Patients treated with FGAs had significantly longer overall survival compared to those who did not receive FGAs (HR= 0.516, 95% CI: 0.368-0.724; p<0.001). This difference was also observed in the subset of patients who developed CRPC after 01 August 2013 (HR 0.50. 95% CI 0.340-0.735; p<0.001). Among those who received FGAs, patients with a PSA50 response had significantly improved overall survival compared to those without biochemical response and those with a PSA response of less than 50%, as demonstrated in Figure 2 (HR=0.280, 95% CI 0.175-0.449; p<0.001 and HR 0.480, 95%CI 0.246-0.938; p=0.003 respectively). Significantly improved overall survival was also demonstrated among the subgroup of patients diagnosed with CRPC following 01 August 2013, who achieved a PSA50 response to FGA compared to those without response, as demonstrated in Figure 3 (HR=0.336, 95% CI 0.178-0.631; p=0.005).

Table 3 displays the results of univariate and multivariate analyses, reporting the effect of each variable on overall survival. Within our cohort, other variables associated with improved overall survival on univariate analysis included PSA doubling time >3 months (HR 0.395, 95%CI 0.254-0.613; p<0.001) and time to development of CRPC >12 months (HR 0.479, 95%CI 0.336-0.684; p<0.001). Variables associated with poorer overall survival included history of ischemic heart disease (HR 1.449, 95%CI1.014-2.072; p=0.042), history of diabetes (HR 1.558, 95%CI 1.060-2.291, p=0.024), ECOG performance status >1 (HR 2.246, 95%CI 1.384-3.645; p=0.001), presence of visceral metastases (HR 1.905, 95%CI 1.110-3.271; p=0.019 and upfront docetaxel in the hormone-sensitive setting (HR 2.597, 95%CI 1.487-4.538; p=0.001). On multivariate analysis use of FGA was no longer associated with improved OS (p=0.648). However, PSA50 response to FGA remained a favourable independent prognostic factor (HR= 0.232, 95%CI 0.112-0.482; <0.001), together with higher PSA doubling-time > 3 months (HR=0.3675; 0.199-0.672; p=0.001). History of diabetes remained a significant poor prognostic factor (HR= 2.701, 95%CI 1.466-4.976; p=0.001).

*Subsequent Systemic Therapy for mCRPC*

Figure 1 demonstrates first-line mCRPC systemic therapy choice for each group stratified by previous FGA use. No significant differences were observed in the proportion of patients who received subsequent systemic therapy based on prior FGA use, nor in the treatment choice following FGA

therapy. The most common systemic therapy received in the first-line setting was enzalutamide (38% in both groups), followed by docetaxel (30% versus 24%) in those who did and did not receive prior FGA respectively. Similarly, PSA50 response rates to any subsequent first-line systemic therapies did not differ based on previous FGA use, including enzalutamide (51% versus 59%, p=0.36), abiraterone acetate (51% versus 42%, p=0.65) or docetaxel (54% versus 48%, p=0.84).

Prior FGA response (PSA50 response versus <50% PSA response versus no biochemical response) did not result in any significant differences in PSA50 response rates for enzalutamide (54%versus 59% versus 42%, p=0.19), abiraterone (47% versus 83% versus 46%, p=0.29), or docetaxel (49% versus 62% versus 56%, p=0.73), when received as first systemic therapy for CRPC. Additionally, prior FGA use did not result in any significant differences in the median TTF for enzalutamide (11.7 months versus 11.9 months, p=0.32) or abiraterone (18.8 months versus 11.7 months, p=0.16), although there was a significant, albeit clinically modest increase in TTF on docetaxel (8.3 vs 7.9 months; 0.039). PSA50 response to FGA did not result in any significant difference in PSA50 to abiraterone, enzalutamide or docetaxel, nor did it result in significant difference in TTF to abiraterone or enzalutamide, however, in those who received docetaxel, TTF was significantly longer in those who had a PSA50 to FGA (9.0 vs 6.6 months; p=0.043).

## DISCUSSION

This retrospective cohort study investigated the role of FGAs in the treatment of mCRPC in an Australian real-world context using the multi-centre ePAD registry. Our findings demonstrate the ongoing use of FGAs among patients with mCRPC, with more than half of the patients in our cohort receiving these agents (51%, n=322). This did not differ significantly when looking exclusively at the cohort who developed CRPC after 01 August 2013 when ARSIs were first reimbursed in Australia on the PBS (46%, n=257). This was an unexpected result given the historically modest added survival benefit, the previously demonstrated superiority of novel anti-androgens and reports of declining use of FGAs in this context (8, 9, 11, 13). In fact, the recent European Association of Urology guidelines suggest there is no role for FGAs after the development of CRPC (14).

Patients treated with FGAs in our cohort were more likely to have lower-risk disease, as evidenced by significantly lower ISUP grade group, longer time to development of CRPC and lower incidence of visceral metastases. This supports the suggestion that FGAs are often used as an initial therapy in lower-risk patients given their favourable side-effect profile, despite reduced efficacy compared to newer systemic therapies (9). Importantly, the use of FGAs did not negatively influence the response to subsequent therapies. Strategies to avoid or delay the long-term toxicities of systemic therapies are being increasingly studied. The treatment landscape for lower-risk disease, specifically oligometastatic mCRPC continues to evolve, with increasing emphasis on localized therapies being another strategy in this setting (15).

The PSA50 response rate to FGAs of 37% in our cohort was consistent with that of historical data. Previous studies have reported varying rates between 20-77% (7-9, 16). Most recently, in a large randomised phase 2 study comparing bicalutamide and the novel ARSI enzalutamide, PSA50 response rate with bicalutamide was 21% (9). In that study, enzalutamide was more efficacious, with PSA50 of 82%, superior progression-free survival and superior quality of life. However, the incidence of adverse events was greater and a higher rate of hypertension and cardiac events was observed, particularly among patients with a prior history of cardiac disease. In our cohort, patients treated with FGAs were more likely to have cardiac risk factors, however there was no difference between the groups with regards to age or ECOG performance status. The higher rate of cardiovascular risk factors among patients treated with FGAs in our cohort may reflect this understanding and the preference to use FGAs rather than novel anti-androgens in those with significant pre-existing comorbidities.

Importantly, neither prior FGA use, nor PSA50 response to FGAs influenced subsequent systemic therapy choice or response in our study. Of note, patients were enrolled into the database between 2016-2019, and therefore contemporary systemic therapies were available to the patients in this cohort, irrespective of the date of development of castration resistance. Although TTF following subsequent docetaxel was slightly longer in those treated with prior FGAs, there were no differences in TTF with subsequent novel anti-androgen use based on prior FGA therapy or response. This is consistent with observations from previous studies. For example, Zhao et al. demonstrated that previous treatment with two FGAs, bicalutamide followed by flutamide did not affect the subsequent efficacy of abiraterone(17). Non-steroidal FGAs were not associated with a difference in abiraterone treatment duration in another study, however previous ketoconazole use was associated with significantly shorter treatment duration (18). For enzalutamide, there is greater concern regarding

the potential cross-resistance with prior FGA use and its impact on the efficacy of subsequent treatment due to its overlapping mechanism of action. However, 87% of patients in the PREVAIL study received prior FGAs and despite this, those treated with enzalutamide demonstrated a significant overall survival benefit (19). Furthermore, a retrospective real world study utilising the CAPRI registry did not demonstrate a difference in enzalutamide treatment duration or PSA response in those treated with FGAs (20). Emerging novel systemic therapies continue to contribute to a changing treatment landscape in mCRPC (21), and will require further analysis in this context.

While there are several established prognostic markers in chemotherapy-naïve mCRPC, the clinical significance of a response to FGA treatment in this context remains unclear, despite the frequent use of FGAs (22). In our study, multivariate analysis did not demonstrate an overall survival benefit in patients treated with FGAs despite significantly longer overall survival on univariate analysis. This is likely explained by the significant differences in other variables between the groups, with those who received prior FGAs having lower risk disease overall. Importantly however, a PSA50 response to FGA treatment was independently associated with increased overall survival on multivariate analysis, demonstrating that it is a significant favourable prognostic marker in mCRPC.

A small retrospective study has similarly demonstrated that a PSA50 response to previous FGA treatment was positively associated with progression-free and overall survival in patients receiving abiraterone following docetaxel (23). The successful sequential use of multiple anti-androgen therapies, predicted by PSA50 responses may reflect disease biology, suggesting a persistent reliance on androgen signalling pathways in these patients. Importantly, this was not accounted for by significantly improved PSA50 response rates to subsequent systemic therapies in our study. However, median TTF to abiraterone and enzalutamide was not reached in patients with prior PSA50 response to FGAs in our cohort and further follow-up is required to evaluate the true long-term outcomes.

Upfront docetaxel is now considered standard-of-care treatment, associated with a survival benefit when combined with ADT, particularly for patients with high volume hormone-sensitive prostate cancer (24, 25). Long-term survival analysis of the CHAARTED trial demonstrated a significant OS benefit in the high-volume disease group only (26), while other studies also demonstrate a benefit in patients with lower metastatic burden (27). Within our mCRPC cohort, patients were significantly less likely to receive FGA treatment if they had previously received upfront docetaxel (4% vs 21%,

p<0.0001). Although the influence of metastatic burden on the magnitude of treatment benefit with upfront docetaxel remains uncertain, the patients in our cohort who received this treatment were more likely to have high volume or higher-risk disease and may thus account for the lower use of FGAs. There are also limited data regarding the use and efficacy of FGAs in the context of upfront chemohormonal therapy.

Novel ARSIs, enzalutamide and abiraterone, have also been shown to improve outcomes in hormone-sensitive metastatic prostate cancer through several randomised clinical trials, independent of metastatic disease burden (28-30). The control arm of the ENZAMET study included an FGA bicalutamide in addition to ADT and enzalutamide also demonstrated superiority in this setting (29). Novel anti-androgens are not subsidised for use in Australia for the hormone sensitive setting. However, these results and the use of upfront docetaxel or ARSIs will likely contribute to the declining use of FGAs in the CRPC setting, especially in patients with higher-risk disease.

We acknowledge the potential limitations of our study. In performing a retrospective cohort study, we relied on data from the ePAD registry, as a snapshot of clinical practice in the Australian context. Accuracy of data relies on clinician documentation and therefore data including ECOG performance status and comorbidities may not always be comprehensively recorded. Furthermore, details regarding the specific FGA used was not captured in the database and therefore any potential differences in outcomes between agents. This also limited data relating to of adverse effects from specific FGAs, and their impact on baseline comorbidities. FGAs are associated with a favourable toxicity profile compared to other systemic therapies and our multivariate analysis results suggest that any toxicities were not significant enough to affect overall survival. A small subset of patients developed CRPC prior to the availability of novel anti-androgens and this may have influenced the decision to commence FGAs in the context of delaying chemotherapy. Longer follow up is required to identify emerging trends in the treatment of mCRPC, following the introduction of novel anti-androgens and upfront systemic therapies as well as the influence on long term outcomes following subsequent systemic therapies as previously discussed.

Despite these limitations, we believe our findings importantly highlight the ongoing use of FGAs in Australia. FGA use in our cohort was associated with a PSA50 response rate of over 30% and did not

negatively affect the efficacy of subsequent systemic therapies. Furthermore, a PSA50 response to FGAs was a favourable independent prognostic factor in our cohort. This is of particular relevance in many countries where novel anti-androgens are not subsidised and the use of FGAs is significantly higher. Furthermore, the timing of introduction of additional systemic therapies may be influenced by PSA50 response to FGAs, in light of our findings.



## CONCLUSION

In a real-world Australian context, FGAs continue to be prescribed to approximately half of mCRPC patients. Our ePAD cohort demonstrates that FGAs were more commonly used in lower-risk mCRPC or those with comorbidities, and did not significantly influence the choice or efficacy of subsequent systemic therapy. A PSA50 response to FGA therapy is a significant independent prognostic marker in mCRPC, associated with significantly improved overall survival. Longer follow-up is required to evaluate the long-term effects on the efficacy of subsequent therapies and potential cross-resistance, particularly in the context of an evolving treatment landscape in hormone-sensitive disease.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
2. Collins A, Sundararajan V, Millar J, Burchell J, Le B, Krishnasamy M, et al. The trajectory of patients who die from metastatic prostate cancer: a population-based study. BJU Int. 2019;123 Suppl 5:19-26.
3. Akakura K, Bolton D, Grillo V, Mermod N. Not all prostate cancer is the same - patient perceptions: an Asia-Pacific region study. BJU Int. 2020;126 Suppl 1:38-45.
4. Berg KD, Thomsen FB, Mikkelsen MK, Ingimarsdottir IJ, Hansen RB, Kejs AM, et al. Improved survival for patients with de novo metastatic prostate cancer in the last 20 years. Eur J Cancer. 2017;72:20-7.
5. Qu LG, Wardan H, Davis ID, Iddawela M, Sluka P, Pezaro CJ. Circulating oestrogen receptor mutations and splice variants in advanced prostate cancer. BJU Int. 2019;124 Suppl 1:50-6.
6. Holzbeierlein J, Lal P, LaTulippe E, Smith A, Satagopan J, Zhang L, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol. 2004;164(1):217-27.
7. Qian SB, Shen HB, Cao QF, Zhang L, Chen YF, Qi J. Bicalutamide 150 mg as secondary hormonal therapy for castration-resistant prostate cancer. Int Urol Nephrol. 2015;47(3):479-84.

8. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. J Clin Oncol. 2016;34(18):2098-106.

9. Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol. 2016;17(2):153-63.

10. Miyake H, Matsushita Y, Watanabe H, Tamura K, Motoyama D, Ito T, et al. Comparative assessment of prognostic outcomes between first-generation antiandrogens and novel androgen-receptor-axis-targeted agents in patients with non-metastatic castration-resistant prostate cancer. Int J Clin Oncol. 2019;24(7):842-7.

11. Kwan EM, Semira MC, Bergin ART, Muttiah C, Beck S, Anton A, et al. Impact of access to novel therapies on the initial management of castrate-resistant prostate cancer: an Australian multicentre study. Intern Med J. 2019.

12. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

13. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet. 2000;355(9214):1491-8.

14. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.

15. Ong WL, Koh TL, Lim Joon D, Chao M, Farrugia B, Lau E, et al. Prostate-specific membrane antigen-positron emission tomography/computed tomography (PSMA-PET/CT)-guided stereotactic ablative body radiotherapy for oligometastatic prostate cancer: a single-institution experience and review of the published literature. BJU Int. 2019;124 Suppl 1:19-30.

16. Kucuk O, Fisher E, Moinpour CM, Coleman D, Hussain MH, Sartor AO, et al. Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235). Urology. 2001;58(1):53-8.

17. Zhao J, Liu N, Sun S, Gou S, Wang X, Wang Z, et al. Light-activated ruthenium (II)-bicalutamide prodrugs for prostate cancer. J Inorg Biochem. 2019;196:110684.

18. McKay RR, Werner L, Fiorillo M, Nakabayashi M, Kantoff PW, Taplin ME. Predictors of duration of abiraterone acetate in men with castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2016;19(4):398-405.

19. Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. Eur Urol. 2017;71(2):151-4.
20. Kuppen M, Westgeest H, Van Den Eertwegh F, Van Moorselaar J, Mehra N, Coenen J, et al. Enzalutamide with or without prior anti-androgen treatment for castration resistant prostate cancer (CRPC): Results from the Dutch CAPRI registry. European Urology Supplements. 2018;17(14):e2891-e3.
21. Hofman MS, Emmett L, Violet J, A YZ, Lawrence NJ, Stockler M, et al. TheraP: a randomized phase 2 trial of (177) Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). BJU Int. 2019;124 Suppl 1:5-13.
22. Choi SY, Ryu J, You D, Jeong IG, Hong JH, Ahn H, et al. Prognostic factors of oncologic outcomes in metastatic chemotherapy-naive castration-resistant prostate cancer treated with enzalutamide in actual clinical practice in East Asia. Urol Oncol. 2018;36(9):401 e11- e18.
23. Li JR, Chiu KY, Wang SS, Yang CK, Chen CS, Ho HC, et al. Effectiveness of Deferred Combined Androgen Blockade Therapy Predicts Efficacy in Abiraterone Acetate Treated Metastatic Castration-Resistant Prostate Cancer Patients after Docetaxel. Front Pharmacol. 2017;8:836.
24. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.
25. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-46.
26. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-7.
27. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019.
28. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-60.
29. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-31.

30. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017;377(4):338-51.

**Table 1 – Baseline Characteristics**

| Characteristics | Prior FGA *N= 322* (51%) | No prior FGA *N= 312* (49%) | Total N=634 | P value |
|---|---|---|---|---|
| **AGE AT CRPC** | | | | |
| Median age (years) | 75 years | 74 years | | |
| ≥ 75 years | 171 (53%) | 149 (48%) | 320 (51%) | 0.2 |
| <75 | 151 (47%) | 163 (52%) | 314 (49%) | |
| **ECOG PERFORMANCE STATUS** | | | | |
| ECOG = 0 | 180 (56%) | 173 (56%) | 353 (56%) | 0.79 |
| ECOG = 1 | 110 (34%) | 103 (33%) | 213 (34%) | |
| ECOG > 1 | 28 (9%) | 29 (9%) | 57 (9%) | |
| Unknown | 4 (1%) | 7 (2%) | 11 (1%) | |
| **BASELINE CORMORBIDITIES** | | | | |
| Ischaemic heart disease | 86 (27%) | 70 (22%) | 156 (25%) | 0.23 |
| Stroke | 29 (9%) | 19 (6%) | 48 (8%) | 0.18 |
| Peripheral vascular disease | 11 (3%) | 12 (4%) | 23 (4%) | 0.83 |
| **CARDIOVASCULAR RISK FACTORS** | | | | |
| Hypertension | 195 (61%) | 152 (49%) | 347 (55%) | **0.0031** |
| Diabetes | 59 (18%) | 51 (16%) | 110 (17%) | 0.53 |
| Hypercholesterolaemia | 137 (43%) | 103 (33%) | 240 (38%) | **0.01** |
| Current smoker | 19 (6%) | 23 (7%) | 42 (7%) | 0.22 |
| Ex-smoker | 92 (29%) | 71 (23%) | 163 (26%) | |
| **ISUP GRADE GROUP** | | | | |
| ≤3 | 82 (25%) | 63 (20%) | 145 (23%) | **0.04** |
| 4-5 | 133 (41%) | 156 (50%) | 289 (46%) | |
| Not known | 108 (24%) | 93 (30%) | 201 (32%) | |
| **TIME TO CRPC** | | | | |
| Median (months) | 25.6 months | 16.0 months | | **<0.0001** |
| ≤ 12 months | 72 (22%) | 121 (39%) | 193 (30%) | **<0.0001** |
| > 12 months | 250 (78%) | 191 (61%) | 441 (70%) | |
| **PSA DOUBLING TIME** | | | | |
| <1 month | 36 (11%) | 41 (13%) | 77 (12%) | **0.02** |
| 1-3 months | 135 (42%) | 94 (30%) | 229 (36%) | |
| 4-6 months | 65 (20%) | 44 (14%) | 109 (17%) | |
| >6 months | 32 (10%) | 43 (14%) | 75 (12%) | |
| Unknown | 54 (17%) | 89 (29%) | 143 (23%) | |
| **VISCERAL METASTASES** | | | | |
| Yes | 16 (5%) | 35 (11%) | 51 (8%) | **0.005** |
| No | 306 (95%) | 277 (89%) | 583 (92%) | |
| **UPFRONT DOCETAXEL** | | | | |
| Yes | 11 (3%) | 68 (22%) | 79 (12%) | **<0.0001** |
| No | 311 (97%) | 235 (78%) | 546 (88%) | |

**Table 2 – Median time to treatment failure during first-line systemic therapy by FGA use and response**

| First-line systemic therapy | Prior FGA | | | No Prior FGA | P value |
|---|---|---|---|---|---|
| | ≥50% response | <50% response | No response | | |
| **Enzalutamide** | 11.7 months | | | 11.9 months | 0.32 |
| **N=240** | Not reached | 11.7 months | 9.0 months | | 0.47 |
| **Abiraterone** | 18.8 months | | | 11.7 months | 0.16 |
| **N=110** | Not reached | 13.7 months | 12.9 months | | 0.49 |
| **Docetaxel** | 8.3 months | | | 7.9 months | 0.039 |
| **N=170** | | | | | |

**Table 3: Univariate and Multivariate Analyses of Overall Survival**

| Variable | Univariate HR (95% CI) | P-value | Multivariate HR (95% CI) | P-value |
|---|---|---|---|---|
| **Age**[1] | 0.995 (0.977-1.013) | 0.597 | 0.972 (0.942-1.003) | 0.081 |
| **ECOG at CRPC (ref <1)** | | | | |
| **≥ 1** | 2.246 (1.384-3.645) | **0.001** | 1.762 (0.592-5.249) | 0.309 |
| **Ischemic Heart Disease** | 1.449 (1.014-2.072) | **0.042** | 1.477 (0.828-2.634) | 0.187 |
| **Peripheral Vascular Disease** | 1.681 (0.818-3.456) | 0.158 | 2.941 (0.844-10.250) | 0.090 |
| **Stroke** | 0.980 (0.513-1.867) | 0.951 | | |
| **Hypertension** | 1.163 (0.823-1.644) | 0.392 | | |
| **Diabetes** | 1.558 (1.060-2.291) | **0.024** | 2.701 (1.466--4.976) | **0.001** |
| **Hypercholesterolaemia** | 1.284 (0.906-1.818) | 0.160 | 0.936 (0.547-1.601) | 0.808 |
| **Smoking History** | 1.291 (0.839-1.985) | 0.245 | | |
| **ISUP Grade Group (Ref ≤ 3)** | | | | |
| **4-5** | 1.363 (0.892-2.082) | 0.151 | 0.874 (0.518-1.474) | 0.614 |
| **Time to CRPC (Ref ≤ 12mo)** | | | | |
| **>12 mo** | 0.479 (0.336-0.684) | **<0.001** | 0717 (0.423-1.214) | 0.215 |
| **PSA doubling time (Ref ≤ 3mo)** | | | | |
| **>3 mo** | 0.395 (0.254-0.613) | **<0.001** | 0.365 (0.199-0.672) | **0.001** |
| **Visceral Metastases** | 1.905 (1.110-3.271) | **0.019** | 1.130 (0.485-2.634) | 0.778 |
| **Upfront Docetaxel** | 2.597 (1.487-4.538) | **0.001** | 2.330 (0.989-5.489) | 0.053 |
| **Prior FGA** | 0.516 (0.368-0.724) | **<0.001** | 1.142 (0.645-2.021) | 0.648 |
| **Prior FGA PSA50 response** | 0.280 (0.175-0.449) | **<0.001** | 0.232 (0.112-0.482) | **<0.001** |

[1]Continuous variable

*Significant p-values <0.05 are shown in bold.*

**Figure 1 – First-line systemic therapy for mCRPC by previous FGA use**

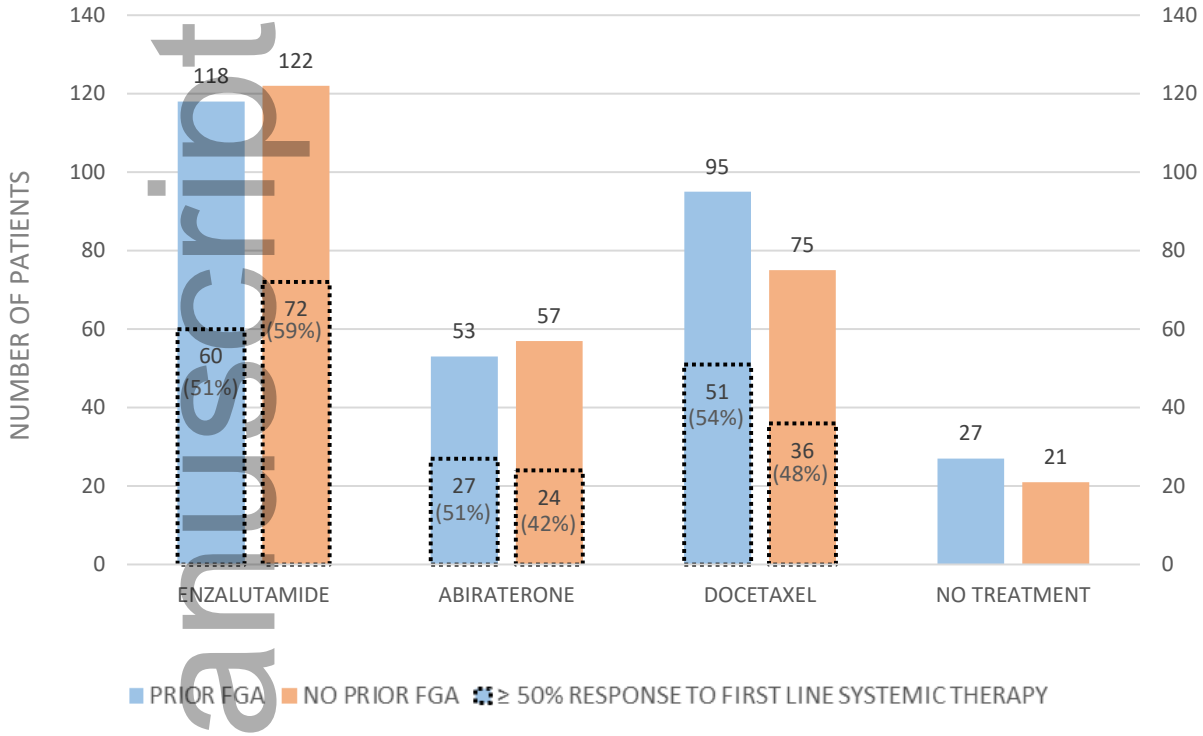
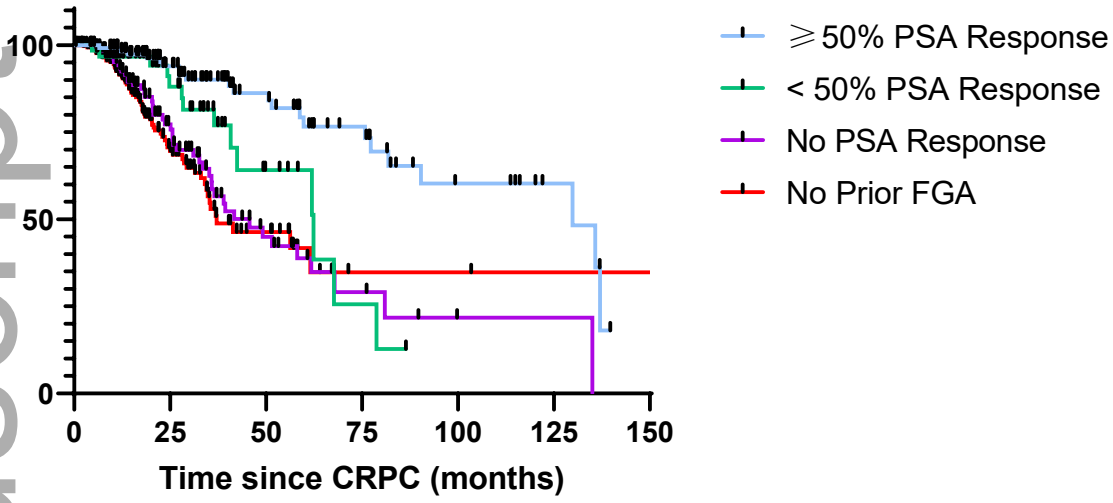
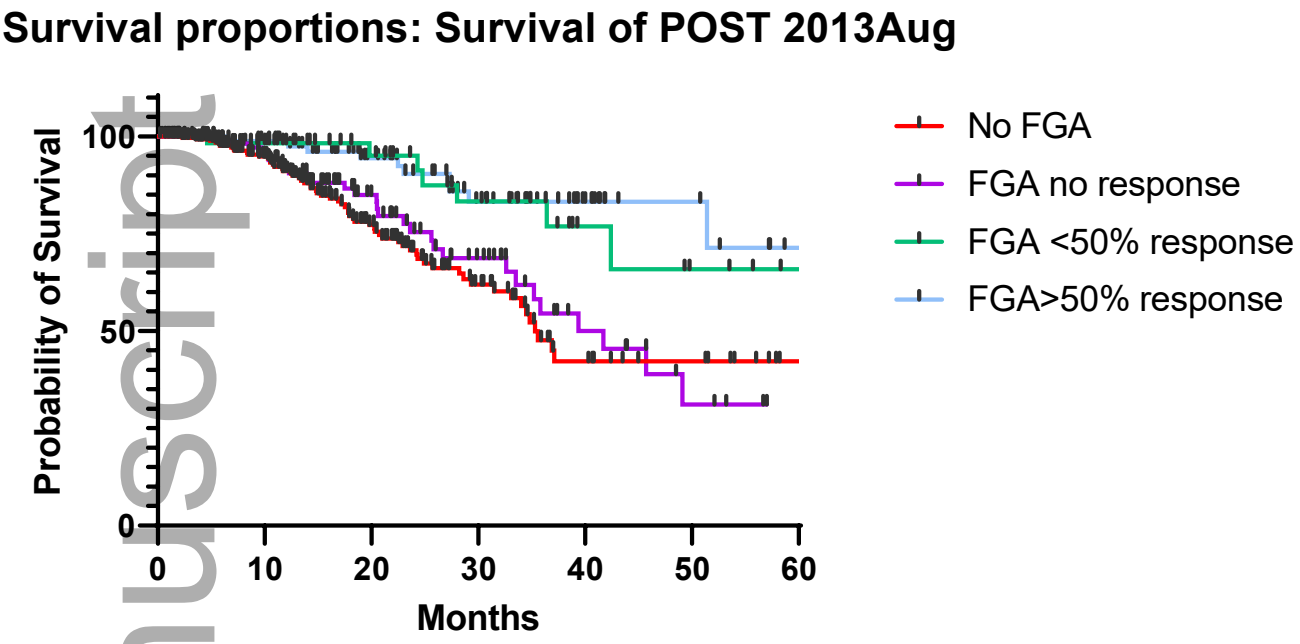


**Figure 2 – Overall survival by response to FGA**




| Number At Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 50% Response | 119 | 79 | 40 | 24 | 11 | 6 | 0 |
| < 50% Response | 63 | 30 | 9 | 3 | 1 | 0 | 0 |
| No Response | 139 | 54 | 18 | 6 | 2 | 1 | 0 |
| No FGA | 312 | 70 | 17 | 3 | 3 | 2 | 1 |

**Figure 3 – Overall survival by response to FGA, post-August 2013**




Number At Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 50% Response | 85 | 78 | 54 | 32 | 18 | 9 | 3 |
| < 50% Response | 56 | 45 | 31 | 21 | 8 | 5 | 2 |
| No Response | 116 | 90 | 54 | 27 | 12 | 5 | 1 |
| No FGA | 300 | 171 | 94 | 42 | 16 | 10 | 2 |