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Prostate Cancer

Androgen Receptor Modulation Optimized for Response–Splice Variant: A Phase 3, Randomized Trial of Galeterone Versus Enzalutamide in Androgen Receptor Splice Variant-7–expressing Metastatic Castration-resistant Prostate Cancer

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Abstract

Background: : Detection of androgen receptor (AR) splice variant-7 (AR-V7) messenger RNA (mRNA) in circulating tumor cells (CTCs) is associated with a suboptimal response to abiraterone and enzalutamide in metastatic castration-resistant prostate cancer (mCRPC). Galeterone inhibits CYP17 and AR, and induces AR protein degradation. We hypothesized that galeterone would be clinically superior to enzalutamide in AR-V7–positive (AR-V7+) mCRPC.
Objective: : To screen and characterize AR-V7+ mCRPC, and evaluate galeterone compared with enzalutamide.
Design, setting, and participants: : This was a multicenter randomized phase 3 trial; enzalutamide-, abiraterone-, and chemotherapy-naïve mCRPC patients had AR-V7 prescreening using a CTC-based mRNA assay.
Intervention: : AR-V7+ patients were randomized (1:1) to open-label galeterone or enzalutamide; planned sample size was 148.
Outcome measurements and statistical analysis: : The primary endpoint was radiographic progression-free survival (rPFS). Baseline AR-V7 status was correlated with patient characteristics.
Results and limitations: : Overall, 953 men were prescreened for AR-V7; 323 (34%) had detectable CTCs, and 73/323 had AR-V7 mRNA. The AR-V7+ prevalence was 8% (73/953; 95% confidence interval [CI] 6–10%). AR-V7 was associated with indicators of advanced and high-volume disease at baseline, including higher prostate-specific antigen (PSA) level ($p < 0.001$), more bone metastases ($p < 0.001$), docetaxel for hormone-sensitive disease ($p < 0.001$), prior first-generation androgen deprivation therapy ($p < 0.001$), and shorter time from diagnosis to enrollment ($p < 0.001$). Of 73 eligible patients, 38 were randomized to galeterone ($n = 19$) or enzalutamide ($n = 19$); 35 dropped out before randomization. Owing to high censorship for the rPFS events, the data monitoring committee recommended early closure based on interim evidence that the primary endpoint would not be met. The PSA50 values were 2/16 (13%) and 8/19 (42%) for galeterone and enzalutamide respectively (proportion difference = −0.278, 95% CI −0.490 to 0.097).
Conclusions: : The prevalence of CTC mRNA AR-V7 in first-line mCRPC was 8% (95% CI 6–10%). AR-V7+ was associated with the characteristics of aggressive and advanced disease. These men had rapid disease progression. Development of galeterone will not be pursued.
Patient summary: : Of men with metastatic castration-resistant prostate cancer, 8% had the androgen receptor splice variant-7 (AR-V7) blood biomarker. The AR-V7+ patients had features of aggressive disease. Thirty-eight men were treated with either galeterone or enzalutamide; the trial was stopped early prior to determining efficacy because too many patients transitioned off the trial due to advancing cancer before having required radiographs.

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1. Introduction

Lethal prostate cancer evolves from hormone-sensitive to metastatic castration-resistant prostate cancer (mCRPC) [1]. The androgen receptor (AR) is central to tumor growth, and androgen deprivation therapy (ADT) is the primary therapy [2]. The AR pathway remains a driver of tumor growth in most mCRPC patients and thus remains a valid therapeutic target. Tumor addiction to AR together with selective pressure from ADT leads to AR pathway alterations including AR gene amplification, overexpression, mutation, splice variants, and increases in adrenal and intratumoral androgens [3]. Each of these alterations is a possible therapeutic target, and the challenge remains designing and aligning therapy to match tumor vulnerabilities.

Second-generation ADT is currently in use for both hormone-sensitive prostate cancer and mCRPC [4]. Abiraterone acetate (hereafter abiraterone) is a potent inhibitor of cytochrome P450 (CYP)17A1 that suppresses extragonadal androgen synthesis; enzalutamide is a next-generation AR antagonist. Abiraterone and enzalutamide have improved survival in mCRPC patients [5–8]. In the prechemotherapy setting, approximately 70–80% of patients respond favorably to abiraterone; however, the response rate and duration of response is much lower in second line [9–11]. An AR-directed therapy effective in the context of primary or secondary resistance to abiraterone/enzalutamide would greatly benefit patients.

Constitutive activation of AR from AR variants with ligand-binding domain truncation is implicated in AR-targeted therapy resistance [12]. The AR isoform encoded by splice variant 7 (AR-V7) lacks the ligand-binding domain; yet, it is constitutively active. AR-V7 can be detected in circulating tumor cells (CTCs) in some cases of mCRPC [13] by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR). Detection of AR-V7 in CTCs (distinguished from tumor detection) has been associated with resistance to enzalutamide and abiraterone in mCRPC [13]. An expanded analysis confirmed that AR-V7 detection was prognostic of poor outcomes [14,15]. Patients with AR-V7 can respond to taxanes [16,17] or theoretically to AR-directed therapy not dependent on AR ligand-binding domain; further analysis is needed to understand the role of AR-V7 in mCRPC.

Galeterone has been reported to inhibit AR signaling through multiple mechanisms: CYP17 inhibition, competitive antagonism of AR, and induction of AR and AR-V7 protein degradation [18]. In phase 1/2 trials, galeterone was tolerable at 2550 mg/d and resulted in reduction in serum androgens and prostate-specific antigen (PSA), as would be expected from CYP17 inhibition even in AR-V7–positive (henceforth AR-V7+) patients [19]. The Androgen Receptor Modulation Optimized for Response—Splice Variant (ARMOR3-SV) program, an open-label, multicenter, phase 3 trial designed to test the hypothesis that galeterone is superior to enzalutamide in CTC AR-V7+ mCRPC, included large-scale screening for CTC-transcript AR-V7 and codevelopment of the AR-V7 assay as a companion diagnostic with galeterone.

2. Patients and methods

2.1. Study population

Informed consent was obtained for AR-V7 prescreening; study consent was subsequently obtained for AR-V7+ patients. Participants had biopsy-confirmed prostatic adenocarcinoma, maintained primary castration, and had asymptomatic or mildly symptomatic progressive mCRPC according to the Prostate Cancer Working Group 2 (PCWG2) [20]. They were Eastern Cooperative Oncology Group (ECOG) $\leq$1 and naïve to abiraterone, enzalutamide, chemotherapy, and investigational agents; docetaxel for hormone-sensitive cancer was allowed. Eligible AR-V7+ patients were randomized (1:1, nonblinded) to daily oral galeterone (2550 mg) or enzalutamide (160 mg). Patients continued study therapy until confirmed radiological progression per Response Evaluation Criteria in Solid Tumors (RECIST 1.1), PCWG2 unequivocal clinical progression, or consent withdrawal. All aspects of the clinical trial and AR-V7 prescreening were funded by Tokai Pharmaceuticals.

2.2. AR-V7 assay

The CTC-based AR-V7 clinical trial assay utilized modification of the methods reported by Antonarakis et al [13]. The ARMOR3-SV program included the codevelopment of an AR-V7 assay as a companion diagnostic.

2.3. Efficacy assessments

The primary objective was to compare radiographic progression between arms, based on assessments by central, blinded, and independent radiologists. Computer tomography (CT) scans and bone scans were performed every 8 wk. Determinations of response or progression were made by two independent radiologists. Radiographic progression-free survival (rPFS) was measured from randomization and based on the occurrence of one of the following: radiographic progression (PCWG2) [20] for bone disease and/or RECIST 1.1 for soft tissue/visceral disease, or death from any cause. Secondary endpoints included time on treatment, PSA50 ($\geq$50% decrease within the first 8 wk) or PSA30 response (PCWG2), time to ECOG deterioration by $\geq$1 point, best overall soft tissue response (RECIST 1.1), time to initiation of next prostate cancer therapy, and galeterone pharmacokinetics (PK).

2.4. Safety assessments

The frequency and intensity of adverse events, and changes in hematologic and chemistry parameters were recorded and compared in cohorts.

2.5. Statistical analysis

Eligibility for randomization required patients to be CTC positive and AR-V7+; AR-V7 status could be ascertained

only in CTC-positive patients. The relationship between baseline characteristics and CTCs (regardless of AR-V7 status), and AR-V7 detection are characterized using descriptive statistics. The p values test the homogeneity of prevalence across the subsets defined by the factor being analyzed. All p values below 0.10 are considered consistent with evidence of differences across subsets.

The primary endpoint was rPFS. The primary statistical analysis was specified as a log-rank test comparing arms (intention to treat). It was hypothesized that the estimated median rPFS for enzalutamide would be approximately 4 mo, while the median rPFS for the galeterone cohort would be 82% longer than that of the enzalutamide cohort (corresponding, under exponential assumptions, to a hazard ratio for rPFS of $\leq$0.55). A one-sided type I error probability of 0.025 and a target power of 90% required 120 rPFS events among 148 total patients. It was anticipated that 2000 patients would be prescreened, based on the assumptions of percentages of patients who would have both CTCs and AR-V7+, to enroll 148 patients [15].

The trial was monitored by an independent data monitoring committee (DMC) governed by a charter based on regulatory guidance for DMCs. The rate of censored events (patient coming off study for reasons other than rPFS) was monitored in a pooled manner by the sponsor because of concerns that clinical events could drive therapy change, resulting in a reduction in the required events.

3. Results

3.1. AR-V7 prescreening

The trial was conducted at 120 sites in nine countries. From December 2015 to July 2016, 953 patients were prescreened; CTCs were detected in 323 (34%, 95% confidence interval [CI] 31–37%) and AR-V7 was detected in 73 of these 323 (23%, 95% CI 18–27%; Fig. 1). Among all the 953 patients who were screened, 73 (8%, 95% CI 6–10%) tested positive for CTC-transcript AR-V7. This detection rate is consistent with an estimated rate of 8–10% for AR-V7+ in mCRPC patients naïve to abiraterone and enzalutamide [15].

AR-V7 status could be ascertained only in patients with CTCs; thus, the following baseline factors were considered for prevalence estimates: Gleason score, years from diagnosis, screening PSA, ECOG performance status (PS), metastases at diagnosis, prior docetaxel (for hormone-sensitive disease), prior ADT (eg, bicalutamide), and number of bone lesions. Figs. 2 and 3 show the prevalence estimates (status probability estimates) defined by these factors for all patients screened for CTCs and AR-V7, respectively. Fig. 4 shows the prevalence of AR-V7 for CTC-positive patients.

CTC detection (Fig. 2) was correlated with Gleason score (31% in Gleason 7 vs 64% in Gleason 10; $p = 0.006$), years from diagnosis (28% in >4.2 yr vs 45% in <4.2 yr; $p < 0.001$, 4.2 yr being median), prior docetaxel for hormone-sensitive disease (32% in docetaxel nonrecipients vs 49% in docetaxel recipients; $p = 0.001$), metastatic disease at diagnosis (30% without vs 41% with metastases at diagnosis; $p = 0.001$), number of bone metastases (21% without bone metastases vs 66% with >21 metastases; $p < 0.001$), ECOG PS (29% in ECOG = 0 vs 43% in ECOG $\geq$ 1; $p < 0.001$), and screening PSA (21% with PSA < 15.5 ng/ml vs 47% with PSA > 15.5 ng/ml; $p < 0.001$). AR-V7 detection in total screened population (Fig. 3) correlated with years from diagnosis (5% in >4.2 yr vs 13% in <4.2 yr; $p < 0.001$), prior docetaxel for hormone-sensitive disease (6% docetaxel nonrecipients vs 22% docetaxel recipients; $p < 0.001$), prior first-generation ADT (4% ADT nonrecipients vs 11% ADT recipients; $p < 0.001$), presence of metastases at diagnosis (6% without vs 10% with metastases; $p = 0.046$), number of bone metastases (4% without any bone metastases vs 30% with >21 bone metastases; $p < 0.001$), ECOG PS (6% ECOG = 0 vs 11% ECOG $\geq$ 1; $p = 0.023$), and screening PSA (3% with PSA < 15.5 ng/m vs 13% with PSA > 15.5 ng/m; $p < 0.001$). Similar to the total screened population, the majority of these factors were associated with AR-V7+ in the CTC-positive cohort (Fig. 4).

3.2. Patients and treatment

Overall, 38 patients were randomized to galeterone (19) or enzalutamide (19); the remaining AR-V7+ patients ($n = 35$) dropped out before randomization due to rapid disease progression or screen failure. Patient characteristics are shown in Table 1.

After 38 patients enrolled, 24 had sufficient data for DMC meeting. After analysis, the DMC recommended trial termination because the trial was unlikely to meet its primary endpoint of rPFS due to rapid progression resulting in a censoring rate of 58%. Twelve patients had come off therapy and seven discontinued without a qualified rPFS event. Most patients coming off the study rapidly transitioned to chemotherapy or palliative care due to unequivocal clinical progression. Five patients had qualified events that could be included in endpoint analysis (one death and four rPFS).

Formal efficacy analysis was not possible due to premature termination of trial and data collection. Of the 38 randomized patients, 23 had CT/magnetic resonance imaging scans reviewed by RECIST 1.1 (11 enzalutamide and 12 galeterone). Three of 23 (13%) patients had declared progression during treatment (all galeterone). Eleven patients had bone scans evaluated centrally, and seven men (six enzalutamide and one galeterone) had a bone scan outside the flare window (16 wk after C1D1); progressive disease was confirmed in two of seven patients (one enzalutamide and one galeterone).

Of the 38 randomized patients, 35 were evaluable for PSA response at 8 wk or the end of treatment whichever came first. PSA50 response was 8/19 (42%) on enzalutamide and 2/16 (13%) on galeterone (proportion difference = −0.278, 95% CI −0.490 to 0.097). PSA response was not confirmed due to study termination. PSA progression according to PCWG1 (not PCWG2 that requires confirmation) is illustrated in Supplementary Fig. 1.

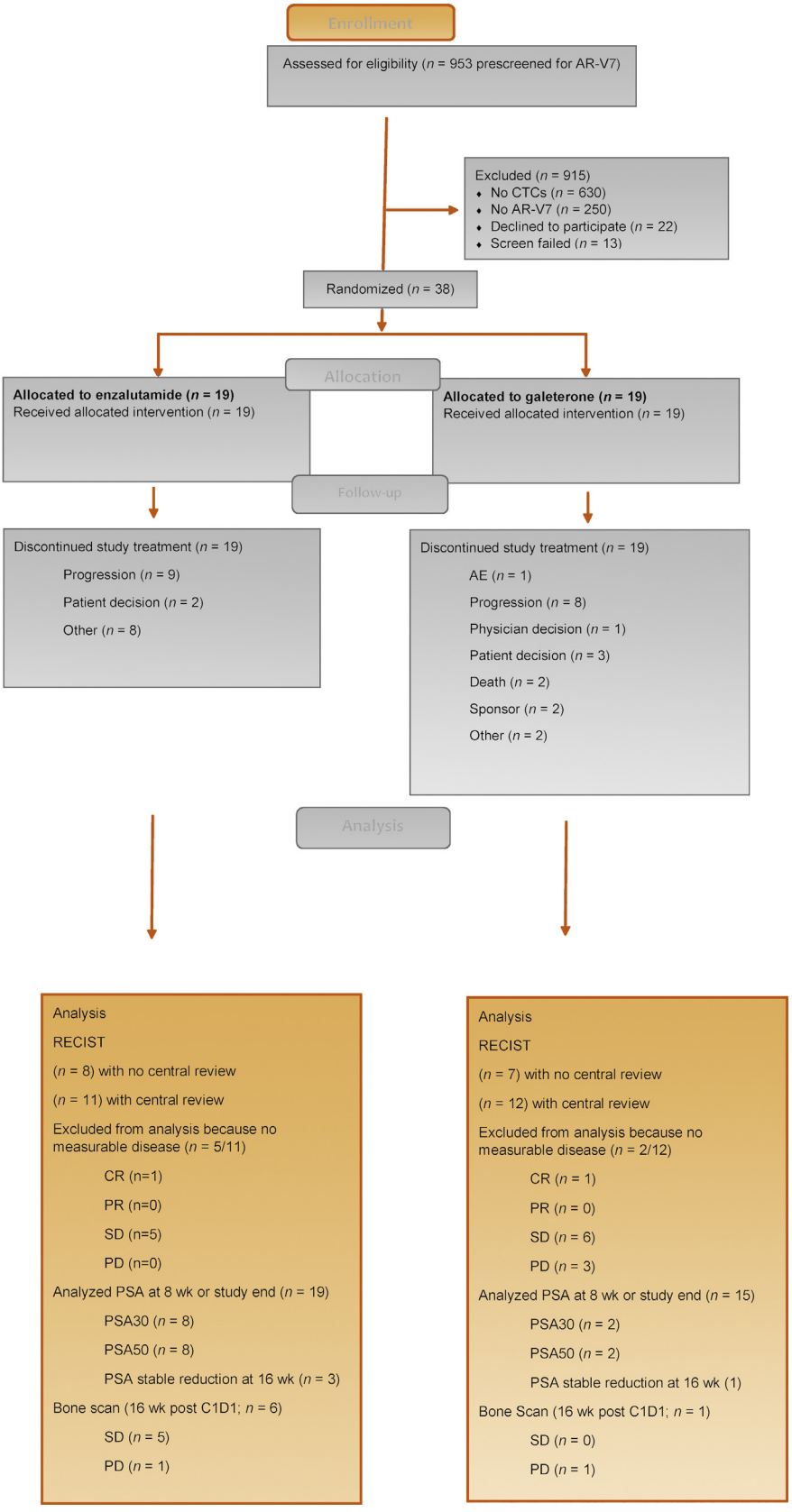

Fig. 1 – CONSORT diagram of patients prescreened for AR-V7 demonstrating those with detectable CTCs and AR-V7. In addition to detectable CTCs, full-length AR was required to detect AR-V7. A total of 38 AR-V7+ patients were randomized to receive either enzalutamide (19) or galeterone (19). AE = adverse event; AR = androgen receptor; AR-V7 = androgen receptor splice variant-7; CR = complete response; CTC = circulating tumor cell; PD = progressive disease; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

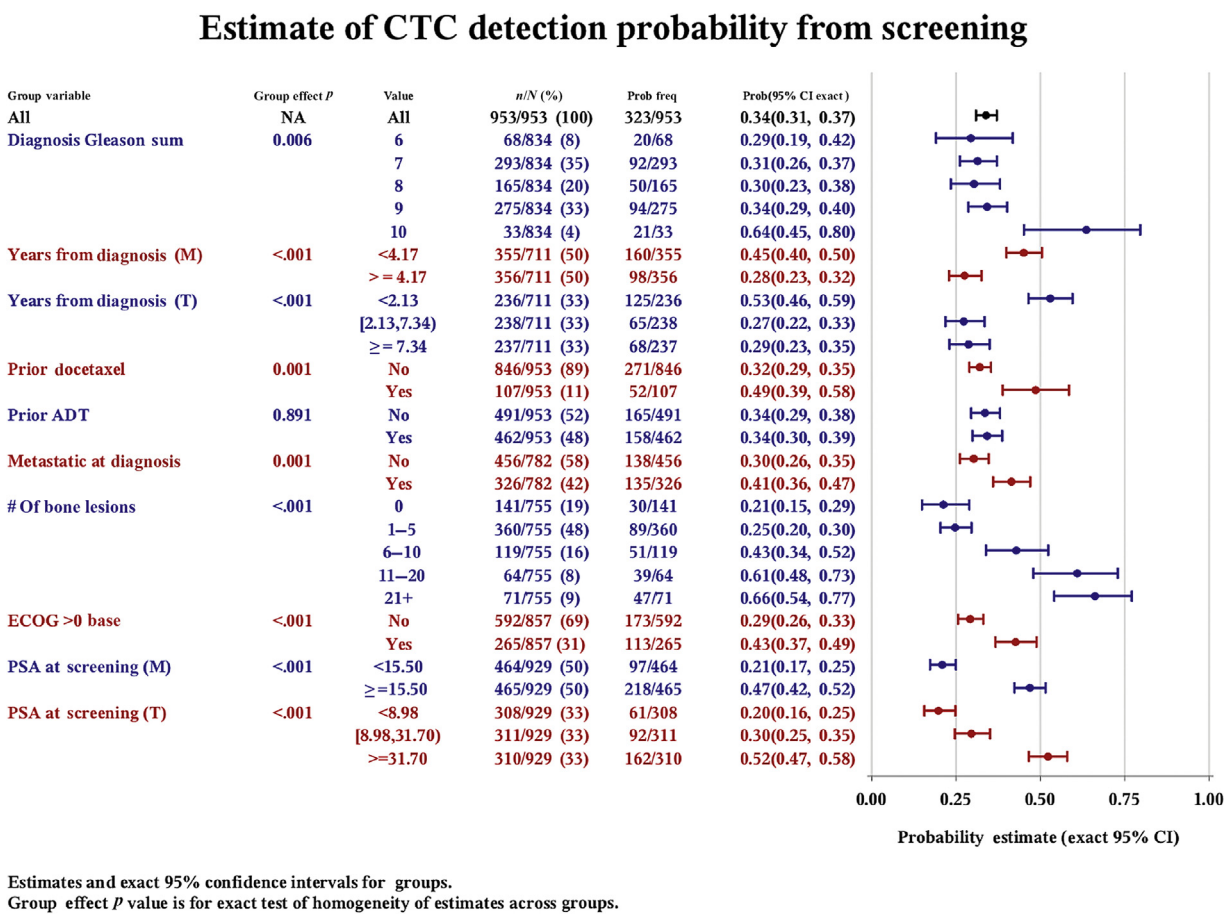

Fig. 2 – Baseline patient characteristics and the probability of circulating tumor cell (CTC) detection ($n = 953$). The p values test the homogeneity of prevalence across the subsets defined by the factor being analyzed. Small p values (below 0.10) are considered consistent with evidence of differences across subsets. ADT = first-generation androgen deprivation therapy (bicalutamide); CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; Freq = frequency; M = median; NA = not available; Prob = probability; PSA = prostate-specific antigen; T = tertile.

Treatment emergent adverse events (TEAEs) for galeterone included fatigue (46%), anorexia (31%), asthenia (31%), nausea (31%), anemia (26%), anxiety (21%), constipation (16%), dizziness (16%), insomnia (16%), and rash (16%). All other TEAEs were reported in <15%. There were four cases of serious adverse reactions: two anemia, one fatigue, and one hepatic failure (possibly related in context of rapidly progressive disease).

PK evaluation was completed on 13 galeterone-treated patients; 10 achieved steady-state levels with galeterone 2550 mg daily (three with dose reductions precluding assessment). The mean Cmax ($n = 10$) was 2.73 μM, consistent with steady-state Cmax estimates of 2.5 μM. A steady-state plasma level of >2 μM was predicted to translate to >10 μM in tumor, a concentration required for AR degradation in vitro [18].

4. Discussion

There remains an urgent need for more durable therapies in mCRPC and for biomarkers to direct the most impactful therapy to appropriate patients. In 2014 when ARMOR3-SV was designed, AR-V7 had been reported as a putative biomarker predicting resistance to abiraterone and enzalutamide. The activity of abiraterone and enzalutamide depends on an intact AR ligand-binding domain; galeterone has AR degrading properties mediated via the proteasome that can impact both AR-FL and AR-Vs [18]. The role of AR-Vs as drivers of tumor growth opposed to a predictive biomarker without a driver role remains unclear [21]; the rationale supporting the efficacy of galeterone in AR-V7+ CRPC remains in either case.

The abrupt early termination of ARMOR3-SV after 38 patients had been enrolled was due to censoring of seven of 12 patients (58%) without confirmation of the primary endpoint (rPFS). Most of these patients had rapid cancer-related deterioration, and treating physicians appropriately determined that they urgently needed non-protocol interventions. When the trial was designed, there were no data on the clinical profiles of CTC + AR-V7+ patients naïve to abiraterone or enzalutamide; thus, the aggressive disease of the targeted population was not anticipated. Radiographic PFS, although a valid endpoint in mCRPC, is not achievable in this select high-risk population,

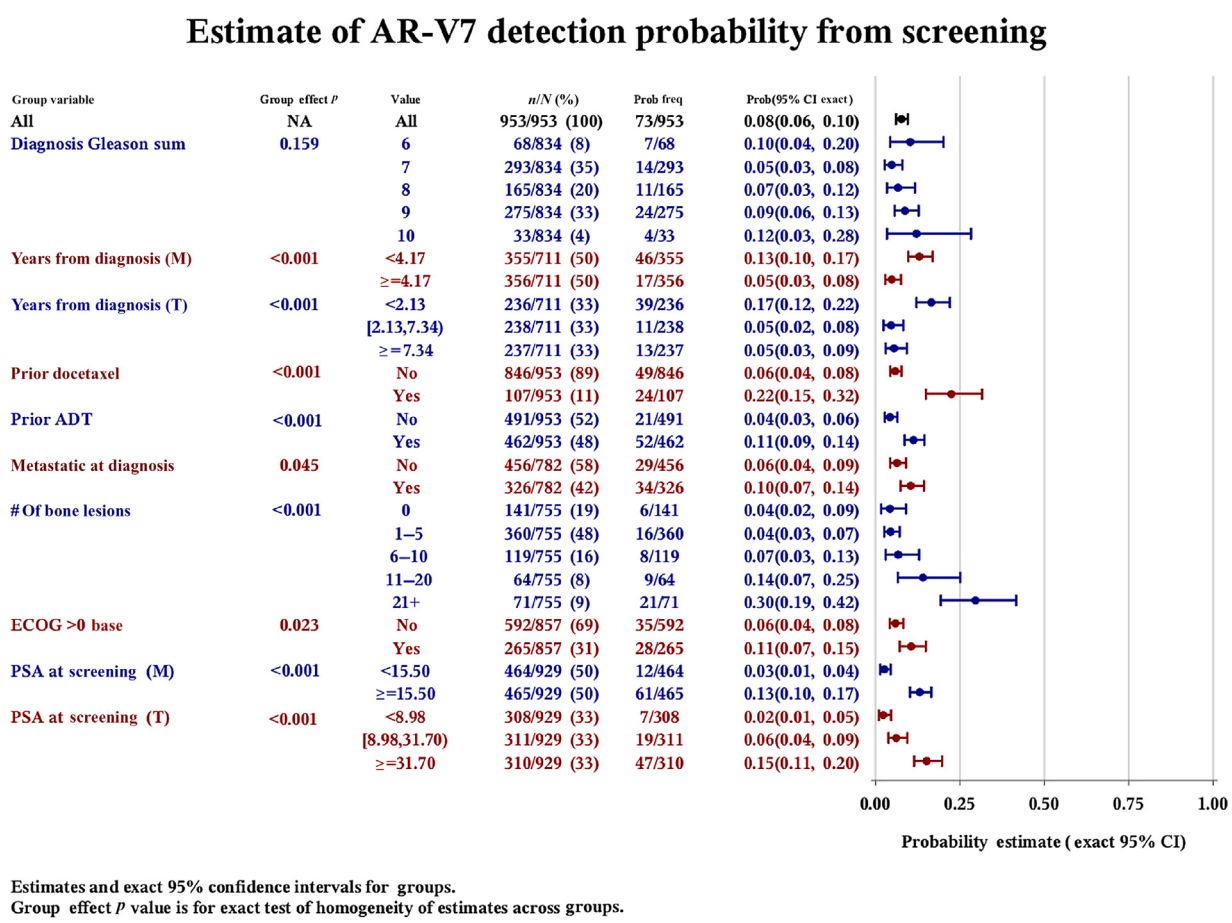

Fig. 3 – Baseline patient characteristics and the probability of AR-V7 detection for the total cohort screened (n = 953). AR-V7 positivity required both detectable CTCs and full-length AR. The p values test the homogeneity of prevalence across the subsets defined by the factor being analyzed. Small p values (below 0.10) are considered consistent with evidence of differences across subsets. ADT = first-generation androgen deprivation therapy (bicalutamide); AR-V7 = androgen receptor splice variant-7; CI = confidence interval; CTC = circulating tumor cell; ECOG = Eastern Cooperative Oncology Group; Freq = frequency; M = median; NA = not available; Prob = probability; PSA = prostate-specific antigen; T = tertile.

and this experience warrants caution for future biomarker-directed trials.

This ARMOR3-SV screening experience is the largest global, multicenter cohort evaluating CTC-transcript AR-V7 and provides valuable insights. A total of 953 patients were prescreened with CTC-transcript RT-PCR assay. As expected, the incidence of AR-V7+ in pre-abiraterone/enzalutamide patients was low (8%) and consistent with a recent report [15]. Other assays including a CTC-based immunohistochemical assay (Epic Sciences) were considered [17], and the RT-PCR assay was chosen because it had the largest published data and could be scaled up to a large international cohort. Recent data demonstrate that the PCR-based AR-V7 assay correlates with CTC counts, AR-V7+ correlates with other poor-prognosis biomarkers, and prognostication related to AR-V7+ is due in part to higher CTC counts [25,26].

CTC AR-V7 messenger RNA (mRNA) positivity (Fig. 3 and 4) was associated with features of biologically aggressive disease: shorter time from diagnosis to study entry, increased bone lesions, higher PSA, metastases at diagnosis, prior docetaxel, and ADT. CTC enumeration was not done; thus, an analysis of AR-V7+ as a reflection of CTC burden is not possible. Consistent with the biological AR-V hypothesis, the prevalence of AR-V7 (but not CTC positivity) increased with prior ADT (bicalutamide) exposure (Fig. 2–4) due to AR-V7 induction by prior therapy targeting the AR ligand-binding domain [22,23]. What was less expected was the positive correlation between higher AR-V7 and exposure to docetaxel for hormone-sensitive disease. Previous studies in mCRPC suggested a reduction in AR-V7 upon docetaxel treatment [16]; the current findings imply that men selected to receive docetaxel for hormone-sensitive disease may have been skewed toward more aggressive features or a higher disease burden, resulting in a higher AR-V7 prevalence especially at the time of disease progression. However, even in the context of aggressive features, AR-V7 was detected in the minority in any subset. For example, AR-V7+ prevalence was 15% with PSA > 31 ng/ml and 30% with >21 bone lesions. The AR-V7 detection rate for men with PSA between 9 and 32 ng/ml was only 6%. These metrics should be considered when considering the cost and clinical utility of AR-V7 testing in early mCRPC.

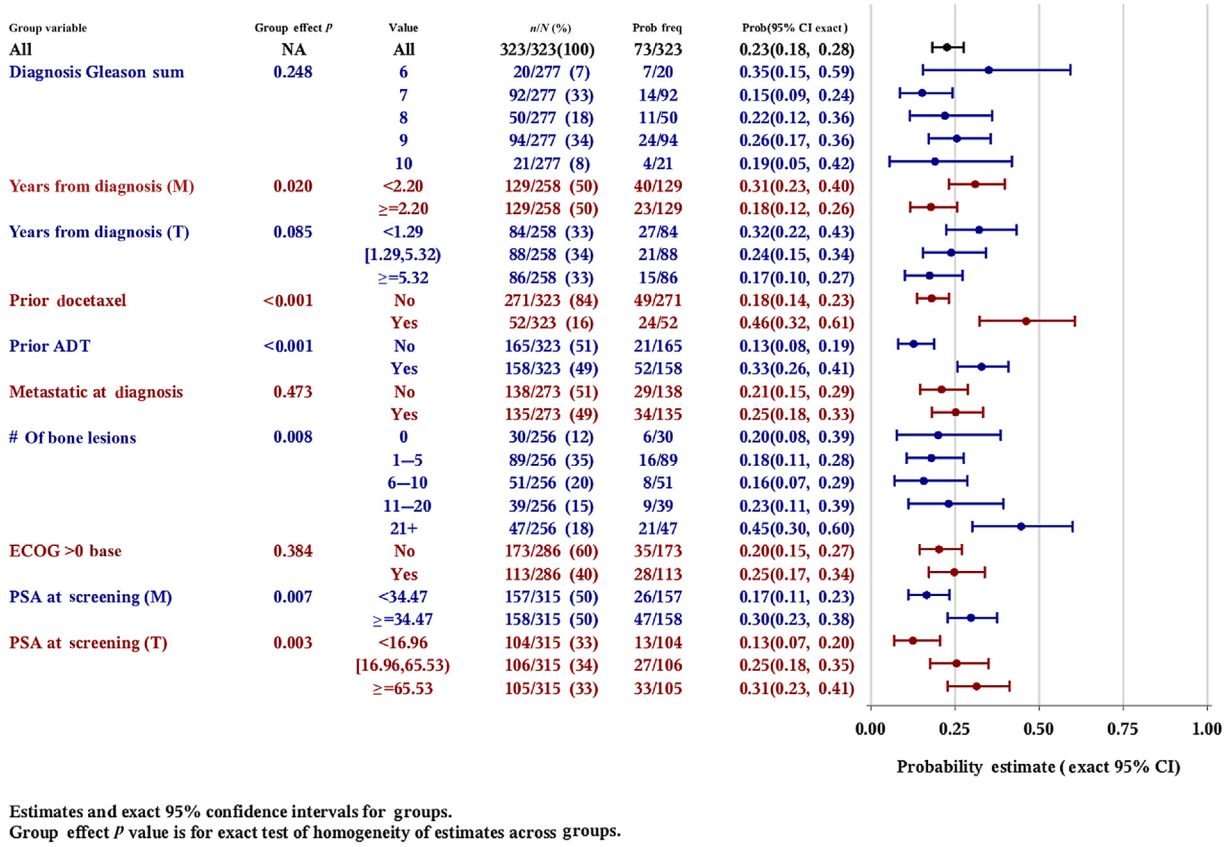

Fig. 4 – Baseline patient characteristics and the probably of AR-V7 detection for the cohort of CTC-positive patients (n = 323). The p values test the homogeneity of prevalence across the subsets defined by the factor being analyzed. Small p values (below 0.10), are considered consistent with evidence of differences across subsets. ADT = first-generation androgen deprivation therapy (bicalutamide); AR-V7 = androgen receptor splice variant-7; CI = confidence interval; CTC = circulating tumor cell; ECOG = Eastern Cooperative Oncology Group; Freq = frequency; M = median; NA = not available; Prob = probability; PSA = prostate-specific antigen; T = tertile.

Table 1 – Characteristics of patients assigned to enzalutamide or galeterone treatment.

Arm		Enzalutamide	Galeterone
Number randomized		19	19
ECOG = 1 (%)		57.9	52.6
Percent having number of bone scan lesions	0	6.7	12.5
	1–5	20.0	43.8
	6–10	20.0	0.0
	11–20	33.3	6.3
	21+	20.0	37.5
Age (SD)	Median (Q1, Q3)	72.0 (62.0, 77.0)	72.0 (62.0, 77.0)
PSA	Median (Q1, Q3)	50.82 (12.830, 144.60)	96.15 (53.600, 313.40)
LDH	Median (Q1, Q3)	264.00 (213.00, 322.00)	294.00 (200.00, 328.00)
HGB	Median (Q1, Q3)	11.90 (10.80, 12.40)	12.35 (11.40, 13.60)
Albumin	Median (Q1, Q3)	4.20 (3.90, 4.50)	4.10 (3.90, 4.20)
Alkaline phosphatase	Median (Q1, Q3)	222.00 (120.00, 280.00)	256.50 (107.00, 675.00)

ECOG = Eastern Cooperative Oncology Group; HGB = hemoglobin; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; Q1 and Q3 = first and third quartiles; SD = standard deviation.
The factors for which means are presented met the assumptions of the Central Limit Theorem.

Little can be concluded about the efficacy of galeterone or enzalutamide. Once the DMC recommended closure, ongoing efficacy assessments were stopped. Galeterone appeared well tolerated: PK assessments suggested drug levels at which AR degradation was expected. The PSA50 response (unconfirmed) was 8/19 (42%) for enzalutamide and 2/16 (13%) for galeterone. One can speculate that AR-V7 detection in first-line mCRPC does not preclude responses to enzalutamide and that galeterone may be a weak AR antagonist/degrader. Future treatment options for these

patients include more potent AR degraders, inhibitors of AR N-terminal or DNA-binding domains, inhibitors of AR complementary pathways (eg, EZH2, PI3K inhibitors) [21], epigenetic modulators of AR (eg, bromodomain/BET inhibitors) [24], or chemotherapy [16,17].

5. Conclusions

In conclusion, 8% of mCRPC patients naïve to abiraterone or enzalutamide had CTC-transcript AR-V7 mRNA detected using an RT-PCR assay. Patients presenting with de novo metastasis, short duration of response to ADT, higher PSA, and high-volume bone disease were more likely to be AR-V7 +. The majority of AR-V7+ patients had clinically aggressive disease that was not controlled by AR-targeting therapies including galeterone or enzalutamide. Novel study designs and alternative treatment approaches are urgently needed for CTCs expressing AR-V7 mCRPC.

Author contributions: Mary-Ellen Taplin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Taplin, Antonarakis, Ferrante, Blumenstein, Saad, Luo, de Bono.
Acquisition of data: Taplin, Antonarakis, Ferrante, Horgan, Blumenstein, Saad, Luo, de Bono.
Analysis and interpretation of data: Taplin, Antonarakis, Ferrante, Horgan, Blumenstein, Saad, Luo, de Bono.
Drafting of the manuscript: Taplin, Antonarakis, Ferrante, Horgan, Blumenstein, Saad, Luo, de Bono.
Critical revision of the manuscript for important intellectual content: Taplin, Antonarakis, Ferrante, Horgan, Blumenstein, Saad, Luo, de Bono.
Statistical analysis: Taplin, Antonarakis, Ferrante, Blumenstein, Saad, Luo, de Bono.
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Administrative, technical, or material support: Horgan.
Supervision: Taplin, Antonarakis, Ferrante, Blumenstein, Saad, Luo, de Bono.
Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.08.034.

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