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Combination therapy in metastatic hormone-sensitive prostate cancer: is three a crowd?

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***Abstract*:** The mainstay of treatment for metastatic prostate cancer is androgen deprivation therapy (ADT). Outcomes with ADT are variable but control of hormone-sensitive prostate cancer (HSPC) can often be achieved for many years. Death from prostate cancer is usually due to the development of escape variants able to survive and proliferate in the setting of castrate levels of serum androgens (metastatic castration-resistant prostate cancer, mCRPC). Several agents can improve survival for patients with mCRPC, including chemotherapy, agents to reduce androgen receptor signalling, the radioisotope radium-223 dichloride, and cellular immunotherapy with sipuleucel-T. Some of these agents have been moved earlier in the disease course and have shown to improve survival in metastatic HSPC also, often to a much greater degree than when the same agents are used in mCRPC. Specifically, survival of metastatic HSPC can be improved with the addition to ADT of any one of docetaxel, abiraterone acetate/prednisone combination, apalutamide, enzalutamide, or darolutamide in combination with docetaxel. Factors affecting outcomes include the volume or burden of disease, timing of metastases relative to the original diagnosis, and patient factors determining the appropriateness of therapy. Unfortunately, uptake of this information by the clinical community remains suboptimal, with many men potentially suitable for combination therapy still receiving only ADT. Some trials have examined the effects of 'triplet' therapies although few were designed specifically to address this question. The best evidence to date suggests that triplet therapy with ADT + abiraterone + docetaxel or ADT + darolutamide + docetaxel, can improve overall survival in metastatic HSPC. Clear opportunities exist to improve survival outcomes for men with metastatic HSPC but need to be balanced against cost, accessibility, toxicity, and patient-specific factors.

Keywords: chemotherapy, doublet therapy, hormone therapy, metastatic hormone-sensitive prostate cancer, prostate cancer, triplet therapy

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Prostate cancer represents one of the earliest applications of targeted molecular therapy for cancer, ever since the use of surgical castration as the earliest form of androgen deprivation therapy (ADT) was shown in 1941 to be effective for metastatic disease.[1] This approach takes advantage of the sensitivity of and dependence on androgen receptor (AR) signalling to maintain and promote the growth and spread of prostate adenocarcinoma. The same work showed that oestrogen supplementation also was active,[2] indicating that other molecular targets might also be of therapeutic value in this disease. Estrogenic drugs, or agents such as aminoglutethimide (an aromatase inhibitor), were widely used for the systemic therapy of metastatic prostate cancer at least up to the 1990s. However, aside from the advent of medical approaches for ADT, very few other systemic therapies were found to be of benefit in metastatic hormone-sensitive prostate cancer (mHSPC) or to prevent development of metastatic castration-resistant prostate cancer (mCRPC). A major

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oncology textbook published in 1997 stated, 'No cytotoxic drug or combination has been shown consistently to be useful in prostate cancer'.[3]

The field was rapidly transformed in the early 2000s, with two papers published in 2004 showing a survival benefit for docetaxel in the treatment of mCRPC,[4,5] followed soon after by evidence for abiraterone acetate (a CYP17/C17,20 lyase inhibitor) with prednisone or prednisolone (referred to here as 'abiraterone' throughout), and for enzalutamide (a 'second generation' AR antagonist), given either after[6,7] or prior to[8,9] docetaxel therapy for mCRPC. These treatments illustrated a profound rethinking at the time of widely held prostate cancer dogma. mCRPC had previously been considered to be indifferent to AR signalling ('androgen-independent prostate cancer') or to other hormonal therapies ('hormone-resistant prostate cancer'). Prostate cancers that proliferated in the context of castrate serum levels of androgens were found often to remain critically dependent upon AR signalling but had found ways to circumvent the relative lack of ligand. Agents such as abiraterone acetate, enzalutamide, or other agents that profoundly inhibit AR signalling were developed and applied in that context. Other treatments have also now been shown to confer survival benefits in mCRPC in specific situations.[10–12]

It was logical to move many of these therapies earlier in the disease course to determine whether further gains in activity could be obtained in prostate cancers that had not already undergone the evolutionary selection pressure of AR inhibition. This review provides perspective on the pivotal trials of these 'doublet' therapies of ADT together with another agent and summarises the limited available data of 'triplet' therapies (Figure 1).

ADT plus docetaxel: GETUG-AFU15, CHAARTED, STAMPEDE (Table 1)

The mechanism of action of docetaxel is complex. It involves inhibition of microtubule disassembly, reduction of expression of anti-apoptotic molecules such as Bcl-2 and multiple other pathways.[14] Part of its effect is mediated by inhibition of migration of the activated AR to the nucleus (Figure 1), which implies that there may be differential effects in prostate cancer depending on whether the cancer cell had developed mechanisms to escape from androgen deprivation.

The first published study of ADT plus docetaxel for mHSPC was the GETUG-AFU 15 trial.[15] This study of 385 participants was probably underpowered, with 80% power to detect what was then an optimistic hazard ratio (HR) for death of 0.62. The study did not meet its primary objective: although there was a 14-month difference in the point estimates of median survival in favour of the combination arm and a HR of 0.88, this did not meet statistical significance. This trial was performed in an era where there was limited access to other life-prolonging therapies on completion of the trial.

The CHAARTED (E3805) trial was presented at the ASCO Annual Scientific Meeting Plenary session in 2014 and rapidly led to change in practice around the world.[16,17] This trial showed a striking survival benefit for addition of docetaxel to ADT for mHSPC, with HR 0.72 and a 10-month improvement in median survival for the study overall. The benefit was later shown to be confined to the group of patients with 'high volume' and synchronous ('de novo') metastatic disease, where the difference in median survival was about 17 months. 'High-volume' disease was defined as four or more bone metastases with at least one beyond the pelvis or vertebral column or visceral metastases. This definition had evolved over time but has been shown to correlate with outcome in various clinical settings, aligning with the perception that different patterns of prostate cancer metastasis probably reflect different disease biology. CHAARTED had a higher proportion of participants with high-volume disease than GETUG-AFU 15, which could account for some of the difference in outcomes. Results from the STAMPEDE trial were presented soon after CHAARTED and were consistent, although again the population was different, with inclusion of a significant proportion of patients without overt metastases.[18]

A meta-analysis of all three studies confirmed the benefit of addition of docetaxel,[19] and there is now broad agreement that most of the benefit is confined to patients with high-volume synchronous metastases. It is still reasonable to offer docetaxel to selected patients with low volume disease or with metachronous timing of metastases, although they may be better served with other options if they are available. The benefits of adding docetaxel to ADT are substantially greater for mHSPC than when it is used for mCRPC: HRs for death are similar (updated HR for death 0.79 in the mCRPC TAX327 study,[20] compared to

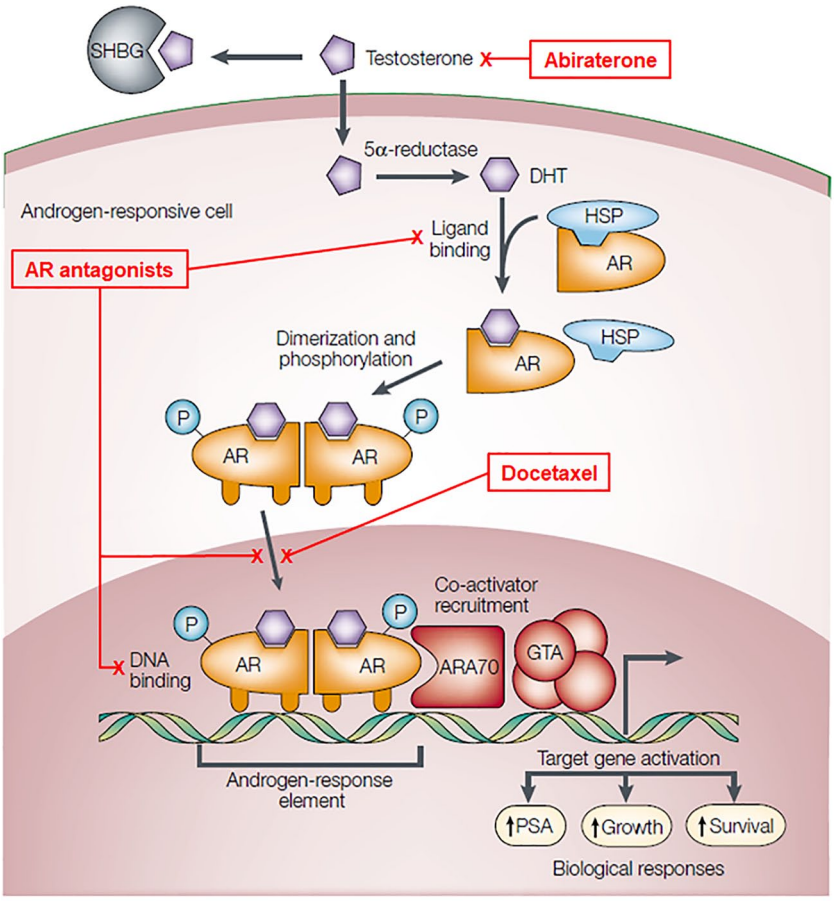

Figure 1. Overview of the androgen receptor signalling pathway. Some of the points where inhibitory agents mediate activity are shown in red.
Modified from Feldman and Feldman[13] with permission.

HR for death 0.77 in a meta-analysis of mHSPC studies[21]), but the increase in median survival is much greater when docetaxel is used in mHSPC (increase of 2.9 months in TAX327,[20] compared to increase in median survival of 16.8 months in CHAARTED[17] or 16 months in STAMPEDE[22]; 13.5 month difference in point estimates not statistically significant for GETUG-AFU15[23]). The apparent discrepancy between HR and improvement in median survival reflects the different prognosis of mHSPC compared to mCRPC and illustrates that unplanned comparisons across disease types can be fraught. However, the difference in observed median survival suggests that docetaxel efficacy is significantly influenced by whether the cancer has previously experienced selection pressure through the AR. Docetaxel should certainly be considered a standard of care for patients with mHSPC who are able to receive it, particularly when other therapies are not easily available.

ADT plus abiraterone (Table 2)

Abiraterone acts by decreasing synthesis of testosterone and other androgens, reducing the concentration of ligand available for binding to and activation of the AR (Figure 1). The LATITUDE[24] and STAMPEDE[25] trials demonstrated the value of adding abiraterone to ADT at the initiation of treatment for mHSPC. The patient populations differed significantly between these two studies. LATITUDE was restricted to 'high-risk' patients, all of whom had synchronous metastatic disease at the time of initial diagnosis. STAMPEDE included 48% of participants with no metastatic disease evident on conventional imaging, of which about half did not have nodal involvement evident either. LATITUDE had co-primary endpoints of overall survival and radiographic progression-free survival (rPFS), whereas the primary endpoint for STAMPEDE was overall survival. Both studies showed clinically important and very substantial improvements in outcomes,

Table 1. Addition of docetaxel to androgen deprivation therapy.

	GETUG-AFU 15 (*N* = 385)	STAMPEDE (*N* = 1086)	CHAARTED (*N* = 790)
Primary endpoint: HR (CI)	OS: 0.88 (0.68–1.14)	OS: 0.81 (0.69–0.95)	OS: 0.72 (0.59–0.89)
Median survival D + ADT *vs* ADT (months)	62.1 *vs* 48.6	59.1 *vs* 43.1	57.6 *vs* 47.2
Prior ADT	Up to 2 months (median ⩽ 15 days)	Up to 3 months	Up to 120 days (median ⩽ 35 days)
Anti-androgen with ADT	64%	94%	42% > 30 days
Synchronous M1	71%	58%	73%
Visceral metastases	13%	~5%	15%
Volume/burden of disease (high|low)	47%|53%	56%*|44%*	65%|35%
Undetectable PSA (⩽0.2)	Not reported	Not reported	32% *vs* 19.6% at 6 months

ADT, androgen deprivation therapy; CI, 95%, confidence intervals; D, docetaxel; HR, hazard ratio; M1, metastatic disease detectable by CT or ^{99m}Tc bone scan; N, number in trial; OS, overall survival; PSA, prostate-specific antigen.

including for overall survival, with HRs for death of 0.66 for LATITUDE and 0.63 for STAMPEDE, and substantial improvements in either median or landmark 3-year overall survival. The initial regulatory approvals for abiraterone in mHSPC were for high-risk disease only. A post hoc analysis of STAMPEDE participants with M1 disease evaluated outcomes according to subsequent designation of low- or high-risk disease according to the criteria used in LATITUDE or CHAARTED.[26] This work demonstrated activity in both high- and low-risk combinations, including synchronous metastatic disease. Abiraterone was therefore the first treatment shown to improve survival in low volume mHSPC when added to ADT (Table 2).

Another ad hoc analysis of STAMPEDE arm A (control standard of care with ADT) compared to arm C (added docetaxel) and arm G (added abiraterone) allowed an indirect comparison of docetaxel with abiraterone.[27] This information needs to be interpreted carefully because of the nature of the analysis, but it showed apparent benefits in favour of abiraterone for the outcome measures of failure-free survival and progression-free survival but was unable to provide conclusive benefit for either agent for metastatic progression-free survival, symptomatic skeletal events, cause-specific survival, or overall survival. It remained reasonable to conclude that either agent should still be considered a standard of care for addition to ADT.

Further studies demonstrating the benefit of abiraterone were presented at major conferences in 2021. The PEACE-1 trial was a 2×2 factorial trial of ADT with the addition of abiraterone, radiation to the primary, both interventions, or ADT alone.[28] All participants had synchronous metastatic disease. Docetaxel was used in 60% of the participants, and this triplet combination is discussed further below. The radiation therapy arms were collapsed in these analyses for assessment of the effect of abiraterone. The trial showed a clear benefit for rPFS for participants with either high- or low-volume disease, with HR for rPFS of 0.50. An overall survival benefit has been demonstrated for the study overall (HR 0.82, 95% confidence intervals 0.69–0.98, $p = 0.030$), which at present is mainly due to benefit in those with high-volume disease; data remain immature for the population with low-volume disease, with few deaths recorded at the time of data analysis.

A meta-analysis of STAMPEDE arms G and J was presented at the ESMO 2021 meeting.[29] This analysis has three major points of distinction from studies involving metastatic HSPC defined by

Table 2. Addition of androgen receptor signalling inhibitors to androgen deprivation therapy. Trials including 'triplet' therapies are shown shaded.

	LATITUDE (*N* = 1199)	STAMPEDE (*N* = 1917)	PEACE-1 (*N* = 1173)	ARASENS (*N* = 1306	TITAN (*N* = 1052)	ARCHES (*N* = 1150)	ENZAMET (*N* = 1125)	STAMPEDE M0 (*N* = 1974)
Agent/comparator	ADT + abiraterone + pred/placebo	ADT + abiraterone + pred / placebo	2 × 2: SoC/ abiraterone/RT/both, ±docetaxel (RT arms collapsed for analysis)	ADT + docetaxel + darolutamide/placebo	ADT + apalutamide/ placebo	ADT + enzalutamide/ placebo	ADT + enzalutamide/NSAA	SoC|SoC + abiraterone + pred, ± enzalutamide
Primary endpoint: HR (CI)	OS: 0.66 (0.56–0.78) rPFS: 0.47 (0.39–0.55)	OS: 0.63 (0.52–0.76)	rPFS: 0.54 (0.46–0.64) OS: 0.82 (0.69–0.98)	OS: 0.68 (0.57–0.80)	OS: 0.65 (0.53–0.79) rPFS: 0.48 (0.39–0.60)	rPFS: 0.39 (0.30–0.50) (OS (2°): 0.66 (0.53–0.81))	OS: 0.67 (0.52–0.86)	MFS: 0.53 (0.44–0.64) OS: 0.60 (0.48–0.73)
Survival ARI + ADT *vs* ADT	Med OS: 53.3 *vs* 36.5 months Med rPFS: 33.0 *vs* 14.8 months	3-year OS 83% *vs* 76%	Med rPFS 4.5 *vs* 2.2 year Med OS: 5.7 *vs* 4.7years	Med OS: NE *vs* 48.9 months	Med OS: NR *vs* 52.2 months Med rPFS: NR *vs* 22.1 months	Med rPFS: NR *vs* 19.0 months 3-year OS: 78% *vs* 69% 5-year OS: 71% *vs* 57%	3-year OS 80% *vs* 72%	6-year MFS: 82% *vs* 69% 6-year OS: 86% *vs* 77%
Relevant "triplet" outcomes	Not applicable	Not applicable	Med rPFS 4.5 *vs* 2.0 years Med OS: NE *vs* 4.4 years	Improved OS Improved secondary endpoints Similar toxicity	Rapid sequencing	Rapid sequencing	No OS benefit at interim analysis. Improved clinical PFS (2°)	Similar efficacy, more toxic
Prior ADT	Up to 3 months (median 1mo)	Up to 3 months	Up to 3 months	Up to 12 weeks	Up to 6 months	Up to 6 months (70% ⩽ 3 months)	Up to 3 months	Up to 3 months
Antiandrogen with ADT	62%	94%	No	Experimental arm only	Experimental arm only	Experimental arm only	Both arms	Experimental arm only
Docetaxel	Exclusion	Exclusion	60% (concurrent)	100% (concurrent)	11% (before apa)	18% (before enza)	45% (concurrent)	Exclusion
Synchronous M1	100%	49%	100%	86%	81%	67%	67%	0% (all M0)
Visceral metastases	Liver 5%, lung 12%	~5%	11%	17%	Liver 2%, lung 10%	48% (incl nodes)	11%	0% (all M0)
Volume/burden of disease (high| low)	100% "high risk"	Unknown* (48% M0)	57%| 43%	NE	63%| 37%	63%| 37%	53%| 47%	100% low
Undetectable PSA (⩽0.2)	47.6% *vs* 7.5% at 6mo	Not reported	Not yet reported	Not reported	68.4% *vs* 28.7% (best response)	68.1% *vs* 17.6% (best response)	Not yet reported	Not reported

Shaded cells denote trials that included 'triplet' therapy (addition of two systemic agents to androgen deprivation therapy).
2°, secondary endpoint; ADT, androgen deprivation therapy; apa, apalutamide; CI, 95% confidence intervals; enza, enzalutamide; HR, hazard ratio; incl, including; M0, no metastatic disease detectable by CT or ^{99m}Tc bone scan; M1, metastatic disease detectable by CT or ^{99m}Tc bone scan; Med, median; MFS, metastasis-free survival; N, number in trial; NE, not evaluable; NR, not reached; NSAA, non-steroidal anti-androgen; OS, overall survival; pred, prednisone; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; RT, radiation therapy; SoC, standard of care.

conventional imaging. First, it included only those participants on these arms who had M0 mHSPC, that is, no evidence of metastatic disease on conventional imaging, although about 13% had N1 disease. Second, the primary endpoint was metastasis-free survival, an endpoint that has been validated as a surrogate for overall survival for high-risk localised prostate cancer through work from the ICECaP collaboration[30] but not for this setting. Third, the analysis represented data from two consecutive studies with contemporaneous controls: Arm A *versus* Arm G, assessing respectively standard care *versus* standard care plus abiraterone; and Arm A *versus* Arm J assessing respectively standard care *versus* the combination of standard care, abiraterone, and enzalutamide. The Arm J triplet therapy analysis is discussed further below. 'Standard care' in this setting involved ADT for all participants, with radiation therapy to the primary, given to the majority of participants. The meta-analysis showed a clear benefit in favour of the abiraterone-containing arms, with HR for metastasis-free survival of 0.53. The analysis also showed benefit for the secondary endpoint of overall survival, with HR of 0.60; medians had not been reached for either arm for either endpoint.

ADT plus an AR antagonist (Table 2)

So-called 'first-generation' AR antagonists ('anti-androgens') have not been shown to prolong survival in prostate cancer. 'Second-generation' anti-androgens include enzalutamide, apalutamide, and darolutamide. These agents have been shown to prolong survival in various prostate cancer clinical settings, and mediate their activity by inhibition of natural ligand binding to AR, without significant agonist activity; inhibition of translocation of the activated AR to the nucleus; and inhibition of expression of genes associated with AR-mediated binding to DNA (Figure 1). The agents have some differences in safety profiles and in penetration of the central nervous system, beyond the scope of this review. Three trials to date have demonstrated benefit for these agents when they are added soon after initiation of ADT for mHSPC.

The TITAN trial added apalutamide to ADT for mHSPC.[31,32] TITAN was double-blind and placebo-controlled, with synchronous metastases in 81% of participants but docetaxel was administered only to 11%. Docetaxel therapy was to be completed prior to commencement of apalutamide. The co-primary endpoints were rPFS and overall survival. Both primary endpoints were met, with HR for overall survival of 0.65 and for rPFS 0.48 at the most recent presentation after 44 months of follow-up. Other clinically relevant secondary endpoints were also demonstrated in favour of apalutamide, including time to castration resistance, and the benefits were achieved without significant adverse impact on health-related quality of life measures. TITAN collected data on outcomes beyond the initial therapy and was able to measure PFS2, defined as the time from randomisation until progression on the next line of systemic therapy.[32] This showed that a PFS2 benefit was observed in favour of apalutamide, suggesting that the benefit was not due to 'stealing' benefit from a subsequent agent.

Two trials have shown benefit for enzalutamide. The first to present data on overall survival was ENZAMET,[33] which was an open-label trial comparing enzalutamide with a 'first-generation' anti-androgen when added to ADT. Synchronous metastases were present in 67% of participants. About 45% of participants in ENZAMET received concurrent docetaxel, and data from this 'triplet' approach are described below. The primary endpoint for ENZAMET was overall survival. Data from the first planned interim analysis at 50% of deaths were presented at ASCO in 2019, with a median follow-up of 34 months. A benefit for enzalutamide was observed at this first analysis, with an HR of 0.67 for overall survival, and about a 60% reduction in the hazard of clinical or PSA progression. Initial minor adverse effects on health-related quality-of-life measures did not persist, and ultimately were outweighed by the benefits of treatment.[34]

The ARCHES trial[35,36] commenced recruitment after ENZAMET but had rPFS as the primary endpoint and was therefore the first trial of the second-generation anti-androgens to present results. ARCHES added enzalutamide to ADT and was placebo-controlled and double-blind, with synchronous metastases in 67% of participants. Only 18% of participants received docetaxel with ADT. The trial showed substantial benefit for participants receiving enzalutamide, with an HR for rPFS of 0.39, and improvement in other key secondary endpoints also. Median follow-up at the first presentation of the data were only 14 months, and data for the secondary endpoint of overall survival were not mature at that

point. Further data were presented at ESMO in 2021 for the final analysis of overall survival at 342 deaths after 44 months median follow-up, and showed an HR for the secondary endpoint of overall survival of 0.66, similar in magnitude to ENZAMET. Data from ARCHES and ENZAMET formed the basis of successful regulatory approvals in various jurisdictions around the world, and were included in the UK NICE recommendations for preferred therapy during the COVID-19 pandemic.[37]

Evidence for 'triplet' therapies (Table 2)

Some of the combination trials discussed above included 'triplet' therapies, where two other systemic interventions were added at the time ADT was commenced. Most of the limited clinical data in this area relate to docetaxel as the third component. The TITAN and ARCHES trials both used docetaxel in addition to ADT plus apalutamide or enzalutamide respectively, but only in a small proportion of patients (Table 2). Treatment with docetaxel was used as a stratification factor for both trials but participants were not randomised to receive docetaxel or not. Both TITAN and ARCHES required docetaxel therapy to be completed prior to commencement of study drug, with participants to be excluded if their cancer progressed prior to commencement of enzalutamide. The median of six cycles of docetaxel meant that there was a longer time from randomisation and initiation of ADT to commencement of study drug in the small proportion of patients in both arms who received docetaxel. Neither trial provided specific safety data in respect of participants who received docetaxel. TITAN and ARCHES therefore included no patients who received concurrent triplet therapy, and in this respect these two trials should be considered as each including a small cohort of patients who received rapid sequencing of therapy in the early mHSPC setting.

The CHAARTED results were released soon after recruitment to ENZAMET commenced. This led to a rapid amendment of the ENZAMET protocol after it had recruited only 88 patients, to allow concurrent docetaxel therapy to be administered. The cohort of participants planned to receive docetaxel was prespecified in the Statistical Analysis Plan as a subgroup of interest; however, the trial was not specifically designed to address the question of whether addition of docetaxel plus enzalutamide to ADT would improve survival. Randomisation was stratified by intent to use docetaxel, but participants were not randomised to receive docetaxel. Participants were required to begin enzalutamide or control therapy within 12 weeks of commencement of ADT, and docetaxel is recommended to begin no sooner than 28 days after commencement of ADT, so the maximum number of cycles of docetaxel that could be received prior to commencement of study drug was two. Limited safety information was available for the triplet combination at that time, so the Independent Data Safety Monitoring Committee reviewed unblinded safety information for the first 49 participants to receive docetaxel on each arm and found no reason to alter the conduct of the study.

Data from the first planned interim analysis of ENZAMET after 50% of the anticipated number of deaths had been recorded formed the basis of the information published to date. The median number of cycles of docetaxel administered was six, and most participants received all cycles of docetaxel concurrently with enzalutamide or control therapy. Overall, 45% of participants received concurrent docetaxel, balanced evenly between the treatment arms. Use of docetaxel varied according to the volume of disease, with docetaxel therapy planned for 61% of those with high-volume disease and 27% of those with low-volume disease.

ENZAMET overall showed a significant survival benefit for addition of enzalutamide to ADT (Table 2). However, the planned subgroup analysis at that time showed that no evidence that addition of enzalutamide led to further improvement in overall survival when docetaxel was already planned to be used with ADT, although an improvement in clinical PFS was observed in this group similar in magnitude to that seen later in PEACE-1. The survival benefit at this time appeared to be confined to the group who did not receive additional docetaxel.

There are several possible reasons for this observation. It is possible that a 'ceiling' effect exists, where maximal survival benefit can be achieved by adding either enzalutamide or docetaxel to ADT, but addition of both gives no further benefit. This now appears to be unlikely, given the results of PEACE-1 reviewed below. An alternative explanation is that the patients who progressed most quickly and died were the ones who contributed most of the information to this interim analysis at 50% of deaths. The biology of

the cancer in this population is almost certainly different from those who have had long-lasting responses to treatment. Further long-term follow-up of the remaining participants will be required to address this question and to determine whether the apparent benefit of triplet therapy on clinical PFS eventually translates into an overall survival benefit, noting that it will still be a planned subgroup analysis. Another possibility is that the benefit of enzalutamide might be most apparent in patients with low-volume disease, where docetaxel was infrequently used. This explanation is possibly true, but there is little information at present that supports this notion because patients with high-volume disease also respond to enzalutamide, particularly if they have synchronous metastatic disease.[38]

ENZAMET has provided the most detailed information to date on toxicity of triplet therapy, but this information must be interpreted carefully. ENZAMET was an open-label study, so investigators and patients knew if they were receiving enzalutamide with docetaxel or not. The investigator-assessed and patient-reported outcomes might therefore be subject to reporting bias. Adverse events such as fatigue were more commonly reported in the enzalutamide treatment arm, and those participants were more likely to discontinue treatment due to adverse events. Some adverse events known to be related to docetaxel but not enzalutamide were also more commonly reported in participants receiving enzalutamide as well, such as peripheral neuropathy, nail discoloration, or lacrimation. It is not clear whether this relates to bias in reporting, or whether enzalutamide truly increases the probability of these events occurring. Notably, there was no convincing signal for worsened toxicity in PEACE-1 and ARASENS.

PEACE-1 underwent several amendments during the period of participant recruitment, taking into account emerging information regarding best practice standard of care. Initially ADT was used alone, but concurrent docetaxel was permitted as part of standard therapy between 2015 and 2017 (592 participants), and was mandatory for the remainder of the study (308 participants). Overall, approximately 60% of participants received a median of six cycles of docetaxel concurrently with ADT as their basic standard therapy. The most recent results from PEACE-1 confirm the previously reported benefit of abiraterone on rPFS and show that there is a survival advantage also (Table 2). Subgroup analyses of the PEACE-1 participants who received docetaxel demonstrate improved rPFS (HR 0.50, 95% confidence intervals 0.40–0.62, $p < 0.0001$; median 4.5 *vs* 2.0 years) for those also receiving abiraterone, with the benefits evident regardless of metastatic burden. Overall survival in this subgroup receiving triplet therapy was also improved (HR 0.75, 95% confidence intervals 0.59–0.95, $p = 0.017$; median not evaluable *vs* 4.4 years), although so far the benefit has been demonstrated only for patients with high-volume disease; very few deaths had yet been reported in those with low-volume disease. Limited safety data have yet been reported but the available information does not suggest safety concerns above those known for the individual components of therapy.

Data from STAMPEDE arm J were also presented at the ESMO 2021 Annual Scientific Meeting.[29] This arm examined the triplet of abiraterone, enzalutamide, and ADT, specifically in patients with M0 disease by conventional imaging. Metastasis-free survival and overall survival were both improved in the combination arm, but there was no evidence that the magnitude of benefit was greater than for participants who receive abiraterone plus ADT without enzalutamide. Secondary outcome measures such as prostate cancer-specific survival and PFS were also similar for the triplet compared to the abiraterone/ADT doublet. Toxicity of the triplet combination was higher, particularly for erectile dysfunction, hypertension, fatigue, and elevated liver enzymes. The investigators concluded that addition of enzalutamide to abiraterone plus ADT increased toxicity but an effect on efficacy was not observed.

ARASENS (NCT02799602) has recently been reported and showed a substantial improvement in overall survival when darolutamide was added to ADT and docetaxel (HR 0.68; 95% confidence intervals (CIs) 0.57–0.80; $p < 0.001$; Table 2).[39] Improvements in favour of triplet therapy were also found in clinically relevant secondary endpoints: time to castration-resistant disease (HR 0.36; 95% CI 0.30–0.42; $p < 0.001$); time to pain progression (HR 0.79; 95% CI 0.66–0.95; $p = 0.01$); symptomatic skeletal event-free survival (HR 0.61; 95% CI 0.52–0.72; $p < 0.001$); and time to first symptomatic skeletal event (HR 0.71; 95% CI 0.54–0.94; $p = 0.02$).[39] Toxicity was remarkably similar between the two arms, suggesting that any adverse events of addition of darolutamide were probably

overshadowed by the effects of baseline therapy with ADT and docetaxel.

Patient-reported outcomes

Toxicity of treatment regimens, particularly that of combination treatments, will influence treatment selection and decision-making by both clinicians and patients. Insight into the true tolerability of treatment is probably best derived from patient-reported outcome measures (PROMs), rather than investigator-assessed toxicity. Several studies have reported PROMs. LATITUDE demonstrated clinical benefit for pain progression, prostate cancer symptoms, fatigue, functional decline, and overall health-related quality of life, when abiraterone was added to ADT for mHSPC.[40] TITAN, ARCHES, and ENZAMET showed either improvement with apalutamide or enzalutamide, or no clinically relevant differences from control, in several PROM measures.[34] Early decreases in various quality of life domains in ENZAMET may in part be attributable to concurrent docetaxel.[34] The comparison of abiraterone and docetaxel in STAMPEDE showed a clinically meaningful improvement in global quality-of-life scores favouring abiraterone in the first year of treatment.[41]

Conclusion

There is now incontrovertible evidence that survival and other clinically relevant outcomes for patients with mHSPC can be improved by addition of other agents to ADT, assuming that these agents are available and that it is safe to administer them to a specific patient. The benefit of docetaxel may be mainly confined to patients with high-volume synchronous mHSPC, although this is contentious. Abiraterone, apalutamide, and enzalutamide benefit patients with either high- or low-volume disease, particularly with synchronous metastases. Apalutamide and enzalutamide benefit those with metachronous low volume disease.[38] Abiraterone improves outcomes for those with M0 HSPC by conventional imaging.

A minimum standard of care until recently was to use doublet therapies. Which drugs to choose? There is no single right answer to this question, but there is also no single wrong answer. Selection of the preferred agent or agents to combine with ADT will depend on local regulatory approval and reimbursement, and also upon patient factors. A patient with diabetes, or cardiac failure, or electrolyte disturbances, might be best treated with apalutamide or enzalutamide. A patient with cognitive impairment, fatigue, or predisposition to seizures, might be best offered abiraterone. A patient who wishes to complete their additional treatment quickly, or avoid prolonged financial or other toxicities, and who is otherwise fit, might best be offered docetaxel. Docetaxel is now cheap, does not require concomitant prednisone when used in the mHSPC setting, and treatment consists of six cycles only of docetaxel with the final dose delivered 15 weeks after the first. A patient who is frail or with multiple comorbidities might still best be treated with ADT alone, particularly if life expectancy due to comorbidities is otherwise limited.

Data for triplet therapies are now emerging. The best information to date comes from the PEACE-1 and ARASENS trials. PEACE-1 provided evidence supporting the use of ADT plus both abiraterone and docetaxel, particularly for patients with synchronous high-volume metastatic disease.[28] ARASENS (NCT02799602) has recently been reported and showed a substantial improvement in overall survival when darolutamide was added to ADT and docetaxel (HR 0.68; 95% confidence intervals 0.57–0.80; $p < 0.001$).[39] ARASENS did not report outcomes based high- and low-volume disease states and did not answer the question of whether docetaxel adds to the combination of ADT plus an AR-targeted therapy such as darolutamide, but nevertheless the results are convincing and are likely to influence practice quickly. Information from other studies, such as longer-term follow-up of ENZAMET, will help determine the place of triplet therapies in therapeutic decision-making.

As at early 2022, a patient for whom any therapy is suitable probably should be offered triplet therapy such as ADT/abiraterone/docetaxel (PEACE-1) or ADT/darolutamide/docetaxel (ARASENS), if these options are available. Unfortunately, the clinical and patient communities have unfortunately not yet implemented even the evidence for doublet therapies effectively into clinical practice.[42–46] The evidence is clear; it is equally clear that we still have far to go to deliver optimal treatment to those who need it most.

Author contributions

Ian D. Davis: Conceptualisation; Data curation; Formal analysis; Project administration;

Visualisation; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: IDD is global co-chair of the ENZAMET trial; and is chair of ANZUP Cancer Trials Group, the lead cooperative group for ENZAMET. No remuneration is received for any of this work. IDD has been a member of the following advisory boards within the last 2 years (all honoraria to ANZUP): Astellas, AstraZeneca, Bayer, Eisai, Ipsen, Janssen, Merck/MSD, Pfizer, and Roche. Research funding (trial funding to Eastern Health or ANZUP): Amgen, Astellas, AstraZeneca, Bayer, BMS, Eisai, Exelixis, Janssen, Medivation, Movember, MSD, Pfizer, Roche/Genentech, and Seagen.

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