Editorial Commentary

Triplet therapy for metastatic hormone sensitive prostate cancer—looking beyond volume of disease

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Prostate cancer is the most commonly diagnosed cancer among men, projected to result in 288,300 new cases and 34,700 deaths in the United States in 2023 (1). While the majority of patients are diagnosed with localized disease and have very favorable outcomes, a subset of patients recur with metastatic disease, and about 5–10% patients initially present with *de novo* or synchronous metastatic prostate cancer (2). Metastatic prostate cancer is associated with significant morbidity, high mortality rates, increasing incidence, and remains a significant health burden worldwide (3).

In the last decade, the treatment paradigm for metastatic hormone sensitive prostate cancer (mHSPC) has drastically changed, as treatment intensification beyond androgen deprivation therapy (ADT) alone is increasingly utilized to prolong overall survival (OS). Combination approaches are now routinely recommended in major oncologic guidelines (4-6). The CHAARTED trial stratified patients into "high volume", (≥4 bony metastases with ≥1 bone metastasis outside the spine pelvis, and/or presence of visceral metastases) or low volume disease, and established the benefit in OS of adding 6 cycles of docetaxel chemotherapy to ADT, mainly in patients with high volume [hazard ratio (HR) =0.63, 95% confidence interval (CI): 0.50–0.79] compared to low volume (HR =1.04, 95% CI: 0.70–1.55) disease (7). Interestingly, the STAMPEDE trial suggested potential OS benefits with the addition of docetaxel in low volume disease, however, this difference was not statistically significant. This finding may be attributed to differences in the proportion of *de novo* versus recurrent patients included in these trials (8). Like CHAARTED, the recent STOPCAP meta-analysis showed the benefit of docetaxel was mostly restricted to patients with *de novo* high volume mHSPC while some patients with low-volume mHSPC with bulky primaries may also benefit (9,10).

LATITUDE established a survival benefit of adding an androgen receptor pathway inhibitor (ARPI), abiraterone, to ADT for *de novo* mHSPC with "high risk" features (2 of ≥3 bony metastasis, visceral metastases, or Gleason score ≥8), a criterion that is still utilized for defining biologically aggressive disease (11). Following this, several large phase III trials demonstrated similar benefits of using ARPI doublets (abiraterone, enzalutamide, apalutamide, and rezvilutamide in STAMPEDE, ARCHES/ENZAMET, TITAN, and CHART respectively) for both high and low volume mHSPC (12-16). Compared to docetaxel chemotherapy, ARPIs offered a convenient orally administered option with excellent safety profiles. As a result, these doublets have become the most commonly adopted standard practice (17) (*Table 1*).

Despite treatment intensification with doublet therapies (ADT plus docetaxel, ADT plus ARPI), subsets of patients with *de novo* high volume or high risk mHSPC still experienced worse survival outcomes compared to recurrent or low volume mHSPC. This led to development of triplet therapy regimens, combining ADT, docetaxel

Table 1 Summary of metastatic hormone sensitive prostate cancer trials to date

Trial	Experimental arm	Control arm	OS	OS stratified by volume of disease
Chemotherapy (docetaxel + ADT)				
CHAARTED (7) (n=790)	Docetaxel ×6, ADT	ADT	mOS, 57.6 *vs.* 47.2 months; HR =0.72, P=0.0018	High volume: 51.2 *vs.* 34.4 months, HR =0.63, P<0.001; low volume: 63.5 months *vs.* not reached, HR =1.04
STAMPEDE (8) M1 (n=1,086)	Docetaxel ×6, ADT	ADT	mOS, 59.1 *vs.* 43.1 months; HR =0.81	High volume: 39.9 *vs.* 35.2 months, HR =0.81, P=0.06; low volume: 93.2 *vs.* 76.7 months, HR =0.76, P=0.11
Doublet therapy (ARPI + ADT)				
LATITUDE (11) (n=1,199, all *de novo*)	Abiraterone, ADT	Placebo, ADT	mOS, 53.3 *vs.* 36.5 months; HR =0.66, P<0.0001	High volume: 49.7 *vs.* 33.3 months, HR =0.62, P<0.0001; low volume: NR *vs.* NR, HR =0.72, P=0.124
STAMPEDE M1 (12) (n=1,003)	Abiraterone, ADT	ADT	mOS, 79.0 *vs.* 46.0 months; HR =0.60, P<0.0001	Not evaluated by volume
ARCHES (13) (n=1,150)	Enzalutamide, ADT	Placebo, ADT	4-year OS, 71% *vs.* 57%; HR =0.66, P<0.001	High volume: NR *vs.* NR, HR =0.66, 95% CI: 0.52–0.83; low volume: NR *vs.* NR, HR =0.66, 95% CI: 0.43–1.03
ENZAMET (14) (n=1,125)	Enzalutamide, SOC*	Non-steroidal antiandrogen, SOC*	Docetaxel cohort (n=503): 5-year OS, 61% *vs.* 56%; HR =0.82, 95% CI: 0.63–1.06	High volume: 5-year OS, 54% *vs.* 51%, HR =0.87, 95% CI: 0.66–1.17; low volume: 5-year OS, 78% *vs.* 67%, HR =0.61, 95% CI: 0.33–1.10
TITAN (15) (n=1,052)	Apalutamide, ADT	Placebo, ADT	mOS, not reached *vs.* 52.2 months; HR =0.65, P<0.0001	High volume: NR *vs.* 38.7 months, HR =0.70, 95% CI: 0.56–0.88; low volume: NR *vs.* NR, HR =0.52, 95% CI: 0.35–0.79
CHART (16) (n=654)	Rezvilutamide, ADT	Bicalutamide, ADT	mOS, not reached *vs.* not reached; HR =0.58, P=0.0001	Refer to OS column, as only patients with high volume disease were included in the study population
Triplet therapy (ARPI + docetaxel + ADT)				
ENZAMET (14) (n=1,125)	Enzalutamide, SOC*	Non-steroidal antiandrogen, SOC*	Docetaxel cohort (n=503): 5-year OS, 61% *vs.* 56%; HR =0.82, 95% CI: 0.63–1.06	High volume: 5-year OS, 54% *vs.* 51%, HR =0.87, 95% CI: 0.66–1.17; low volume: 5-year OS, 78% *vs.* 67%, HR =0.61, 95% CI: 0.33–1.10
PEACE-1 (18) (2×2 factorial) (n=1,173, all *de novo*)	Abiraterone, radiation, SOC*; abiraterone, SOC*; radiation, SOC*	SOC*	Docetaxel cohort (n=710): mOS, not reached *vs.* 4.43 years; HR =0.75, P=0.017 with addition of abiraterone	High volume: 5.14 *vs.* 3.47 years, HR =0.72, P=0.019; low volume: data immature, HR =0.83, P=0.66
ARASENS (19) (n=1,305)	Darolutamide, docetaxel, ADT	Placebo, docetaxel, ADT	4-year OS, 62.7% *vs.* 50.4%; HR =0.68, P<0.001	High volume: NR *vs.* 42.4 months, HR =0.69, 95% CI: 0.57–0.82; low volume: NR *vs.* NR, HR =0.68, 95% CI: 0.41–1.13

*, SOC was ADT + docetaxel after STAMPEDE and CHAARTED were reported. ADT, androgen deprivation therapy; mOS, median overall survival; SOC, standard of care; NR, not reached; HR, hazard ratio; CI, confidence interval; ARPI, androgen receptor pathway inhibitor.

chemotherapy, and ARPI to simultaneously target androgen receptor (AR)-dependent and AR-independent cancer cells at the outset. The benefit of triplet therapy was first suggested by ENZAMET (ADT, docetaxel, enzalutamide) then PEACE-1 (ADT, docetaxel, abiraterone), summarized in *Table 1*. These two trials were not primarily designed to evaluate a triplet therapy approach: ENZAMET compared enzalutamide to a nonsteroidal antiandrogen (NSAA) with both arms receiving ADT, while PEACE-1 added abiraterone to a standard of care (SOC) arm of ADT. Unlike ARASENS, many patients did not receive upfront docetaxel, as chemotherapy was administered per physician's discretion in ENZAMET and was only mandated later on in the amended protocol of PEACE-1 after the CHAARTED results were published (14,18).

ARASENS: summary of findings and recent subgroup analysis

ARASENS was a double-blinded phase III trial that randomized 1,305 patients with mHSPC to receive upfront triplet therapy (ADT, docetaxel for 6 cycles, and darolutamide 600 mg po twice daily until disease progression) versus ADT, docetaxel, and placebo (19). As this trial mandated the use of docetaxel as SOC at the outset, it enrolled patients with unfavorable disease characteristics. Most patients had high volume disease (77%), *de novo* presentation (86%), and a higher proportion of visceral metastases (17% in ARASENS *vs.* 11% in each of ENZAMET and PEACE-1). In other words, the ARASENS population represents a small subset of mHSPC patients with high-risk disease, for which docetaxel is planned. Overall, treatment arms were well balanced. After 44 months of follow-up, the primary endpoint of OS was met, with triplet therapy significantly improving 4-year OS rate (62.7% *vs.* 50.4%, HR =0.68, 95% CI: 0.57–0.80). Median OS was not reached in the experimental arm and was 42.4 months in the control group. The OS benefit was clinically significant, despite most patients (75.6%) in the control arm had received a life-prolonging therapy upon subsequent progression, 66% of which included an ARPI. The safety analysis suggested most of the toxicities were driven by docetaxel, as the rate of grade 3–4 adverse events were very similar between the two arms (66.1% triplet therapy *vs.* 63.5% ADT plus docetaxel in the overall population).

The recent subgroup analysis by Hussain *et al.* confirmed that patients with high volume disease (HR =0.69; 95% CI, 0.57–0.82) derived significant OS benefits from the addition of darolutamide to ADT plus docetaxel. Although not statistically significant, the results from ARASENS suggest potential OS benefit in patients with low volume disease (HR =0.68, 95% CI: 0.41–1.13) (19). Darolutamide also significantly prolonged time to metastatic castrate resistant prostate cancer (mCRPC) across volume of disease (HR =0.41 in high volume, HR =0.21 in low volume), as well as time to subsequent therapy.

While the OS data in the low volume subgroup is intriguing (and somewhat resembles the docetaxel data from STAMPEDE), one has to keep in mind that this represents a small subset of patients (n=300, 23%) in this trial, and longer follow up is needed. Most patients with low volume mHSPC likely benefit more from the addition of ARPI rather than docetaxel, and patients with *de novo* low volume mHSPC may also derive some benefit in disease control from radiation to the prostate primary (20,21). However, there are select cases of *de novo*, low volume mHSPC with additional high-risk features that should be considered for triplet therapy, outlined below.

Applying the ARASENS regimen to clinical practice

Given the rapidly evolving treatment landscape of mHSPC, one critical question remains, which is the role of adding docetaxel to ADT plus ARPI which is now the most commonly used treatment intensification regimen. None of the triplet therapy trials were designed to answer this question, as control arms in ENZAMET, PEACE-1, and ARASENS were ADT (or ADT plus NSAA in ENZAMET) plus docetaxel rather than the more contemporary doublet of ADT plus ARPI. Although there is no definitive evidence comparing survival benefits of triplet versus doublet therapy with ADT plus ARPI, ARASEC (NCT05059236) and ARANOTE (NCT04736199) are both evaluating ADT plus darolutamide in mHSPC, which will offer interesting data in this context. We also note that in PEACE-1 and LATITUDE, the median OS was longer with ADT, docetaxel, and abiraterone in *de novo* high volume patients (61 months) than ADT & abiraterone (53.3 months). In the absence of definitive comparative data, this suggests there may be a role for docetaxel in selected patients presenting with aggressive mHSPC (11,18). This paradigm is further supported by several recent meta-analyses showing a potential benefit of triplet therapy over ADT plus ARPI doublet therapy in patients with high volume mHSPC

(22-24). However, to definitely answer this question, a randomized controlled trial would be needed.

In our perspective, the supporting data for triplet therapy is mainly for patients with *de novo* high volume mHSPC, and one should acknowledge that the ARASENS population reflects an overall small proportion of biologically aggressive mHSPC when translating results into practice. Patients who are being considered for docetaxel should be offered a concurrent ARPI (darolutamide or abiraterone), given the OS benefits shown by ARASENS and PEACE-1 over ADT plus docetaxel. As outlined by recent ASCO guidelines, for chemo-eligible patients with high volume mHSPC who decline or cannot access an ARPI (e.g., due to insurance constraints), ADT plus docetaxel may be offered instead of triplet therapy. Docetaxel can overcome some of the financial toxicities associated with ARPIs due to the low drug cost and fixed treatment duration. While docetaxel is associated with notable adverse events in some, quality of life data from CHAARTED show most patients recover by 6 months, representing an acceptable treatment option (25). However, these patients should be made aware that ADT plus docetaxel confers inferior OS compared to triplet therapy. At present, in an era of treatment intensification with doublet (commonly ADT plus ARPI) and triplet (ADT, docetaxel, plus ARPI) regimens, ADT alone should not be routinely offered. Very rarely, there are special situations where patients are not fit to receive chemotherapy and/or an ARPI due to serious comorbidities conferring safety concerns or limiting overall prognosis, in which case ADT alone may be reasonable.

It should be noted that mHSPC is a highly heterogeneous disease, and in the absence of readily available predictive biomarkers, disease volume at presentation alone is likely insufficient for informing disease biology and predicting treatment outcomes. In ENZAMET, which included a relatively heterogenous patient population, explorative post hoc analysis did not identify any prognostic subgroup which clearly benefited from the addition of docetaxel. We see from clinical practice that there are subsets of patients with high volume disease who experience long term survival, while some patients with low volume disease demonstrate rapid treatment resistance. It is also important to recognize disease volume defined on conventional imaging is somewhat arbitrary and is subject to significant interobserver variation (26). Novel functional imaging such as prostate specific membrane antigen positron emission tomography (PSMA PET) has much higher sensitivity and is increasing utilized. Currently, there is no high-level evidence on using PSMA PET to guide decision making. Frequently, PSMA PET will upstage low volume disease defined by conventional imaging to high volume disease, conferring risks of over-treatment (adding docetaxel) and under-treatment (omitting radiation to the primary). In select cases where bone scans demonstrate nonspecific lesions in the bone, PSMA PET may play a role in confirming the presence of bone metastases for these lesions. However, the overall extent of disease volume demonstrated on PSMA PET should not be routinely used to define disease volume for the purpose of treatment selection.

In addition to volume, other disease factors also associate with poor outcomes and should be taken into account when considering triplet therapy. From large retrospective analyses, it has been shown that patients with liver metastases experience worse outcomes, whereas patients with high volume bone-only or pulmonary-predominant metastases have a more favorable prognosis (27). In PEACE-1, ARASENS, and ENZAMET, all these patients would have been analyzed as high-volume disease, and it is unclear whether the triplet regimen may be over-treating some patients with more favorable disease biology in the high-volume disease category. In addition, patients with homologous recombination deficiency (HRD) mutations, PTEN/RB1/TP53 loss (clinical predilection for neuroendocrine disease), bulky and symptomatic primaries, and younger age at diagnosis, often exhibit aggressive disease biology despite combination hormonal therapy, and should be considered for triplet therapy despite low-volume of disease (28-30). On the other hand, pending further validation studies, Speckle-type POZ protein (SPOP) mutations are associated with favorable responses to abiraterone, and these patients may be sufficiently treated with an ADT plus ARPI doublet (31).

The safety profile of triplet therapy must be considered in a disease where patients' symptom burden is overall minimal after starting ADT. Docetaxel is associated with short term risks such as neutropenic infections, and long-term toxicities including peripheral neuropathy. Financial toxicity from more frequent clinic visits, infusions, potential hospitalizations are also important contributors of informed decision making with the patient. Real-world data has consistently shown the low uptake of docetaxel in patients with mHSPC, and further work is needed to understand the relevant barriers and hurdles to broaden the use of docetaxel across subgroups of patients with aggressive disease (32). Looking at the safety profile across the triplet

Table 2 Ongoing phase 2 and 3 trials evaluating triplet therapy in mHSPC

Trial	Phase	Estimated enrollment	Experimental arm	Control arm	Primary endpoint	Trial status	Chemotherapy allowed
NCT04734730	2	70	ADT, abiraterone, talazoparib	N/A	PSA nadir at 12 months	Active, recruiting	No
NCT04126070	2	60	ADT, docetaxel, nivolumab	N/A	PSA nadir at 7 months	Active, recruiting	Yes
NCT03246347	2	40	ADT, enzalutamide, docetaxel	N/A	12-month PSA CR	Active, not recruiting	Yes
NCT04191096 (KEYNOTE 991)	3	1,251	ADT, enzalutamide, pembrolizumab	ADT, enzalutamide, placebo	rPFS and OS	Active, not recruiting	Yes
NCT04493853 (CAPITELLO-281)	3	1,000	ADT, abiraterone, capivasertib	ADT, abiraterone, placebo	rPFS	Active, recruiting	N/A
NCT04821622 (TALAPRO-3)	3	550	ADT, enzalutamide, talazoparib	ADT, enzalutamide, placebo	rPFS	Active, not recruiting	No
NCT04497844 (AMPLITUDE)	3	692	ADT, abiraterone, niraparib	ADT, abiraterone, placebo	rPFS	Active, not recruiting	Yes
NCT04720157 (PSMAddition)	3	1,126	ADT, ARPI, 177-lutetium	ADT, ARPI	rPFS	Active, not recruiting	No

mHSPC, metastatic hormone sensitive prostate cancer; ADT, androgen deprivation therapy; rPFS, radiographic progression free survival; OS, overall survival; PSA, prostate specific antigen; PSA CR, PSA complete response; ARPI, androgen receptor pathway inhibitor.

therapy trials, ARASENS demonstrate that darolutamide is a very well tolerated ARPI when combined with chemotherapy. In the high volume subgroup of ARASENS, the rate of grade 3–4 adverse events only increased by 0.7% and the rate of treatment discontinuation increased by 2.6% from adding darolutamide (19). Darolutamide is also a structurally distinct ARPI with limited potential for drug-drug interactions.

Looking into the future, ARASENS, PEACE-1, and ENZAMET pave the road for more exciting triplet or quadruplet combinations, especially biomarker driven approaches with the shift towards precision medicine. Several clinical trials (*Table 2*) are now exploring combinations of ARPI with targeted therapies, checkpoint inhibitors, and radioligand therapies (PARP inhibitors, PTEN inhibitors, PD1 inhibitors, lutetium). Notably, the control arm in these trials includes an ADT plus ARPI doublet, which was a major critique in existing triplet therapy studies to date. Recently, Bossi *et al.* showed that among the PEACE-1 low-volume mHSPC cohort, while radiation improved radiographic progression free survival (rPFS) and time to serious genitourinary events for patients who received the triplet regimen of ADT, docetaxel, and abiraterone compared to SOC (ADT plus docetaxel), it did not improve OS (21). In practice, the addition of radiation to the prostate primary for low volume mHSPC (often on the backbone of ADT & ARPI) is a well-adopted paradigm due to the positive OS data shown by STAMPEDE, and potential OS benefit in the HORRAD trial (33). The seemingly conflicting data between PEACE-1 and STAMPEDE may be due to differences in the study population, as reflected by the median baseline prostate specific antigen (PSA), proportion of T3/T4 disease, and the use of systemic therapy which could also improve local control (only 18% of patients were planned for docetaxel in STAMPEDE). Currently, we still offer prostate primary radiation for patients with low volume disease and those with bulky primaries, given the treatment is well tolerated and can delay serious pelvic complications from disease progression. In the future, the OS benefit of radiation to the primary in patients with low volume mHSPC in an era of more effective systemic therapies warrants further evaluation, and it would be interesting to explore this question in other triplet therapy trials such as ARASENS.

Overall, early treatment intensification at the outset has significantly improved the outcomes of patients with mHSPC. However, many patients still harbor mHSPC with aggressive disease biology and demonstrate suboptimal

outcomes, outside of volume alone. The current triplet regimen of ADT, docetaxel, and ARPI marks the beginning of a new era in mHSPC, and the recent ARASENS data supports ADT, docetaxel and darolutamide as another SOC in select patients. Applying the data to our practice, we would prefer using the ARASENS regimen for mainly patients with *de novo* high volume mHSPC and especially for individuals with high-risk visceral metastases such as liver metastases. The role for triplet therapy in individuals with low volume mHSPC requires more nuanced case-by-case review, taking into account aggressive disease features, tolerability of chemotherapy, and patient preferences.

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