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Platinum Opinion

Lutetium-177-PSMA-617 in Metastatic Castration-resistant Prostate Cancer: Limitations of the VISION Trial

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Prostate cancer treatment options have increased over the past two decades. First-generation androgen deprivation agents followed by taxane-based chemotherapy have been joined by second- and third-generation androgen receptor targeting agents (ARTAs: abiraterone, enzalutamide, apalutamide, and darolutamide) and other novel therapeutics (olaparib, radium-223, sipuleucel-T, and pembrolizumab) [1]. This armamentarium is expanding yet again after publication of results from the VISION trial (NCT03511664).

VISION is a phase 3 study that randomized patients with metastatic castration-resistant prostate cancer to lutetium-177-PSMA-617 (Lu-PSMA) therapy in combination with standard of care (SOC) or to SOC alone. VISION met its alternate primary endpoints, with significant and large improvements in imaging-based progression-free survival (PFS; median 8.7 vs 3.4 mo; $p < 0.001$) and overall survival (OS; median 15.3 vs 11.3 mo; $p < 0.001$) [2]. On the basis of the VISION results, the US Food and Drug Administration (FDA) granted regular approval for Lu-PSMA on March 23, 2022 for "adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy" [3].

We congratulate the investigators for bringing a novel agent that improves pain and reduces disease burden to the US market, but highlight three concerns limiting the external validity of the results reported. All three limitations are related to the control arm (Fig. 1). First, VISION limited the choice of SOC, ostensibly because only the safety of some drugs was established in combination with Lu-PSMA, but this unfairly led to a suboptimal control arm, beneath the best available care outside of the trial setting. Second, we discuss how incentives to enroll patients in a trial may result in soft inclusion or exclusion criteria that further worsen the quality of care in the control arm. Third, we discuss the impact of a high attrition rate in the control arm, which subverts randomization and further penalizes the control arm.

First, trial investigators limited the use of cytotoxic chemotherapies (eg, cabazitaxel), systemic radioisotopes, immunotherapies, and investigational drugs in both arms of VISION [2]. The only systemic anticancer options permitted were hormone therapies, including novel ARTAs such as abiraterone and enzalutamide. When considering baseline characteristics, 54.3% (152/280) of the patients in the control arm had previously received two or more ARTA regimens. In other words, patients were enrolled and allocated to the same treatment under which they had already experienced disease progression. The remaining 45.7% of patients had previously received one ARTA. It has been shown that while enzalutamide after abiraterone may have modest efficacy in this setting, abiraterone after enzalutamide results in almost no activity [4]. In the VISION trial, 73.6% of patients in the control arm had previously received enzalutamide. Thus, almost three-quarters % of patients in the control arm were unlikely to experience any response in this study. Moreover, many had better alternative choices.

Only 38.2% of the patients in the control arm had received previous taxane therapy with cabazitaxel. Cabazitaxel exhibited a 2.6-mo OS advantage over abiraterone and enzalutamide in the CARD trial [5]. Yet prohibition of taxane therapy on protocol was a design feature of VISION, leading to a subpar control arm. We previously described how a restricted choice for therapy in the control arm may lead to suboptimal care for patients [6], and this occurred in the VISION trial.

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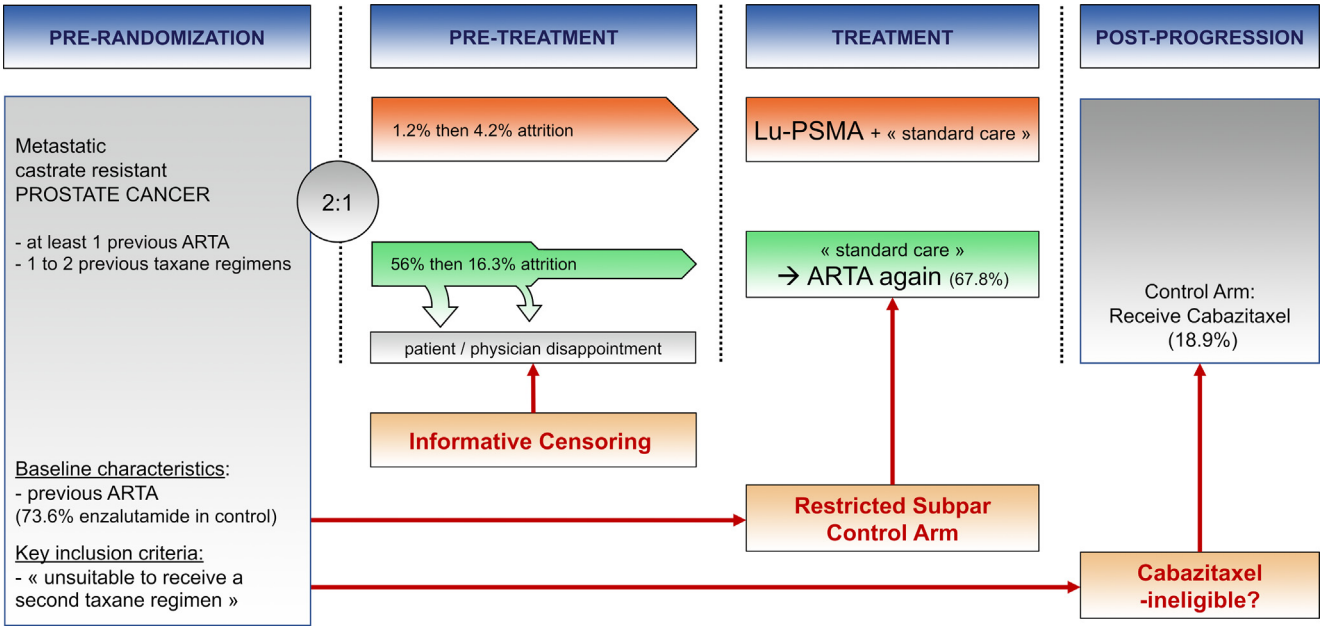

Fig. 1 – Three design features penalizing the control arm in the VISION trial. ARTA = androgen receptor targeting agent (abiraterone, enzalutamide, others). Standard care options were restricted, and comprised hormone therapies including ARTA, biphosphonates, denosumab, glucocorticoids or radiotherapy.

The investigators stated that the rationale for restrictions on the use of other therapies was that they had yet to determine if it was safe to combine these treatments with Lu-PSMA [2]. However, concerns regarding safety profiles in conjunction with other routinely used therapies should have been addressed before conducting a large phase 3 randomized controlled trial (RCT). More importantly, although this rationale may be logically used to restrict the number of treatments in the Lu-PSMA arm, it is misguided to apply the same justification to hinder the control arm. A trial could limit the SOC allowed to be paired with the experimental drug while allowing unfettered choice in the control arm.

A second issue is that some patients may have been wrongly included in VISION when they had better alternatives outside of the trial. According to the VISION protocol, patients who had previously received a taxane and were deemed eligible for a second taxane before enrolment were excluded [2]. However, nearly one-fifth of the patients received a taxane as postprotocol therapy, with 16.2% receiving cabazitaxel (18.9% of patients in the control arm). How can a patient initially deemed ineligible for a therapy be eligible for this therapy later in the course of a metastatic cancer? This might happen if a dramatic clinical improvement occurs as the result of the investigational (or control) therapy. However, for highly selected patients with good performance status (0 to 1) and no severe comorbidities, as in the VISION trial, this is unlikely to explain the phenomenon. Patients in VISION should have received cabazitaxel before beginning the trial if they were able to receive it after being exposed to a suboptimal control treatment.

Third, withholding of life-prolonging therapies probably contributed to the large attrition rate in the control arm. During the first phase of enrolment, 56% (47/84) of patients in the control arm withdrew from the trial. This is a staggeringly high discontinuation rate that is unprecedented in modern trials [7]. In response, the investigators initiated "enhanced trial-site education measures" (ie, education to justify the subpar control arm). Even this failed to eliminate the issue: 16.3% (32/196) of patients withdrew after this implementation, far more than the corresponding rates of 1.2% (2/166) and 4.2% (16/285) for the experimental arm.

Disproportionate dropout means that randomization was subverted, alongside the reliability of downstream endpoints. The central assumption of the Kaplan-Meier method is that "at any time patients who are censored have the same survival prospects as those who continue to be followed" [8]. In the VISION trial, this rule was probably violated. It is likely that patients remaining in the control arm, in spite of an inferior control arm, had more advanced disease with fewer therapeutic options in comparison to patients who dropped out to receive an appropriate SOC outside the trial; alternatively they may have been of different socioeconomic status with fewer resources or knowledge of how to seek care outside the trial. This phenomenon probably further penalized the control arm, selecting for patients with poorer prognosis. In the regulatory space, early censoring is one of the primary reasons why the FDA panel ruled against approving quizartinib for acute myeloid leukemia, despite an OS advantage in the efficacy analysis [9]. Nonetheless, Lu-PSMA was granted approval on the basis of the VISION trial, which had similar concerns.

Comparison of a new therapy against something that is not current practice hinders the generalizability and applicability of the results obtained. The Helsinki Declaration states that the goal of medical research should "never take precedence over the rights and interests of individual research subjects" [10]. Despite this prohibition, weak or inferior control arms in clinical studies are prevalent [11]. In fact, one-third (33%) of RCTs involving genitourinary

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malignancies have had suboptimal control arms [12]. VISION is emblematic of this concern. Proponents of the VISION design may contend that the control arm reflects the SOC globally; however, this position fails to account for the direct and indirect costs of Lu-PSMA. Use of this therapy necessitates PSMA positron emission tomography imaging and radionucleotide manufacturing capacity, a technology financially out of reach for many nations.

In short, the VISION trial captures many challenges in modern oncology trials: the use of inferior SOC, bizarre rationales to justify those choices, and high rates of drop out or censoring (Fig. 1). Proponents of Lu-PSMA rightly point to the strong response rate with this therapy, yet this was established long before and independent of the VISION trial. VISION did not seek to establish whether Lu-PSMA was highly active (it is), but where in the therapeutic strategy it could be used to ensure a patient benefit. Because the control arm was unacceptable, patients dropped out at unacceptable rates. VISION may have satisfied the regulators, but it does not satisfy the longstanding principles of medical ethics or evidence-based medicine. Future trials are still needed to answer how we can use Lu-PSMA to increase patient survival or quality of life. A study by the Australian group failed to show that Lu-PSMA is superior to cabazitaxel in terms of OS [13], and future studies are needed. Our patients expect therapies that are not merely active but are used in a way that maximizes their health; designing ethical clinical trials is the first step in this endeavor.

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