AHFS Final Determination of Medical Acceptance: Off-label Use of Abiraterone Plus Prednisolone and Androgen Deprivation Therapy (ADT) for Nonmetastatic Castration-sensitive Prostate Cancer

Drug: Abiraterone

Off-label Use: Nonmetastatic Castration-sensitive Prostate Cancer

Criteria Used in Selection of Off-label Use for Review:

- ASCO guideline update – results from the STAMPEDE trial

Strength of Evidence: Level 2 (moderate strength/quality)

Grade of Recommendation: Recommended use (accepted)

Narrative Summary:

In 2021, the American Society of Clinical Oncology (ASCO) released a guideline update regarding the initial management of castration-sensitive (noncastrate) advanced, recurrent, or metastatic prostate cancer.[10001] An Expert Panel evaluated the clinical data of combination therapies as compared to castration alone for men with castration-sensitive locally advanced nonmetastatic prostate cancer.[10001] The Panel concluded that abiraterone in combination with prednisolone and androgen deprivation therapy (ADT) should be considered for men with castration-sensitive, locally advanced, nonmetastatic prostate cancer, versus castration monotherapy, based on results from the STAMPEDE trial.[10002]

The STAMPEDE investigators utilized a multigroup, multistage platform design to investigate if the earlier administration of abiraterone in men on long-term ADT (orchiectomy or gonadotropin-releasing hormone [GnRH] agonists or antagonists) could improve survival.[10002]

Men included in this study (N=1917) had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced or disease that was treated prior with radical surgery or radiotherapy and was currently relapsing with high-risk features (in men no longer receiving therapy, a prostate specific antigen [PSA] >4 ng/mL with a doubling time of <6 months, a PSA >20 ng/mL, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment).[10002] Men with clinically significant cardiovascular disease were excluded from the study.[10002] Patients were randomly assigned in an open-label fashion to ADT alone (n=957) or ADT in combination with abiraterone 1000 mg and prednisolone 5 mg once daily (n=960).[10002] Of these, 915 patients had advanced prostate cancer and no metastases; 455 were randomly assigned to ADT alone and 460 to ADT plus abiraterone and prednisolone.[10001]

Androgen deprivation therapy was administered for at least 2 years.[10002] Patients with node-negative, nonmetastatic disease were required to undergo local radiotherapy at 6 to 9 months post-randomization while those with positive nodes were encouraged to receive such therapy.[10002] For patients with nonmetastatic disease with radiotherapy planned, treatment was to continue for 2 years or until any type of disease progression, whichever occurred first.[10002] For patients with nonmetastatic disease with no radiotherapy or those with metastatic disease, treatment continued until PSA, radiologic, or clinical progression or until another therapy was initiated.[10002] The primary outcome was overall survival, defined as time from randomization to death from any cause.[10002] The intermediate primary outcome was failure-free survival, defined as the time to the earliest of biochemical failure, disease progression, or death.[10002]

The median age of patients in the ADT monotherapy and combination therapy groups was 67 years.[10002] Seventy-eight percent of patients in each group had a World Health Organization (WHO) performance status of 0, with the remaining 22% of patients in each group having a WHO performance status of 1 or 2.[10002] In the ADT monotherapy group, 27% of patients had newly diagnosed, node-negative, nonmetastatic disease; 20% had newly diagnosed, node-positive, nonmetastatic disease; and 1% had previously treated nonmetastatic disease.[10002] In the combination therapy group, the percentages for these groups were 26%, 19%, and 3%, respectively.[10002] The remaining patients in either group had newly diagnosed or previously treated metastatic disease.[10002]

Results revealed a significant improvement in overall survival (for patients with metastatic and nonmetastatic disease) with combination therapy as compared to ADT alone at a median follow-up of 40 months; 184 deaths in the combination group versus 262 in the monotherapy group.[10002] The 3-year overall survival rate was 83% in the combination group versus 76% in the monotherapy group.[10002] A subgroup analysis of overall survival among men with nonmetastatic disease was premature as few patients died by the study publication date.[10001,10002] Failure-free survival was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone.[10001] Combination therapy was associated with a 79% relative improvement in this

outcome, although treatment duration was 2 years or less.[10001,10002] Regarding safety, grade 3 to 5 adverse events occurred more frequently in patients in the combination group as compared to the ADT alone group (47% versus 33%).[10002]

The prior clinical study was also included in a meta-analysis of primary results from 2 randomized, controlled, phase 3 trials of the STAMPEDE platform protocol that included patients with high-risk, or relapsing with high-risk features, nonmetastatic prostate cancer and a WHO performance status of 0-2.[10003] The other included trial compared ADT with ADT plus enzalutamide 160 mg once daily, abiraterone, and prednisolone (same doses as above STAMPEDE trial).[10003] A total of 1974 nonmetastatic patients were randomly assigned in both trials to standard of care (control) or with combination therapy.[10003] The primary endpoint was metastasis-free survival, defined as time from randomization to death from any cause or to distant metastases confirmed by imaging.[10003]

Overall, there were 180 metastasis-free survival events in the combination therapy groups and 306 in the control groups with a median follow-up of 72 months.[10003] Results revealed that metastasis-free survival was significantly longer in the combination therapy groups as compared to the control groups, with 6-year metastasis-free survival improved from 69% (control) to 82% (combination therapy).[10003] There was no evidence of a difference in metastasis-free survival when comparing concurrent administration of abiraterone and enzalutamide to abiraterone alone.[10003] Secondary endpoints, including overall survival, prostate-cancer specific survival, biochemical failure-free-survival, and progression-free survival were also significantly longer in the combination therapy versus control groups.[10003]

Based on current evidence, abiraterone plus prednisolone and ADT for the treatment of nonmetastatic castration-sensitive prostate cancer has Level 2 (moderate strength/quality) evidence supporting its use.[10001,10002] Currently available data include results from a multigroup, multistage platform design study with randomization and an open-label treatment approach.[10001,10002,10003] Based on these data, abiraterone plus prednisolone and ADT should be considered for men with nonmetastatic, castration-sensitive, locally advanced prostate cancer.[10001] Nonmetastatic patients with node-positive disease should also receive radiotherapy and those without lymph node involvement should have high-risk features as noted in the STAMPEDE trial in order to receive abiraterone combination therapy.[10002]

Dosage

When abiraterone is used in combination with prednisolone and ADT for the treatment of nonmetastatic castration-sensitive prostate cancer, the usual dosage administered in clinical studies is 1000 mg orally once daily.[10001,10002]

References:

10001. Virgo KS, Rumble B, de Wit R, et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update. *J Clin Oncol*. 2019;39:1274-1305.

10002. James ND, de Bono JS, Spears MR, et al for the STAMPEDE investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377:338-51.

10003. Attard G, Murphy L, Clarke NW, et al on behalf of the STAMPEDE investigators. Abiraterone and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomized controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399:447-60.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote:

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 7 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 4 votes

Reasonable choice (Accepted, with possible conditions): 3 votes

Not fully established (Equivocal): 0 vote

Not recommended (Unaccepted): 0 votes

Reviewer Comments on Level of Evidence and Grade of Recommendation:

Support the additional use of abiraterone in this extended patient population. The disease site was the same as the trial that yielded FDA approval. Toxicities seemed in line with what is seen in combination therapy for the FDA approved indication. Provides good alternative option for first line therapy in this patient population.

The benefit of using abiraterone in non-metastatic patients is marginal and it should be considered only in select patients, to reflect the study population. The higher toxicity is another factor to consider, so prescribing should be personalized based on performance status and patient comorbidities. High-risk features should be listed to ensure the right patients are being prescribed

this treatment, instead of all non-metastatic patients. Also should highlight the need for radiotherapy in node+ patients.

STAMPEDE study design and outcomes, as well as ASCO guidelines, support this recommendation.

I agree with the recommendations of Level 2 evidence based on the nonmetastatic population subgroup analysis of STAMPEDE that has premature OS data at this time (and OS is the primary endpoint of the trial), and failure free survival being an intermediate endpoint. Recommendations for use of this being a recommended and acceptable therapy aligns with ASCO guidelines updates and specifically Recommendation 2.1 in the guidelines.

The data clearly demonstrates that this population can benefit from this additional option. This could be particularly beneficial in patients with seizure disorders who may not be the best candidates for other therapies such as darolutamide, enzalutamide, etc.

Consensus Vote (7 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 7 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 5 votes

Reasonable choice (Accepted, with possible conditions): 2 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Recommended use (Accepted)

Reviewer Comments on Level of Evidence and Grade of Recommendation:

Strong evidence for metastasis-free survival in combination group; similar side effect profile and patient population studied.

With the additional evidence in the STAMPEDE meta-analysis, and the caveat that the indication be applied only to patients with at least high risk features, the reviewer was comfortable considering this treatment as recommended use based on Level 2 evidence.

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Isabel Houlzet PharmD, BCOP; Sandra Cuellar PharmD, BCOP; Christine Gegeckas PharmD, BCOP, Kathleen Wiley, MSN, RN, AOCNS; Chase Ayres PharmD, BCOP; Donald Moore BCPS, BCOP; Kirollos Hanna PharmD, BCPS, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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