Poster 133

Enzalutamide (ENZA) Versus Bicalutamide (BIC) in Patients With Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC): A Prespecified Subgroup Analysis of the STRIVE Trial

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Objective

To compare the efficacy and safety of enzalutamide vs bicalutamide in patients with nonmetastatic castration-resistant prostate cancer from the STRIVE trial.

Conclusion

Compared to bicalutamide, enzalutamide improved progression-free survival (PFS) and increased time to prostate-specific antigen (PSA) progression in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC). The benefit of enzalutamide treatment on PFS was consistent across subgroups. The safety profile of enzalutamide in this subset of patients was consistent with those seen in prior phase 3 studies.

Context

Despite evidence demonstrating the efficacy of enzalutamide and the improvement in progression-free survival compared with bicalutamide, patients with nmCRPC are still commonly treated with bicalutamide in many parts of the world. Clinicians should be aware of the clinical benefit of adding enzalutamide, rather than bicalutamide, to androgen deprivation therapy (ADT) in men with nmCRPC.

Background

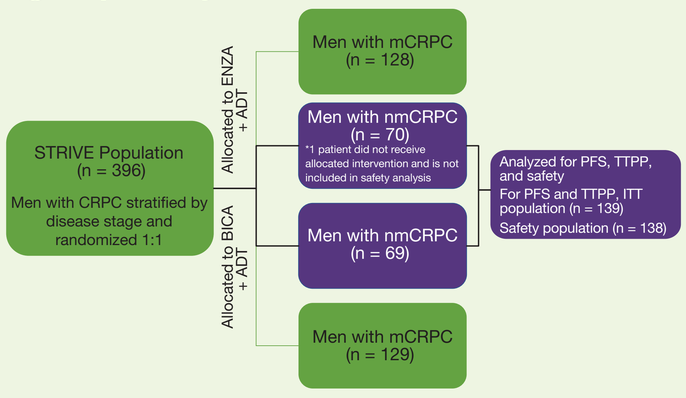
- Enzalutamide significantly reduced the risk of prostate cancer progression or death compared with bicalutamide in the STRIVE trial (hazard ratio [HR], 0.24; 95% CI, 0.18 to 0.32; $P < .0001$) in patients with CRPC, either nonmetastatic (nmCRPC) or metastatic (mCRPC).[1]
- Patients with nmCRPC are still commonly treated with bicalutamide in many parts of the world, despite this evidence demonstrating improvement in survival with enzalutamide compared with bicalutamide.
- Here we report results from a prespecified subgroup analysis of the STRIVE trial in patients with nmCRPC to highlight the clinical benefit of enzalutamide over bicalutamide in these patients.

Methods

The design of this prespecified subgroup analysis of the STRIVE trial (NCT01664923) is presented in **Figure 1**.

- In STRIVE, patients were stratified by disease stage (nmCRPC vs mCRPC) and randomized to enzalutamide 160 mg/day plus ADT or bicalutamide 50 mg/day plus ADT.
- In this subgroup analysis, men from STRIVE with nmCRPC (n = 139) were assessed for PFS, time to PSA progression, and safety.

Figure 1. Design of the STRIVE Prespecified Subgroup Analysis



Abbreviations: ADT, androgen deprivation therapy; BICA, bicalutamide; CRPC, castration-resistant prostate cancer; ENZA, enzalutamide; ITT, intention-to-treat; mCRPC, metastatic CRPC; nmCRPC, nonmetastatic CRPC, PFS, progression-free survival; TTPP, time to PSA progression.

Results

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Demographic and baseline patient characteristics were generally well balanced between treatment arms.
  - Patients in the bicalutamide group were older (median age, 77.0 years vs 73.5 years)
  - Patients in the bicalutamide group had a longer PSA doubling time (median, 5.3 months vs 3.9 months; **Table 1**).

Figure 2. (A) Progression-free Survival (PFS) and (B) Time to Prostate-specific Antigen (PSA) Progression (TTPP) in the Population of Men with nmCRPC from the STRIVE Trial

Abbreviations: BIC, bicalutamide; ENZA, enzalutamide, HR, hazard ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; NR, not reached.

Table 1. Patient Demographics and Baseline Characteristics in the Population of Men with nmCRPC from the STRIVE Trial

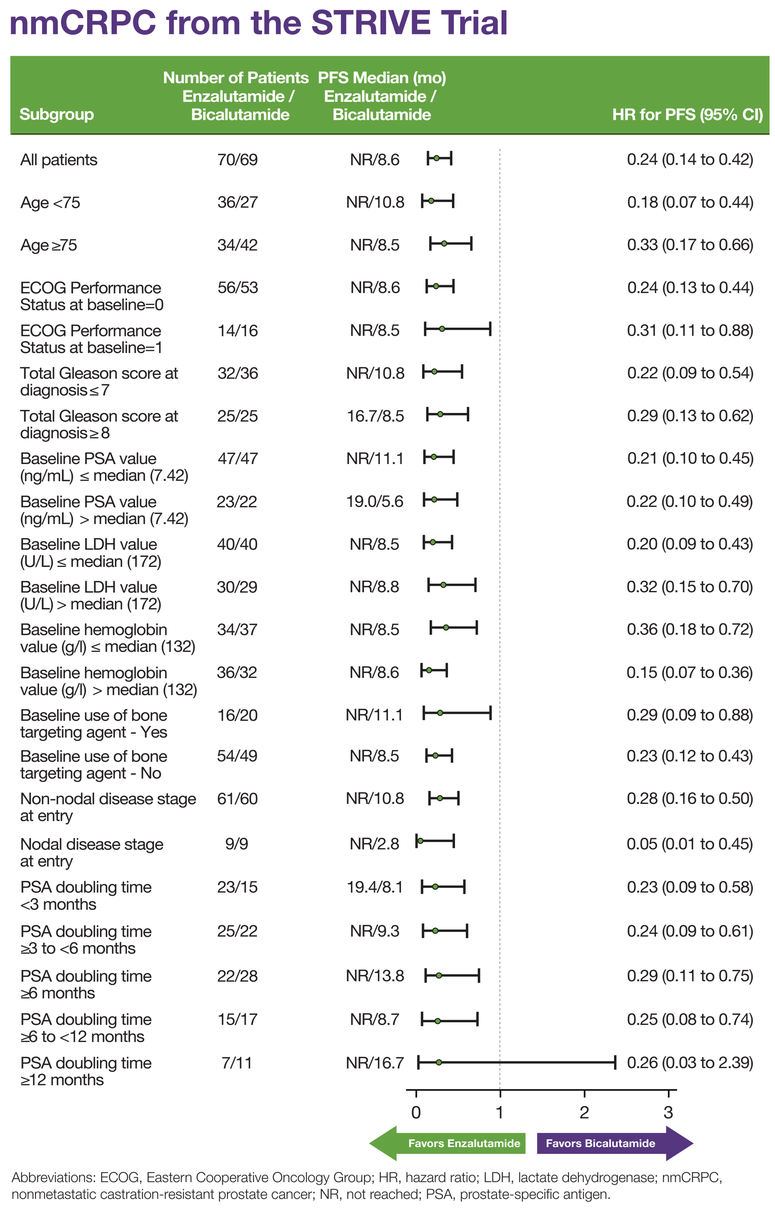
Characteristic	Enzalutamide (n = 70)	Bicalutamide (n = 69)
Age, years		
< 65, no. (%)	11 (15.7)	4 (5.8)
65 to 74, no. (%)	25 (35.7)	23 (33.3)
≥ 75, no. (%)	34 (48.6)	42 (60.9)
Mean (SD)	73.1 (8.89)	77.0 (7.46)
Median (range)	73.5 (50.0-92.0)	77.0 (58.0-91.0)
Race, no. (%)		
White	53 (75.7)	58 (84.1)
Black or African American	15 (21.4)	9 (13.0)
Asian	0	1 (1.4)
Other	2 (2.9)	1 (1.4)
Baseline ECOG PS, no. (%)		
0	56 (80.0)	53 (76.8)
1	14 (20.0)	16 (23.2)
Baseline pain score by BPI-SF, no. (%)		
0-1	59 (84.3)	59 (85.5)
2-3	11 (15.7)	10 (14.5)
Disease stage at study entry per CRF, no. (%)		
M0/N0	61 (87.1)	60 (87.0)
M0/N1	9 (12.9)	9 (13.0)
PSADT, months	n = 70	n = 65
Mean (SD)	5.3 (4.18)	7.9 (7.77)
Median (range)	3.9 (0.6-23.6)	5.3 (0.5-42.5)
PSADT category, no. (%)	n = 70	n = 65
< 3 months	23 (32.9)	15 (21.7)
≥ 3 to < 6 months	25 (35.7)	22 (31.9)
≥ 6 months	22 (31.4)	28 (40.6)
History of prior CV disease, no. (%)		
Yes	22 (31.4)	22 (31.9)
No	48 (68.6)	47 (68.1)
Baseline ECG result, no. (%)		
Normal	21 (30.0)	19 (27.5)
Abnormal, not clinically significant	49 (70.0)	50 (72.5)

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CRF, case report form; CV, cardiovascular; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSADT, prostate-specific antigen doubling time; SD, standard deviation.

PFS AND TIME TO PSA PROGRESSION

- At a median of 17 months of follow-up, men with nmCRPC receiving enzalutamide had a 76% reduced risk of progression or death (HR, 0.24; 95% CI, 0.14 to 0.42) and an 82% reduced risk of PSA progression (HR, 0.18; 95% CI, 0.10 to 0.34; **Figure 2**) compared with those receiving bicalutamide.
- The benefit from enzalutamide treatment for PFS was consistent across all subgroups examined; however, the benefit did not reach statistical significance in patients with a PSA doubling time ≥ 12 months (**Figure 3**).

Figure 3. Subgroup Analysis of Progression-free Survival (PFS) in Population of Men with nmCRPC from the STRIVE Trial



Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; nmCRPC, nonmetastatic castration-resistant prostate cancer; NR, not reached; PSA, prostate-specific antigen.

SENSITIVITY ANALYSIS

- A sensitivity analysis based on different censoring rules for the nmCRPC population did not affect the PFS benefit observed with enzalutamide versus bicalutamide (**Table 2**).

Table 2. Prespecified Sensitivity Analyses Evaluating the Effect of Various Censoring Rules for the ITT Population of Men with nmCRPC from the STRIVE Trial

	Enzalutamide (n = 70)	Bicalutamide (n = 69)
Primary analysis of PFS		
Median (95% CI), months	NR (19.4, NR)	8.6 (8.1-11.1)
HR (95% CI)	0.24 (0.14-0.42)	
P value	< .0001	
Sensitivity analysis #1: PFS to assess the impact of unconfirmed PD[a]		
Median (95% CI), months	NR (19.0, NR)	8.6 (8.1-11.1)
HR (95% CI)	0.26 (0.15-0.43)	
P value	< .0001	
Sensitivity analysis #2: PFS to assess the impact of treatment discontinuation[b]		
Median (95% CI), months	19.4 (14.1, NR)	8.5 (5.9-11.1)
HR (95% CI)	0.40 (0.26-0.62)	
P value	< .0001	
Sensitivity analysis #3: PFS to assess the impact of prostate cancer therapies[c]		
Median (95% CI), months	NR (19.4, NR)	8.6 (8.1-11.1)
HR (95% CI)	0.24 (0.14-0.42)	
P value	< .0001	
Sensitivity analysis #4: PFS to assess the impact of disease progression at an unscheduled visit[d]		
Median (95% CI), months	NR (19.4, NR)	8.6 (8.1-11.1)
HR (95% CI)	0.24 (0.14-0.42)	
P value	< .0001	

[a]Censoring due to unconfirmed progressive disease was defined as an event at treatment, the earliest occurrence of PSA progression, radiographic progression, or death. All event types occurring the same day were considered concurrent. [b]Censoring due to treatment discontinuation was defined as an event at the time of treatment discontinuation. [c]Censoring due to prostate cancer therapies (antineoplastic or radiation therapy) was defined as an event at the earliest initiation of such therapy. [d]Patients who were not known to have had a PFS event at the time of analysis data cutoff were censored at the date of the last assessment (PSA or radiographic, whichever was later) prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, and 2 or more consecutive missed PSA or tumor assessments.
Abbreviations: HR, hazard ratio; ITT, intention to treat; nmCRPC, nonmetastatic castration-resistant prostate cancer; NR, not reached; PD, progressive disease; PFS, progression-free survival; PSA, prostate-specific antigen.

SAFETY

- The median time on treatment was longer for patients receiving enzalutamide than for those receiving bicalutamide (17.8 months vs 12.3 months).
- For patients treated with enzalutamide, the proportion of patients with ≥ 1 adverse event was similar in men with nmCRPC (92.8%) and men with mCRPC (93.8%). Conversely, for patients treated with bicalutamide, the proportion of patients with ≥ 1 adverse event was higher in men with mCRPC (92.2%) than men with nmCRPC (84.1%).
- Compared to men receiving bicalutamide, the most frequently reported adverse events (unadjusted for treatment exposure) in men with nmCRPC receiving enzalutamide were fatigue (36.2% vs 21.7%), hot flash (20.3% vs 2.9%), decreased appetite (17.4% vs 5.8%), dizziness (17.4% vs 4.3%), and nausea (17.4% vs 13.0%; **Table 3**).
- These safety data are consistent with those observed in the larger phase 3 trial of enzalutamide versus placebo and in trials assessing the safety of other novel hormonal therapies

Table 3. Safety in the Population of Men with nmCRPC from the STRIVE Trial[a]

	Enzalutamide (n = 69)[b] All	Bicalutamide (n = 69)[c] All
Patients with ≥ 1 TEAE, no. (%)	64 (92.8)	58 (84.1)
TEAE (≥ 10% in either group), no. (%)		
Fatigue	25 (36.2)	15 (21.7)
Hot flash	14 (20.3)	2 (2.9)
Decreased appetite	12 (17.4)	4 (5.8)
Dizziness	12 (17.4)	3 (4.3)
Nausea	12 (17.4)	9 (13.0)
Arthralgia	11 (15.9)	6 (8.7)
Fall	11 (15.9)	6 (8.7)
Back pain	9 (13.0)	5 (7.2)
Hypertension	8 (11.6)	5 (7.2)
Dyspnea	7 (10.1)	5 (7.2)
Musculoskeletal pain	7 (10.1)	4 (5.8)
Diarrhea	6 (8.7)	8 (11.6)
Constipation	5 (7.2)	12 (17.4)
Urinary tract infection	1 (1.4)	11 (15.9)
Patients with Grade ≥ 3 TEAEs (≥ 2% in either group), no. (%)		
Any	29 (42.0)	26 (37.7)
Fatigue	4 (5.8)	2 (2.9)
Arthralgia	3 (4.3)	1 (1.4)
Congestive cardiac failure	3 (4.3)	1 (1.4)
Decreased appetite	0	2 (2.9)
Hypertension	3 (4.3)	2 (2.9)
Chest pain	2 (2.9)	0
Hematuria	2 (2.9)	1 (1.4)
Hydronephrosis	2 (2.9)	1 (1.4)
Hyperglycemia	2 (2.9)	0
Hypokalemia	1 (1.4)	2 (2.9)
Syncope	2 (2.9)	3 (4.3)
Urinary retention	0	3 (4.3)
Urinary tract infection	0	2 (2.9)

[a]The median duration of treatment for enzalutamide vs bicalutamide in this population was 17.8 months vs 12.3 months. [b]The safety population of patients receiving enzalutamide in STRIVE included 197 patients, of which 69 had nmCRPC. [c]The safety population of patients receiving bicalutamide in STRIVE included 198 patients, of which 69 had nmCRPC.
Abbreviations: nmCRPC, nonmetastatic castration-resistant prostate cancer; TEAE, treatment-emergent adverse event.

Plain Language Summary

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References: 1. Penson DF, et al. *J Clin Oncol.* 2016;34:2098-2106.

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