ZYTIGA® (abiraterone acetate)
ZYTIGA - STAMPEDE Trial

SUMMARY

- **S**ystemic **T**herapy in **A**dvancing or **M**etastatic **P**rostate Cancer: **E**valuation of **D**rug **E**fficacy: STAMPEDE (NCT00268476) is an ongoing, randomized, controlled, multi-arm, multi-stage, and multicenter trial which includes patients initiating long-term androgen deprivation therapy (ADT) for the first time for locally advanced or metastatic prostate cancer.[1]
- In the initial analysis, 1917 patients were randomized 1:1 to receive ZYTIGA 1000 mg daily plus prednisolone 5 mg daily with ADT (combination group; n= 960) or ADT alone (n=957). At a median follow-up of 40 months, there were 184 deaths in the combination group compared with 262 in the ADT alone group. The 3-year survival rate was 83% in the combination group compared with 76% in the ADT alone group (HR for death: 0.63; 95% CI, 0.52-0.76; *P*<0.001). There were 248 treatment-failure events in the combination group compared with 535 in the ADT alone group. The 3-year failure-free survival (FFS) was 75% in the combination group compared to 45% in the ADT alone group (HR for treatment failure: 0.29; 95% CI, 0.25-0.34; *P*<0.001). Grade 3-5 adverse events (AEs) occurred in 47% of patients in the combination group, including nine grade 5 AEs, and in 33% of patients in the ADT alone group, including three grade 5 AEs.[1]
    - Additional analyses, including subgroup analyses for patients with high- and low-risk nonmetastatic and metastatic disease and long-term results, are summarized below.[2-4]
- In a subset analysis of ZYTIGA plus prednisolone/prednisone with standard of care (SOC; n=377) and docetaxel plus prednisolone/prednisone with SOC (n=189), at a median follow-up of 48 months, the overall survival (OS) HR was 1.16 (95% CI, 0.82-1.65; P=0.40); FFS HR was 0.51 (95% CI, 0.39-0.67; P<0.001) with HR<1 favoring the ZYTIGA plus prednisolone with SOC group. A total of 48% and 50% of patients, respectively, in the ZYTIGA plus prednisolone/prednisone with SOC and docetaxel plus prednisolone/prednisone with SOC groups experienced a grade 3-5 AE.[5]
    - Results of quality of life (QOL) evaluation in patients with prostate cancer being treated with docetaxel plus prednisolone/prednisone and SOC vs ZYTIGA plus prednisone and SOC have been reported.[6]
- In a meta-analysis of 2 combination trials of ZYTIGA plus prednisolone/prednisone with ADT (n=459) vs ADT (n=455) and ADT plus ZYTIGA plus prednisolone/prednisone with enzalutamide (n=527) vs ADT (n=533), at a median follow-up of 72 months, metastasis-free survival (MFS) HR was 0.53 (95% CI, 0.44-0.64; *P*<0.0001). Grade 3-5 AEs occurred, respectively, in 130 and 172 patients in the control groups of the ZYTIGA and ZYTIGA with enzalutamide trials and 169 and 298 patients in the combination groups of the ZYTIGA and ZYTIGA with enzalutamide trials.[7]
    - In an analysis of OS, the ADT plus ZYTIGA plus prednisolone plus enzalutamide trial (N=916) had an HR of 0.65 (95% CI, 0.55-0.77; $P=1.4\times10^{-6}$), with 9% of patients receiving docetaxel plus ADT. In the ADT plus ZYTIGA plus prednisolone trial (N=1003), HR for OS was 0.62 (95% CI, 0.53-0.73; $P=1.4\times10^{-9}$). The interaction HR was 1.05 (95% CI, 0.83-1.32; *P*=0.71) with no evidence of between-trial heterogeneity (I^2P=0.70).[8]
    - In the ADT plus ZYTIGA plus prednisolone trial, at a median follow-up of 95.8 months, 30% and 48% of patients in the ADT alone and ADT plus ZYTIGA plus prednisolone groups, respectively, were alive at 7 years. The restricted mean survival time, respectively, was 50.4 and 60.6 months in the ADT alone and ADT plus ZYTIGA plus prednisolone groups ($P=6.6\times10^{-9}$).[8]
- Results of clinical quantification of transcriptome signatures and evaluation of nodal burden as prognostic biomarkers in ancillary studies of patients starting ADT

with/without ZYTIGA plus prednisolone for advanced prostate cancer and the ZYTIGA plus prednisolone plus docetaxel trials in patients with metastatic hormone-sensitive prostate cancer from STAMPEDE, respectively, have been reported.[9,10]
- Two open-label, randomised, controlled, phase 3 trials of the STAMPEDE platform protocol concluded that while ZYTIGA significantly improves survival when added to ADT in metastatic prostate cancer, its combination with enzalutamide does not provide additional survival benefits and increases toxicity.[11]
- Additional relevant citation identified in the published literature are cited here.[12]

CLINICAL DATA

The ongoing STAMPEDE trial includes patients initiating long-term ADT (orchiectomy or gonadotropin-releasing hormone [GnRH] agonists or antagonists) for the first time for locally advanced or metastatic prostate cancer. This study uses a multigroup, multistage (also called multi-arm, multistage [MAMS]) platform design to evaluate whether the addition of further treatments to ADT improves OS if used in this setting.[1]

ZYTIGA plus Prednisolone with ADT vs ADT Alone

James et al (2017)[1] evaluated the efficacy of ZYTIGA in combination with prednisolone in patients with locally advanced or metastatic prostate cancer who had not previously received hormone therapy and were initiating long-term ADT (N=1917).

Study Design Methods

- Randomized, controlled, MAMS, multicenter trial
  - Patients from 111 sites in the United Kingdom and 5 sites in Switzerland were included.
- Patients were randomized 1:1 to receive ZYTIGA 1000 mg daily plus prednisolone 5 mg daily with ADT (combination group) or ADT alone.
- Local radiotherapy was mandatory for patients with node-negative, nonmetastatic disease and optional for those patients with node-positive nonmetastatic disease.
- For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until prostate-specific antigen (PSA), radiologic, or clinical progression or until another treatment was started.
- For patients with nonmetastatic disease with radiotherapy planned, treatment was to continue for 2 years or until any type of progression, whichever came first.
- Patients included had prostate cancer that was:
  - Newly diagnosed and metastatic, node-positive, or high-risk locally advanced (defined as having ≥2 of the following disease characteristics: a tumor stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng/mL) OR
  - Disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (defined as a PSA level >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment)
- Key exclusion criteria: clinically significant cardiovascular disease (severe angina, recent myocardial infarction, or a history of cardiac failure)
- **Primary endpoint**: OS
- **Intermediate primary outcome**: FFS, defined as the time to the first of the following forms of treatment failure: biochemical PSA failure; progression of local, lymph-node, or distant metastases; or death from prostate cancer
- **Secondary endpoints**: AEs, symptomatic skeletal events, PFS (ie, FFS biochemical failure), prostate cancer-specific survival, and quality of life

Results

Patient Characteristics

- Median age was 67 years and median PSA level was 53 mg/mL.
- Patient baseline characteristics are described in Table: Patient Baseline Characteristics.

Patient Baseline Characteristics[1]

	ZYTIGA Plus Prednisolone With ADT (n=960)	ADT Alone (n=957)
Disease group, n (%)		
Newly diagnosed node-negative, nonmetastatic disease	253 (26)	256 (27)
Newly diagnosed node-positive, nonmetastatic disease	182 (19)	187 (20)
Newly diagnosed metastatic disease	465 (48)	476 (50)
Previously treated nonmetastatic disease	25 (3)	12 (1)
Previously treated metastatic disease	35 (4)	26 (3)
WHO performance status, n (%)[a]		
0	745 (78)	744 (78)
1 or 2	215 (22)	213 (22)
Gleason score, n (%)		
≤7	221 (23)	223 (23)
8 to 10	715 (74)	721 (75)
Unknown	24 (2)	13 (1)
Metastases at randomization, n (%)		
None	460 (48)	455 (48)
Any metastases	500 (52)	502 (52)
Bone	434 (45)	448 (47)
Liver	7 (1)	8 (1)
Lung	21 (2)	21 (2)
Nodal	142 (15)	150 (16)
Other	23 (2)	26 (3)
Planned or current long-term ADT, n (%)		
LHRH-based	951 (99)	943 (99)
Bicalutamide	5 (1)	5 (1)
Orchiectomy	3 (<1)	5 (1)
Dual androgen blockade	1 (<1)	4 (<1)
Radiotherapy planned, n (%)		
No	564 (59)	561 (59)
Yes	396 (41)	396 (41)

Abbreviations: ADT, androgen deprivation therapy; LHRH, luteinizing hormone–releasing hormone; WHO, World Health Organization.
[a]WHO performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.

Efficacy

- The median follow-up was 40 months.
- The median duration of treatment with ZYTIGA was 23.7 months in the patients whose therapy was capped at 2 years and 33.2 months in the patients who could continue through progression.
    - 51% discontinued due to progression, and 20% discontinued for toxicity.
- The reported rate of use of radiotherapy was 39% in the combination group and 40% in the ADT alone group.
- There were 184 deaths in the combination group as compared with 262 in the ADT alone group. A survival advantage was observed in the combination group, with a 3-year survival of 83% compared with 76% in the ADT alone group (HR, 0.63; 95% CI, 0.52-0.76; *P*<0.001).
    - The HR in patients with nonmetastatic disease was 0.75 and 0.61 in patients with metastatic disease.
- Based on central review, 140 of the 184 deaths in the combination group (76%) and 216 of the 262 deaths in the ADT alone group (82%) were attributed to prostate cancer. The competing-risks subhazard ratio for death from prostate cancer was 0.58 (95% CI, 0.47-0.72).
- Additional results are summarized in Table: Efficacy Outcome Measures.

Efficacy Outcome Measures[1]

	ZYTIGA Plus Prednisolone With ADT (n=960)	**ADT Alone (n=957)**	**Hazard Ratio (95% CI)**	***P* value**
Failure-free survival				
Treatment-failure events, n	535	248	-	-
3-year FFS, %	75	45	0.29[a] (0.25-0.34)	<0.001
RMST[b], months	43.9	30.0	-	-
Other efficacy outcome measures				
Radiologic or clinical progression or death from prostate cancer events, n	198	379	-	-
3-year PFS, %	80	62	0.40[c] (0.34-0.47)	<0.001
Symptomatic skeletal events, n	113	203	-	-
3-year rate without skeletal events, %	88	78	0.46[d] (0.37-0.58)	<0.001

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; FFS, failure-free survival; PFS, progression-free survival, RMST; restricted mean survival time.
[a]Hazard ratio for treatment failure.
[b]There was evidence of nonproportional hazards (*P*=0.001), so results are presented for restricted mean failure-free survival time in the first 54 months after randomization, resulting in a difference of 13.9 months (95% CI, 12.3-15.4).
[c]Hazard ratio for radiologic or clinical progression or death from prostate cancer.
[d]Hazard ratio for symptomatic skeletal events.

- Exploratory analyses of PFS and prostate cancer-specific survival within subgroups of age at randomization suggested a favorable treatment effect regardless of age, with proportionally fewer events noted in patients ≥70 years of age compared to patients <70 years of age.
- Treatment options for patients are summarized in Table: Treatment After Progression.

Treatment After Progression[1]

	ZYTIGA Plus Prednisolone With ADT (n=960)	ADT Alone (n=957)
Patients with progression, n (%)	248 (26)	535 (56)
Reported new treatment, n (%)	196 (79)	477 (89)
Reported "life-prolonging treatment", n (%)	131 (53)	310 (58)
Docetaxel	115 (46)	200 (37)
Enzalutamide	25 (10)	138 (26)
ZYTIGA	8 (3)	120 (22)
Cabazitaxel	15 (6)	28 (5)
Radium-223	19 (8)	24 (4)
Other treatments, n (%)		
Antiandrogens	83 (33)	387 (72)
Dexamethasone	52 (21)	113 (21)
Zoledronic acid	40 (16)	78 (15)
Prednisolone	33 (13)	83 (16)
Stilboestrol	8 (3)	14 (3)
Other chemotherapy	11 (4)	10 (2)
Other bisphosphonate	4 (2)	9 (2)
Strontium-89	0 (0)	2 (<1)
COX-2 inhibitor	1 (<1)	0 (0)
Abbreviation: ADT, androgen deprivation therapy; COX-2, cyclooxygenase-2.		

Additional Analyses

- In a 5-year follow-up analysis, after a median follow-up of 6.1 years, 244 and 329 deaths occurred in the ZYTIGA plus prednisolone with SOC (SOC was ADT) and SOC alone groups, respectively (adjusted HR, 0.60; 95% CI, 0.50-0.71; *P*<0.0001). Median survival in the ZYTIGA plus prednisolone with SOC and SOC alone groups was 79 and 46 months, respectively. The 5-year survival was 60% in the ZYTIGA plus prednisolone with SOC group and 41% in the SOC alone group. The relative effect of ZYTIGA was similar among patients with low- and high-risk disease (low-risk HR, 0.54; 95% CI, 0.40-0.74 and high-risk HR, 0.54; 95% CI, 0.43-0.69, respectively).[4]
    - Additional results are summarized in Table: Additional Efficacy Outcome Measures at 5-Year Follow-up.

Additional Efficacy Outcome Measures at 5-Year Follow-up[4]

	ZYTIGA Plus Prednisolone With SOC (n=501)	SOC Alone (n=502)	Hazard Ratio (95% CI)	*P* value
Failure-free survival				
Events, n	282	437	-	-
5-year FFS, %	45	13	0.34 (0.29-0.40)	<0.0001

	ZYTIGA Plus Prednisolone With SOC (n=501)	SOC Alone (n=502)	Hazard Ratio (95% CI)	*P* value
Progression-free survival				
Events, n	241	323	-	-
5-year PFS, %	54	37	0.58 (0.49-0.69)	<0.0001
Metastatic progression-free survival				
Events, n	230	309	-	-
5-year metastatic PFS, %	56	40	0.60 (0.50-0.71)	<0.0001
Skeletal-related events				
Events, n	76	100	-	-
5-year rate without skeletal-related events, %	82	76	0.56 (0.41-0.76)	0.0008
Disease-specific survival				
Events, n	156	255	-	-
5-year disease-specific survival, %	72	50	0.49 (0.39-0.60)	<0.0001

Abbreviations: CI, confidence interval; FFS, failure-free survival; PFS, progression-free survival; SOC, standard of care.

- A subgroup analysis of randomized patients with high-risk M0 disease (n=915; median follow-up of 38 months) showed FFS was improved with ZYTIGA plus prednisolone with SOC in patients with N0M0 disease (HR, 0.14; 95% CI, 0.07-0.30) with 3 year FFS of 98% compared to 80% with SOC. In N+M0 disease, FFS was improved with ZYTIGA plus prednisolone with SOC (HR, 0.26; 95% CI, 0.17-0.40), and MFS was also favorable for both subgroups: N0M0 HR=0.62 (95% CI, 0.33-1.14) and N+M0 HR=0.47 (95% CI, 0.29-0.78).[2]
- Another subgroup analysis of evaluable randomized patients classified as having low- (n=428) or high-risk (n=473) M1 disease demonstrated that those receiving ZYTIGA plus prednisolone with SOC had OS improvements (the study primary endpoint) in both the high-risk (HR, 0.54; 95% CI, 0.41-0.70) and low-risk (HR, 0.66; 95% CI, 0.44-0.98) groups. A total of 191 and 354 FFS events occurred in the ZYTIGA plus prednisolone with SOC and ADT alone groups, respectively. There was an absolute improvement of 44% in the 3-year FFS in patients with low-risk disease among patients treated with ZYTIGA plus prednisolone with SOC compared to ADT alone (76% vs 32%; HR, 0.25; 95% CI, 0.17-0.33). There was an absolute improvement of 33% in the 3-year FFS in patients with high-risk disease among patients treated with ZYTIGA plus prednisolone with SOC compared to ADT alone (45% vs 12%; HR, 0.31; 95% CI, 0.25-0.39). No evidence of heterogeneity between risk groups was found in OS or FFS (*P*-interaction=0.39 and 0.29, respectively). An exploratory analysis among patients with low-volume disease showed improvement in OS among patients treated with ZYTIGA plus prednisolone with SOC compared to patients treated with ADT alone (83% vs 77%; HR, 0.64; 95% CI, 0.42-0.97). The 3-year FFS among patients with low-volume disease in the ZYTIGA plus prednisolone with SOC group was 74% compared to 32% in the ADT alone group (HR, 0.26; 95% CI, 0.19-0.36). No evidence of heterogeneity of effect by the ZYTIGA plus prednisolone with SOC group among patients with high- or low-volume disease was observed for OS or FFS (*P*-interaction=0.77 and 0.47, respectively).[3]

Safety

- Grade 3-5 AEs reported in the safety population are summarized in Table: Grade 3-5 Adverse Events.
- There were 12 grade 5 AEs reported overall.
  - Combination group (n=9): 2 events of pneumonia (1 including sepsis), 2 events of stroke, and 1 event each of dyspnea, lower respiratory tract infection, liver failure, pulmonary hemorrhage, and chest infection
  - ADT alone group (n=3): 2 events of myocardial infarction and 1 event of bronchopneumonia

Grade 3-5 Adverse Events[1]

	ZYTIGA Plus Prednisolone With ADT	ADT Alone
Safety population, n	948	960
Patients with an AE, n (%)		
Any grade	943 (99)	950 (99)
Grade 3-5	443 (47)	315 (33)
Grade 5 only	9 (1)	3 (<1)
Grade 3-5 AEs, n (%)		
Endocrine disorders[a]	129 (14)	133 (14)
Cardiovascular disorder	92 (10)	41 (4)
Hypertension	44 (5)	13 (1)
Myocardial infarction	10 (1)	9 (1)
Cardiac dysrhythmia	14 (1)	2 (<1)
Musculoskeletal disorders	68 (7)	46 (5)
Gastrointestinal disorders	49 (5)	40 (4)
Hepatic disorders	70 (7)	12 (1)
Increased ALT	53 (6)	4 (<1)
Increased AST	10 (1)	2 (<1)
General disorders	45 (5)	29 (3)
Fatigue	21 (2)	15 (2)
Edema	5 (1)	0 (0)
Respiratory disorders	44 (5)	23 (2)
Dyspnea	18 (2)	7 (1)
Laboratory abnormalities	34 (4)	21 (2)
Hypokalemia	12 (1)	3 (<1)

Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Includes hot flashes and impotence.

ZYTIGA plus Prednisolone with ADT vs Docetaxel plus Prednisolone with ADT

Sydes et al (2018)[5] evaluated survival in a STAMPEDE subset directly comparing ZYTIGA plus prednisolone/prednisone with SOC to docetaxel plus prednisolone/prednisone with SOC (N=566).

Study Design Methods

- Patients were contemporaneously randomized 2:1:2 to receive:
  - SOC: long-term ADT or 2+ years ADT (plus radiotherapy for some non-metastatic disease [M0])
  - Docetaxel 75 mg/m^2 every 3 weeks for 6 cycles plus prednisolone/prednisone 10 mg daily with SOC (n=189) OR
  - ZYTIGA 1000 mg plus prednisolone/prednisone 5 mg orally daily with SOC (n=377)
- Duration of treatment with ZYTIGA plus prednisolone/prednisone was capped after 2 years in M0 patients having radical radiotherapy.
- **Primary endpoint**: death from any cause

Results

Patient Characteristics

- Treatment groups were well balanced.
  - M1: n=342 (60%)
  - Gleason 8-10: n=429 (76%)
  - World Health Organization (WHO) performance status 0: n=449 (79%)
- Median age was 66 years, and median PSA level was 56 ng/mL.

Efficacy

- The median follow-up was 48 months.
- There were 105 deaths in the ZYTIGA plus prednisolone/prednisone group with SOC and 44 in the docetaxel plus prednisolone/prednisone with SOC group.
- No heterogeneity was observed by baseline metastasis status (M0/M1; *P*=0.69).
- With HR<1 favoring the ZYTIGA plus prednisolone/prednisone with SOC group, OS HR was 1.16 (95% CI, 0.82-1.65; *P*=0.40), and event-free survival was:
  - FFS, HR=0.51; 95% CI, 0.39-0.67; *P*<0.001
  - PFS, HR=0.65; 95% CI, 0.48-0.88; *P*=0.005
  - Metastatic PFS, HR=0.77; 95% CI, 0.57-1.03; *P*=0.079
  - SRE, HR=0.83; 95% CI, 0.55-1.25; *P*=0.375

Safety

- A total of 48% and 50% of patients in the ZYTIGA plus prednisolone/prednisone with SOC and docetaxel plus prednisolone/prednisone with SOC groups experienced a grade 3-5 AE. Grade 3-5 AEs included: endocrine disorder, febrile neutropenia, neutropenia, general disorder (fatigue or edema), musculoskeletal disorder, cardiovascular disorder (hypertension, myocardial infarction, and cardiac dysrhythmia), gastrointestinal disorder, hepatic disorder (increased aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), respiratory disorder (dyspnea), renal disorder, and lab abnormalities (hypokalemia).

Meta-Analysis of ZYTIGA plus Prednisolone with ADT vs ADT and ZYTIGA plus Prednisolone with Enzalutamide vs ADT

Attard et al (2022)[7] conducted a meta-analysis to evaluate the results of 2 trials of the STAMPEDE platform protocol involving ZYTIGA and prednisolone with or without enzalutamide for patients with high-risk non-metastatic prostate cancer.

Study Design Methods

- Patients were randomized 1:1 to receive SOC alone or with combination therapy:

- SOC: 3 years ADT, which could include luteinizing-hormone-releasing hormone agonists and antagonists and surgery (plus radiotherapy [required for node-negative disease and encouraged for node-positive disease]) OR
- SOC plus ZYTIGA 1000 mg plus prednisolone/prednisone 5 mg orally daily alone (ZYTIGA trial) or with enzalutamide 160 mg orally once daily (ZYTIGA and enzalutamide trial)
  - ZYTIGA and enzalutamide therapy was continued for 2 years or until progression, whichever occurred first.

- **Primary endpoint**: MFS
- **Secondary endpoints**: OS, prostate cancer-specific survival, FFS, PFS, and toxicity/AEs
- **Stratifications:** randomization center, age (<70 vs ≥70), planned use of prostate radiotherapy, nodal involvement, WHO performance status, type of ADT, and regular, long-term use of aspirin or non-steroidal anti-inflammatory drugs

Results

Patient Characteristics

- A total of 1974 non-metastatic patients were assigned in both trials.
- Baseline characteristics of patients were well balanced between treatment groups.
- Median age was 68 years, and median PSA level was 34 ng/mL.
- Patient baseline characteristics are described in Table: Select Patient Baseline Characteristics.

Select Patient Baseline Characteristics[7]

	Combination Group in ZYTIGA Trial (n=459)	Control Group in ZYTIGA Trial (n=455)	Combination Group in ZYTIGA and Enzalutamide Trial (n=527)	Control Group in ZYTIGA and Enzalutamide Trial (n=533)
Nodal status of newly diagnosed patients, n (%)				
N0	253 (55)	256 (56)	325 (62)	327 (61)
N1	181 (39)	187 (41)	187 (35)	190 (36)
Nodal status of relapsed patients, n (%)				
N0	14 (3)	7 (2)	7 (1)	8 (2)
Nx	10 (2)	5 (1)	7 (1)	7 (1)
N0	1 (<1)	0	1 (<1)	1 (<1)
WHO performance status, n (%)				
0	370 (71)	375 (82)	429 (81)	435 (82)
1-2	89 (19)	80 (17)	98 (19)	98 (18)
Gleason score, n (%)				
<8	107 (23)	105 (23)	98 (19)	95 (18)
8 to 10	351 (77)	348 (76)	427 (81)	437 (82)
Missing	1 (<1)	2 (<1)	2 (<1)	1 (<1)
T stage at randomization, n (%)				
T0-T2	30 (7)	39 (9)	26 (5)	30 (6)
T3-T4	423 (92)	41 (90)	493 (94)	496 (93)

	Combination Group in ZYTIGA Trial (n=459)	Control Group in ZYTIGA Trial (n=455)	Combination Group in ZYTIGA and Enzalutamide Trial (n=527)	Control Group in ZYTIGA and Enzalutamide Trial (n=533)
TX	6 (1)	5 (1)	8 (2)	7 (1)
Local radiotherapy as SOC, n (%)				
No	87 (19)	83 (18)	58 (11)	62 (12)
Yes	372 (81)	372 (82)	469 (89)	471 (88)
Abbreviations: ADT, androgen deprivation therapy; SOC, standard of care; WHO, World Health Organization.				

Efficacy

- The median follow-up was 72 months (85 months in the ZYTIGA trial and 60 months in the ZYTIGA and enzalutamide trial).
- A total of 451/459 patients randomly assigned to ZYTIGA and prednisolone started treatment; 512/527 patients randomly assigned to ZYTIGA, prednisolone, and enzalutamide started both treatments, and 1 patient started only ZYTIGA and prednisolone.
- Eighty-four of the 964 patients (9%) continued treatment beyond 24 months.
- The planned rate of use of local radiotherapy was 1684/1974 patients (85%), namely for newly diagnosed patients, 99% and 71% for node-negative and node-positive patients, respectively, and 7% for previously treated patients.
- Efficacy results are summarized in Table: Efficacy Outcome Measures.
- A preplanned subgroup analysis evaluated 294 MFS events in the ZYTIGA trial and 192 MFS events in the ZYTIGA and enzalutamide trial.
    - Strong effects were observed in each trial (ZYTIGA trial: HR, 0.54; 95% CI, 0.43-0.68; $P<0.0001$; ZYTIGA and enzalutamide trial: HR, 0.53; 95% CI, 0.39-0.71; $P<0.0001$), with no difference in treatment effect (interaction HR, 1.02; 95% CI, 0.70-1.50; $P=0.91$) and no between-trial heterogeneity (I^2 $P=0.90$).
    - Analysis of treatment effect on MFS for baseline randomization stratification factors in the control groups and combination groups found statistically significant heterogeneity for WHO performance status 1-2 (I^2 $P=0.00656$) or use of non-steroidal inflammatory drugs or aspirin (I^2 $P=0.0052$).
- A preplanned subgroup analysis evaluated 237 deaths in the ZYTIGA trial and 146 deaths in the ZYTIGA and enzalutamide trial.
    - Strong effects were observed in both trials (ZYTIGA trial: HR, 0.63; 95% CI, 0.48-0.82; $P<0.0005$; ZYTIGA and enzalutamide trial: HR, 0.54; 95% CI, 0.39-0.76; $P<0.0004$), with no between-trial heterogeneity (I^2 $P=0.51$).

Efficacy Outcome Measures[7]

	Combination Groups (n=986)	Control Groups (n=988)	Hazard Ratio (95% CI)	*P* value
Metastasis-free survival				
MFS events, n	180[a]	306[b]	-	-
Median MFS, months	NR	NR	0.53 (0.44-0.64)	<0.0001
6-year MFS, %	82	69	-	-
Overall survival				
Deaths, n	147[c]	236[d]	-	-

	Combination Groups (n=986)	Control Groups (n=988)	Hazard Ratio (95% CI)	*P* value
Median OS, months	NR	NR	0.60 (0.48-0.73)	<0.0001
6-year OS, %	86	77	-	-
Prostate cancer-specific survival				
Deaths attributed to prostate cancer, n/N (%)	73/147 (50)	142/236 (60)	-	-
Median prostate cancer-specific survival, months	NR	NR	0.49 (0.37-0.65)	<0.0001
6-year prostate cancer-specific survival, %	93	85	-	-
Other efficacy outcome measures				
Radiologic or clinical progression or death from prostate cancer, n	138	277	-	-
Median PFS, months	NR	NR	0.44 (0.36-0.54)	<0.0001
Treatment failure (including PSA progression) events, n	204	402	-	-
Median FFS, months	NR	86	0.39 (0.33-0.47)	<0.0001

Abbreviations: CI, confidence interval; FFS, failure-free survival; MFS, metastasis-free survival; NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
[a]There were 111 and 69 events in the combination groups of the ZYTIGA trial and the ZYTIGA and enzalutamide trial, respectively.[13] Of the 180 events, 93 were deaths and 87 were extra-pelvic metastases.
[b]There were 183 and 123 events in the control groups of the ZYTIGA trial and the ZYTIGA and enzalutamide trial, respectively.[13] Of the 306 events, 117 were deaths and 189 were metastases.[13]
[c]There were 95 and 52 deaths in the combination groups of the ZYTIGA trial and the ZYTIGA and enzalutamide trial, respectively.
[d]There were 142 and 94 deaths in the control groups of the ZYTIGA trial and the ZYTIGA and enzalutamide trial, respectively.

- In an analysis of OS, the ADT plus ZYTIGA plus prednisolone plus enzalutamide trial (N=916) had an HR of 0.65 (95% CI, 0.55-0.77; $P=1.4x10^{-6}$), with 9% of patients receiving docetaxel plus ADT. In the ADT plus ZYTIGA plus prednisolone trial (N=1003), HR for OS was 0.62 (95% CI, 0.53-0.73; $P=1.4x10^{-9}$). The interaction HR was 1.05 (95% CI, 0.83-1.32; $P=0.71$) with no evidence of between-trial heterogeneity ($I^2P=0.70$).[8]
- In the ADT plus ZYTIGA plus prednisolone trial, at a median follow-up of 95.8 months, 30% and 48% of patients, respectively, in the ADT alone and ADT plus ZYTIGA plus prednisolone groups of the ADT plus ZYTIGA plus prednisolone trial were alive at 7 years. The restricted mean survival time was 50.4 months in the ADT alone and 60.6 months in the ADT plus ZYTIGA plus prednisolone groups ($P=6.6x10^{-9}$).[8]

Safety

- Grade 3-5 AEs reported in the safety population are summarized in Table: Grade 3-5 Adverse Events.
- There were 7 grade 5 AEs reported overall.
  - None in the control groups.
  - Three in the combination group of the ZYTIGA trial (rectal adenocarcinoma, pulmonary hemorrhage, and respiratory disorder, n=1 each).
  - Four in the combination group of the ZYTIGA and enzalutamide trial (septic shock, n=2; sudden death, n=2).

Grade 3-5 Adverse Events[7]

Events, n (%)	Combination Group in ZYTIGA Trial (n=451)		Control Group in ZYTIGA Trial (n=455)		Combination Group in ZYTIGA and Enzalutamide Trial (n=513)		Control Group in ZYTIGA and Enzalutamide Trial (n=533)	
Grade 3-5	169 (37)		130 (29)		298 (57)		172 (32)	
AEs	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Erectile dysfunction	41 (9)	0	48 (11)	0	71 (14)	0	55 (10)	0
Hypertension	23 (5)	0	6 (1)	0	73 (14)	0	8 (2)	0
ALT increased	23 (5)	2 (<1)	0	0	59 (12)	5 (1)	4 (1)	0
Fatigue	10 (2)	-	4 (1)	-	49 (10)	-	12 (2)	-
AST increased	2 (<1)	0	1 (<1)	0	17 (3)	2 (<1)	0	0
Insomnia	8 (2)	-	1 (<1)	-	7 (1)	-	1 (<1)	-
Hypokalemia	4 (1)	1 (<1)	1 (<1)	0	6 (1)	0	1 (<1)	0
Anemia	1 (<1)	1 (<1)	3 (1)	2 (<1)	2 (<1)	0	2 (<1)	0
Dizziness	1 (<1)	-	0	-	4 (1)	-	1 (<1)	-
Constipation	1 (<1)	0	3 (1)	0	1 (<1)	0	0	0
Cough	5 (1)	0	0	0	0	0	0	0
Nausea	0	-	1 (<1)	-	3 (1)	-	0	-
Cognitive disturbance	2 (<1)	0	0	0	2 (<1)	0	0	0
Dyspepsia	1 (<1)	0	0	0	2 (<1)	0	0	0
Anorexia	0	0	0	0	1 (<1)	0	1 (<1)	0
Headache	0	0	0	0	2 (<1)	0	0	0
Anxiety	-	-	-	-	1 (<1)	0	0	0
Depression	-	-	-	-	1 (<1)	0	0	0

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

- In an analysis of OS, the percentage of patients reporting grade 3-5 toxicity in the first 5 years was 38.5% in the ADT alone and 54.5% in the ADT plus ZYTIGA plus prednisolone groups of the ADT plus ZYTIGA plus prednisolone trial and 45.2% in the ADT alone and 67.9% in the ADT plus ZYTIGA plus prednisolone plus enzalutamide groups of the ADT plus ZYTIGA plus prednisolone plus enzalutamide trial. Liver derangement and hypertension were the most frequent; however, no specific incidence was reported.[8]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 29 August 2024.

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