ZYTIGA® (abiraterone acetate)
ZYTIGA - Coronavirus Disease 2019 (COVID-19)

SUMMARY

- No prospective clinical studies evaluating the efficacy and safety of ZYTIGA in patients with active infections, including novel coronavirus disease 2019 (COVID-19), have been published. In addition, no published data were identified regarding the use of a COVID-19 vaccine in patients receiving ZYTIGA. For more information on the use of vaccines and treatments for COVID-19, please contact the product manufacturers directly.
- In a retrospective, population-based, epidemiological study that evaluated the effect of androgen-inhibiting therapies on COVID-19 outcomes (hospitalization, intensive care, and death), patients with prostate cancer who received androgen-deprivation therapy (ADT) plus ZYTIGA or enzalutamide had a higher risk of mortality due to COVID-19 (hazard ratio [HR], 2.51; 95% confidence interval [CI], 1.52-4.16) after adjustment for age and comorbidities. No difference in outcomes was observed between patients receiving ZYTIGA plus ADT and patients receiving enzalutamide plus ADT (Table: Outcomes in Patients in Group 3 Receiving Enzalutamide or ZYTIGA).[1]
- ZYTIGA is indicated in combination with prednisone/prednisolone.[2] Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.[3-5] For more information regarding GnRH analog therapy, please contact the manufacturer directly.
- Data to assess incidence of COVID-19 in patients with cancer, including patients with prostate cancer receiving ADT, have been published.[6-11]

COVID-19 Prophylaxis or Infection in Patients Receiving ZYTIGA plus Prednisone

- If a patient is suspected to have been exposed to COVID-19, but is asymptomatic, providers should follow local and institutional guidelines to weigh risk vs benefit of the individual patient's treatment with ZYTIGA plus prednisone based on the nature and status of the patient's underlying cancer, comorbidities, concomitant medications, and the potential risks associated with COVID-19 infection.
- For prophylaxis, or if a patient has a confirmed COVID-19 infection, physicians should consider the risk vs benefit of continuing ZYTIGA based on the nature and status of the patient's underlying cancer, comorbidities, and the potential risks associated with the COVID-19 infection. Providers should refer to product labeling for additional information, including pharmacokinetics, safety, dosage & administration, dose modifications, monitoring, and drug-drug interactions for other medications used concomitantly in the prevention or management of COVID-19 infection.[12]

Select COVID-19 Resources for Providers Treating Patients with Cancer

Please note: this is not a complete list of publicly available resources pertaining to this topic.

- The Centers for Disease Control and Prevention (CDC) provides clinical care considerations for clinicians caring for patients with confirmed infection and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[13] Additionally, the National Institutes of Health (NIH) provides considerations and guidance for specific populations, including patients with cancer, and notes these patients may be at increased risk for severe illness.[14]
    - Interventions should be based on patient presentation and the clinical judgment of the treating physician. For the latest information from the CDC, visit: COVID-19.
- The American Cancer Society (ACS) and the American Society of Clinical Oncology (ASCO) recognize that cancer patients and cancer survivors often have weakened immune systems, increasing their risk for serious illness from infections such as the

coronavirus. ASCO recommends that oncologists and health care teams should discuss with their patients how best to protect against infections, such as coronavirus.[15,16]

- ASCO advises oncologists to use the best available evidence in caring for patients who may be exposed to or infected with the coronavirus, referring to the following as general sources of information: Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), US Food and Drug Administration (FDA), and US CDC.[17] ASCO has also developed resources related to caring for patients with cancer in the context of the coronavirus pandemic for clinicians and the cancer care delivery team[18], visit: ASCO Coronavirus Resources.
- Additional cancer organizations, including the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), have published resources for healthcare professionals, visit: NCCN COVID-19 Resources and ESMO COVID-19 and Cancer.
- For the latest global information and guidance from the World Health Organization (WHO) regarding the current outbreak of COVID-19, including daily updates, visit: Coronavirus Disease (COVID-19) Pandemic.

BACKGROUND

Concomitant Use with Corticosteroids and GnRH Analogs

Abiraterone acetate is converted in vivo to abiraterone, a 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor, and is indicated in combination with prednisone/prednisolone. Mineralocorticoid effects, such as hypertension, hypokalemia and edema, resulting from CYP17 inhibition may be ameliorated by coadministration with a corticosteroid, which lowers adrenocorticotropic hormone (ACTH) and steroids upstream of the CYP17 blockade.[1]

The efficacy and safety of ZYTIGA plus prednisone was studied in 3 phase 3, randomized, double-blind, placebo-controlled, multicenter clinical studies included in product labeling (COU-AA-301, COU-AA-302, and LATITUDE):[3-5,19,20]

- ZYTIGA was administered as 1,000 mg orally (PO) once daily in all studies.
- COU-AA-301 and COU-AA-302 evaluated ZYTIGA plus prednisone/prednisolone 5 mg PO **twice** daily in patients with metastatic castration-resistant prostate cancer (mCRPC) who received prior docetaxel or were chemotherapy naïve, respectively.
- LATITUDE evaluated ZYTIGA plus a lower dose of prednisone/prednisolone, 5 mg PO **once** daily, in patients with metastatic high-risk castration-sensitive prostate cancer (CSPC).
- All patients in these studies received a GnRH analog or had prior bilateral orchiectomy. For more information regarding GnRH analog therapy, please contact the manufacturer directly.
- Patients with active and uncontrolled infection or other medical conditions that would make prednisone/prednisolone use contraindicated were excluded from COU-AA-301, COU-AA-302, and the LATITUDE clinical studies.

Long-term use of moderate or high corticosteroid doses (eg, ≥20 mg/day of prednisone) has an established adverse event profile, including infections.[21] The rates of infection, dosing modifications (including dose reductions and interruptions) for infection, and discontinuations due to infection for ZYTIGA and prednisone/prednisolone are included in the 3 phase 3 study summaries below: COU-AA-301, COU-AA-302, and LATITUDE.[22-24]

CLINICAL DATA

Epidemiological Analysis of the Risk Associated with Androgen Inhibition in COVID-19 Outcomes

A retrospective, population-based, epidemiological study was conducted to evaluate the effect of androgen-inhibiting therapies on COVID-19 outcomes (hospitalization, intensive care, and death) in patients with prostate cancer from the Swedish national registers (N=7894).[1]

This analysis was performed in the age group of 50-81 years (n=5824). Patients were categorized as follows: those who received a single anti-androgen treatment (group 1; n=358), who received surgical or chemical castration (ADT; group 2; n=334), who received ADT plus ZYTIGA or enzalutamide (group 3; n=152), and prostate cancer patients with no ongoing or prior hormonal therapy (control group, n=4980). Patients in groups 1, 2, and 3 were older and had higher comorbidity scores than those in the control group. Patients in group 3 had a significantly higher comorbidity score than those in group 2 (P<0.001). Unadjusted analyses showed that the risk for hospitalization, need for intensive care (only group 1), and death due to COVID-19 were higher in patients who received androgen-inhibition treatment. After adjusting for age and comorbidities, patients in group 3 had a higher risk of mortality due to COVID-19 (HR, 2.51; 95% CI, 1.52-4.16).[1] No difference in outcomes was observed between patients in group 3 who received ZYTIGA plus ADT and patients who received enzalutamide plus ADT (Table: Outcomes in Patients in Group 3 Receiving Enzalutamide or ZYTIGA).[25]

Outcomes in Patients in Group 3 Receiving Enzalutamide or ZYTIGA[25]

Outcomes, n (%)	Enzalutamide	ZYTIGA	COR (95% CI)	AOR (95% CI)
Hospitalization	45 (42.9)	21 (44.7)	0.93 (0.46-1.86; P=0.834)	0.88 (0.43-1.80; P=0.718)
Intensive care	4 (4.3)	2 (5.0)	0.85 (0.15-4.86; P=0.859)	0.96 (0.16-5.54; P=0.960)
Fatal outcome	15 (14.3)	9 (19.1)	0.70 (0.28-1.75; P=0.449)	0.69 (0.27-1.74; P=0.428)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio.

Phase 3 COU-AA-301 Study

COU-AA-301 was a phase 3, randomized, double-blind, placebo-controlled, multinational study evaluating the use of ZYTIGA 1,000 mg PO daily plus prednisone 5 mg PO **twice** daily vs placebo plus prednisone in patients with mCRPC and disease-progression after docetaxel-based chemotherapy (N=1195). Patients were excluded from the study if they had serious or uncontrolled coexistent nonmalignant disease, including active and uncontrolled infection.[3,19]

Infection-related deaths that occurred in the study included 1 patient each in the ZYTIGA plus prednisone group for enterococcal infection, sepsis, septic shock, staphylococcal infection, and urosepsis and 1 patient for urosepsis and 2 patients for pneumonia in the placebo plus prednisone group.[22] The incidence of infections that occurred with a ≥2% absolute increase in frequency and study drug dose modifications (including dose reductions and interruptions) and discontinuation in the ZYTIGA plus prednisone group compared to the placebo plus prednisone group in the safety population. See tables: Infections in Phase 3 COU-AA-301 Study and Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 COU-AA-301 Study.

Infections in Phase 3 COU-AA-301 Study[22]

n (%)	ZYTIGA Plus Prednisone Group (n=791)			Placebo Plus Prednisone Group (n=394)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Urinary tract infection	91 (11.5)	17 (2.1)	0	28 (7.1)	2 (0.5)	0
Upper respiratory tract infection	43 (5.4)	0	0	10 (2.5)	0	0

Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 COU-AA-301 Study[22]

n (%)	ZYTIGA Plus Prednisone Group (n=791)	Placebo Plus Prednisone Group (n=394)
	Any Grade	Any Grade
Dose modification of ZYTIGA or placebo	14 (1.8)	5 (1.3)
Dose modification of prednisone or prednisolone	10 (1.3)	5 (1.3)
Discontinuation of any study drug	10 (1.3)	7 (1.8)

Efficacy and safety analyses were not performed separately for patients with a concurrent infection in the COU-AA-301 study.

Phase 3 COU-AA-302 Study

COU-AA-302 was a phase 3, randomized, double-blind, placebo-controlled, multinational study evaluating the use of ZYTIGA 1,000 mg PO daily plus prednisone 5 mg PO **twice** daily vs placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088). Patients were excluded from the study if they had active infection or other medical condition that would make prednisone/prednisolone use contraindicated.[4]

Infection-related deaths that occurred in the study included 2 patients each for pneumonia and respiratory tract infection and 1 patient for lung infection in the ZYTIGA plus prednisone group and none in the placebo plus prednisone group.[23] The incidence of infections that occurred in ≥5% of patients with a ≥2% absolute increase in frequency and study drug dose modifications and discontinuation in the ZYTIGA plus prednisone group compared to the placebo plus prednisone group in the safety population. See tables: Infections in Phase 3 COU-AA-302 Study and Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 COU-AA-302 Study.

Infections in Phase 3 COU-AA-302 Study[23]

n (%)	ZYTIGA Plus Prednisone Group (n=542)			Placebo Plus Prednisone Group (n=540)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Upper respiratory tract infection	69 (12.7)	0	0	43 (8)	0	0
Nasopharyngitis	58 (10.7)	0	0	44 (8.1)	0	0

Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 COU-AA-302 Study[23]

n (%)	ZYTIGA Plus Prednisone Group (n=542)	Placebo Plus Prednisone Group (n=540)
	Any Grade	Any Grade
Dose modification of ZYTIGA or placebo	17 (3.1)	12 (2.2)
Dose modification of prednisone/prednisolone	13 (2.4)	15 (2.8)
Discontinuation of any study drug	5 (0.9)	3 (0.6)

Efficacy and safety analyses were not performed separately for patients with a concurrent infection in the COU-AA-302 study.

Phase 3 LATITUDE Study

LATITUDE was a phase 3, randomized, double-blind, placebo-controlled, multinational study evaluating the use of ZYTIGA 1,000 mg PO daily plus prednisone 5 mg PO **once** daily with ADT vs placebos with ADT in patients with newly diagnosed, high-risk metastatic CSPC (N=1199). Patients were excluded from the study if they had active infection or other medical condition that would make prednisone use contraindicated.[5,20]

Infection-related deaths that occurred in the study included 3 patients for pneumonia and 1 patient each for lower respiratory tract infection and lung infection in the ZYTIGA plus prednisone group and 1 patient each for pneumonia, bronchopneumonia, and urosepsis and 2 patients for sepsis in the placebo plus prednisone group.[24] The incidence of infections that occurred in ≥5% of patients with a ≥2% absolute increase in frequency and study drug dose modifications and discontinuation in the ZYTIGA plus prednisone group compared to the placebos plus prednisone group in the safety population. See tables: Infections in Phase 3 LATITUDE Study and Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 LATITUDE Study.

Infections in Phase 3 LATITUDE Study[24]

n (%)	ZYTIGA + Prednisone + ADT Group (n=597)			Placebos + ADT Group (n=602)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Urinary tract infection	44 (7.4)	6 (1.0)	0	23 (3.8)	5 (0.8)	0
Upper respiratory tract infection	42 (7.0)	1 (0.2)	0	29 (4.8)	1 (0.2)	0
Abbreviation: ADT, androgen deprivation therapy.						

Study Drug Dose Modifications and Discontinuation due to the Treatment Emergent Adverse Event-Infection in Phase 3 LATITUDE Study[24]

n (%)	ZYTIGA + Prednisone + ADT Group (n=597)	Placebos + ADT Group (n=602)
	Any Grade	Any Grade
Dose modification of ZYTIGA or placebo	23 (3.9)	5 (0.8)

Discontinuation of any study drug	4 (0.7)	3 (0.5)
Abbreviation: ADT, androgen deprivation therapy.		

Efficacy and safety analyses were not performed separately for patients with a concurrent infection in the LATITUDE study.

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 08 August 2024.

REFERENCES

1. Welén K, Rosendal E, Gisslén M, et al. A phase 2 trial of the effect of antiandrogen therapy on COVID-19 outcome: no evidence of benefit, supported by epidemiology and in vitro data. *Eur Urol*. 2022;81(3):285-293.

2. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol*. 2009;27(23):3742-3748.

3. de Bono JS, Logothetis CJ, Molina A, et al. Protocol for: Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

4. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

5. Fizazi K, Tran NP, Fein L, et al. Protocol for: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

6. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol*. 2020;31(8):1040-1045.

7. Caffo O, Zagonel V, Baldessari C, et al. On the relationship between androgen-deprivation therapy for prostate cancer and risk of infection by SARS-CoV-2. *Ann Oncol*. 2020;31(10):1415-1416.

8. Koskinen M, Carpen O, Honkanen V, et al. Androgen deprivation and SARS-CoV-2 in men with prostate cancer. *Ann Oncol*. 2020;31(10):1417-1418.

9. Caffo O, Gasparro D, Di Lorenzo G, et al. Incidence and outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients with metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2020;140:140-146.

10. Crolley VE, Hanna D, Joharatnam-Hogan N, et al. COVID-19 in cancer patients on systemic anti-cancer therapies: outcomes from the CAPITOL (COVID-19 Cancer PatIenT Outcomes in North London) cohort study. *Ther Adv Med Oncol*. 2020;12:1758835920971147.

11. Ünlü S, Shin JJ, Par-Young J, et al. Effect of androgen–androgen receptor directed therapy on COVID-19 outcome in prostate cancer patients. *Cancer Investig*. 2023;41(1):77-83.

12. Gougis P, Fenioux C, Funck-Brentano C, et al. Anticancer drugs and COVID-19 antiviral treatments in patients with cancer: What can we safely use? *Eur J Cancer*. 2020;136:1-3.

13. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Centers for Disease Control and Prevention. Accessed 2024-08-08. Available via: https://cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

14. Special considerations in adults and children with cancer. National Institutes of Health. Accessed 2024-08-08. Available via: https://covid19treatmentguidelines.nih.gov/special-populations/cancer/

15. Common questions about the new coronavirus outbreak. 2020. American Cancer Society. Accessed 2024-08-08. Available via: https://cancer.org/latest-news/common-questions-about-the-new-coronavirus-outbreak.html.

16. Coronavirus 2019: What People with Cancer Need to Know. Cancer.Net. Accessed 2024-08-08. Available via: https://cancer.net/blog/2020-03/coronavirus-2019-what-people-with-cancer-need-know.

17. Resources for Oncologists Caring for Patients Affected by Novel Coronavirus. ASCO Connection. Accessed 2024-08-08. Available via: https://connection.asco.org/magazine/asco-member-news/resources-oncologists-caring-patients-affected-novel-coronavirus.

18. ASCO Coronavirus Resources. American Society of Clinical Oncology. Accessed 2024-08-08. Available via: https://asco.org/asco-coronavirus-information.

19. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

20. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

21. Fizazi K, Chi KN, de Bono JS, et al. Low incidence of corticosteroid-associated adverse events on long-term exposure to low-dose prednisone given with abiraterone acetate to patients with metastatic castration-resistant prostate cancer. *Eur Urol*. 2016;70(3):438-444.

22. Data on File. Clinical Study Report Protocol COU-AA-301. Johnson & Johnson Pharmaceutical Research & Development, LLC. EDMS-ERI-16890604; 2010.

23. Data on File. Clinical Study Report Protocol COU-AA-302. Janssen Research & Development, LLC; 2012.

24. Data on File. Clinical Study Report Protocol 212082PCR3011. Janssen Research & Development, LLC. EDMS-ERI-174764142; 2019.

25. Welén K, Rosendal E, Gisslén M, et al. Supplement for: A phase 2 trial of the effect of antiandrogen therapy on COVID-19 outcome: no evidence of benefit, supported by epidemiology and in vitro data. *Eur Urol*. 2022;81(3):285-293.