ZYTIGA® (abiraterone acetate)
ZYTIGA - IMAAGEN Study

SUMMARY

- **IMAAGEN** (**IM**pact of **A**biraterone **A**cetate in Prostate-Specific Anti**GEN**) is a phase 2, multicenter, single-arm, open-label study of ZYTIGA plus daily prednisone for the treatment of high-risk, non-metastatic castration-resistant prostate cancer (nmCRPC) in 131 patients with rising prostate-specific antigen (PSA) and castrate levels of serum testosterone. PSA was significantly reduced, with 86.9% achieving a 50% reduction in PSA during cycles 1-6 (PSA50; *P*<0.0001) and 59.8% achieving a 90% reduction in PSA (PSA90). Median time to PSA progression (TTPP) was 28.7 months (95% CI, 21.2-38.2 months). Median time to radiographic evidence of disease progression was not reached but was estimated to be 41.4 months (95% CI, 27.6 months-not estimable) by sensitivity analysis (n=15). Adverse events (AEs), grade ≥3 AEs, and serious AEs (SAEs) were reported in 96.2%, 61.1%, and 43.5% of patients, respectively. The most common AEs were hypertension, fatigue, and hypokalemia reported in 42.0%, 39.4%, and 33.6% of patients, respectively.[1]

CLINICAL DATA

IMAAGEN Study

Ryan et al (2018)[1] evaluated the safety and efficacy of ZYTIGA plus prednisone for the treatment of nmCRPC in patients with rising PSA levels despite castrate levels of testosterone (N=131).

Study Design/Methods

- Phase 2, multicenter, single-arm, open-label, proof-of-concept study (NCT01314118)
- Patients were enrolled from April 2011 to July 2013.
- Patients received ZYTIGA 1,000 mg plus prednisone 5 mg orally daily.
  - Enrolled patients continued androgen deprivation therapy (ADT) or had orchiectomy.
  - Study treatment continued until radiographic evidence of metastatic disease progression, withdrawal of consent, or intolerable toxicity.
- PSA assessments were conducted at baseline, after cycles 3 and 6, and every 2 cycles thereafter. Imaging studies were conducted at baseline, after cycles 3 and 6, and every 3 cycles thereafter.
- The study included patients with confirmed nmCRPC and serum testosterone levels <50 ng/dL, a rising PSA level defined as either absolute PSA ≥10 ng/mL at screening, or a PSA doubling time (PSADT) of ≤10 months.
- After meeting all other entry criteria, patients underwent technetium bone scan as well as either computed tomography (CT) or magnetic resonance imaging (MRI) scan to confirm non-metastatic status.
- **Select exclusion criteria:** prior or current evidence of local disease progression or metastatic disease per modified Response Evaluation Criteria in Solid Tumors (RECIST); prior chemotherapy for CRPC; prior aminoglutethimide or ketoconazole for the treatment of prostate cancer; or current antiandrogen therapy
- **Primary endpoint:** proportion of patients with ≥50% reduction in PSA levels during cycles 1-6 of treatment (1 cycle=28 days)
- **Secondary endpoints:**
  - TTPP defined as the time between initiation of ZYTIGA plus prednisone and the time that a ≥25% increase and an absolute increase of ≥2 ng/mL from the nadir is documented, which is confirmed by a second value obtained after ≥3 weeks
  - Time to radiographic evidence of disease progression
  - Proportion of patients achieving a ≥30% (PSA30), PSA50, or PSA90 reduction in PSA by the end of cycle 6

- Changes in PSA levels from baseline and over time, and testosterone levels from baseline and after cycles 3 and 6
- Safety

Results

Patient Characteristics

- Median age: 72 years (range, 48-90 years)
- 85.5% of patients had a performance status of 0; 82.4% of patients were White and 14.5% of patients were Black.
- Median Gleason score (n=125) at baseline: 7 (range, 4-10)
- Mean testosterone level at baseline (n=116): 10.308 ng/dL
- Median PSA level at screening: 11.9 ng/mL (range, 1.3-167.8 ng/mL)
- Median PSADT among 52 patients with PSA <10 ng/mL: 3.4 months (range, 1.1-9.4 months)

Efficacy

- The median treatment duration was 22.14 months (range, 0.1-52 months), the median number of study treatment cycles initiated was 25 (range, 1-57 cycles), and estimated median follow-up in the study was 40 months.
- There were 122 patients evaluable for PSA response during the core treatment phase.
- During cycles 1-6, 86.9% of patients achieved ≥50% reduction in PSA levels (95% CI, 80.9%-92.9%; *P*<0.0001).
  - Patients achieving a ≥30% reduction in PSA levels: n=111 (91%)
  - Patients achieving a ≥90% reduction in PSA levels: n=73 (59.8%)
- PSA levels that were considered undetectable (<0.2 ng/mL) were achieved in 27 patients (22.1%), and 7 patients (5.7%) had PSA levels that were <0.02 ng/mL.
- Testosterone levels were reduced by approximately 96% by the end of cycle 3 and remained so by the end of cycle 6.
- The median TTPP was 28.7 months (95% CI, 21.2-38.2 months).
- At the time of this analysis, 31 patients (23.7%) had radiographic evidence of disease progression as reported by investigators.
  - The remaining 100 patients (76.3%) were censored, having discontinued treatment prior to disease progression, or were continuing the study without confirmed progression. At 48 months, 62% of patients were estimated to be progression free.
  - The median time to radiographic disease progression was not reached; however, a sensitivity analysis of 15 patients with unconfirmed progression that led to study discontinuation showed the median time to radiographic progression was estimated to be 41.4 months (95% CI, 27.6 months-not estimable).
- Post hoc analyses
  - Patients with baseline testosterone ≥12.5 ng/dL (n=29) experienced significantly longer TTPP (*P*=0.03) and a nonsignificant increase in radiographic evidence of disease progression (*P*=0.12) as compared with patients with baseline testosterone <12.5 ng/dL (n=94).
  - Analyses after 3 cycles of therapy grouped patients into ranges of PSA reduction (<50% [n=17]; 50%-<90% [n=46]) and demonstrated that a greater reduction in PSA was associated with prolonged TTPP (median 15.7, 21.3, and 38.2 months, respectively [*P*=0.003]) and prolonged time to radiographic evidence of disease progression (median 14.8 months, 24.8 months, and not reached, respectively [*P*=0.002]).
  - While Black patients (n=19) had higher baseline PSA levels compared to other races (median 27.8 ng/mL), TTPP and time to radiographic evidence of disease progression were similar.

- In a biomarker study in 30 long-term responders, no AR-V7, KLK2, KLK3, PITX2, and TMP.ERG expression was detected. In these patients, expression of genes crucial for T cell effector function and anti-tumor immune response (ie, GZMB, GZMK, PRF1, and CD3e) were expressed at high levels as demonstrated via microarray analysis. Pro-inflammatory cytokine expression, such as IFNgamma and IL-6, and expression of known checkpoint molecules, such as LAG-3 and PD-1, was low.[2]

Safety

- All patients were evaluable for safety. AEs were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
- 96.2% of patients reported AEs, of which 90.1% were drug related.
- 15.3% of patients had AEs which led to study treatment discontinuation.
  - No patient discontinued ZYTIGA plus prednisone due to mineralocorticoid excess or required prednisone dose escalation for management.
- 43.5% of patients had an SAE, of which 22.1% were drug related.
  - Grade 5 AEs were reported in 5 patients (4%), and 2 additional deaths due to grade 4 injury (motorcycle accident) and grade 3 pneumonia were recorded. Six patients had a single SAE (injury, pneumonia, aspiration pneumonia, myocardial infarction, congestive cardiac failure, and coronary artery disease). One patient had sepsis, pneumonia, and acute respiratory failure.
  - The most common AEs are summarized in Table: Common Adverse Events Reported in ≥15% of Patients.

Common Adverse Events Reported in ≥15% of Patients[1]

	Any Grade n (%)	**Grade ≥3 n (%)**
Arthralgia	20 (15.3)	0 (0)
Back pain	21 (16.0)	2 (1.5)
Constipation	22 (16.8)	1 (0.8)
Cough	22 (16.8)	0 (0)
Diarrhea	25 (19.1)	2 (1.5)
Dizziness	25 (19.1)	1 (0.8)
Fatigue	52 (39.7)	1 (0.8)
Headache	22 (16.8)	1 (0.8)
Nausea	28 (21.4)	1 (0.8)
Upper respiratory tract infection	21 (16.0)	0 (0)
Vomiting	21 (16.0)	0 (0)
AEs of Special Interest	**Any Grade**	**Grade 3[a]**
Hypertension	55 (42.0)	31 (23.7)
Hypertensive crisis	1 (0.8)	1 (0.8)
Hypokalemia	44 (33.6)	9 (6.9)
Peripheral edema	33 (25.2)	2 (1.5)
Pleural effusions	4 (3.1)	1 (0.8)
Abbreviation: AE, adverse event. [a]No grade ≥4 events reported.		

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 21 January 2025.

REFERENCES

1. Ryan CJ, Crawford ED, Shore ND, et al. The IMAAGEN Study: Effect of Abiraterone Acetate and Prednisone on Prostate Specific Antigen and Radiographic Disease Progression in Patients with Nonmetastatic Castration Resistant Prostate Cancer. *J Urol*. 2018;200(2):344-352.

2. Chornoguz O, Shen D, Kapoor G, et al. IMAAGEN study biomarker analysis in patients with long term response to abiraterone acetate with prednisone for non-metastatic castrate resistant prostate cancer [abstract]. *Cancer Res*. 2018;78(13, suppl. 10):Abstract LB-212.