Supplementary Online Content

Slovin S, Clark W, Carles J, et al. Seizure rates in enzalutamide-treated men with metastatic castration-resistant prostate cancer and risk of seizure: the UPWARD study. *JAMA Oncol*. Published online December 7, 2017. doi:10.1001/jamaoncol.2017.3361

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Additional Methods Descriptions

Patient Inclusion and Exclusion Criteria

Patients were eligible if they had histologically confirmed metastatic adenocarcinoma of the prostate, ongoing androgen deprivation therapy with a gonadotropin-releasing hormone analog or prior orchiectomy, and disease progression characterized by ≥1 of the following: prostate-specific antigen progression (defined by a minimum of two rising prostate-specific antigen levels with an interval of ≥1 week apart; Prostate Cancer Clinical Trials Working Group 2 guidelines), bone disease progression (defined by Prostate Cancer Clinical Trials Working Group 2 guidelines), soft tissue disease progression (defined by Response Evaluation Criteria In Solid Tumors, version 1.1), and Eastern Cooperative Oncology Group performance status of 0-2. Enrolled patients were required to have ≥1 potential risk factor for seizure, including: a history of seizure (due to any cause except a single febrile seizure in childhood); transient ischemic attack, traumatic brain injury, or head injury with loss of consciousness; cerebrovascular accident, arteriovenous malformations of the brain, or brain infection; unexplained loss of consciousness within the past 12 months; presence of space-occupying lesion in the brain or primary brain tumor; presence of Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer; or current use of medication that may lower the seizure threshold (eTable 1).

Exclusion criteria included: history of exposure to enzalutamide; severe concurrent disease, infection, or co-morbidity; current treatment with anti-seizure medication; history of seizure in the 12 months prior to screening; rapidly progressive visceral disease; clinical signs suggestive of high or imminent risks for pathologic fracture, spinal cord compression, and/or cauda equina syndrome; absolute neutrophil count <1500/μL; platelet count <100000/μL or hemoglobin <5.6 mmol/L (9 g/dL); total bilirubin levels ≥1.5 × upper limit of normal or alanine aminotransferase/aspartate aminotransferase levels ≥2.5 × upper limit of normal; estimated creatinine clearance of <30 mL/min; resting systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening; received an investigational agent within 4 weeks or five half-lives, whichever was longer, prior to day 1; and any condition that, in the investigator's opinion, made the patient unsuitable for study participation.

Evaluation of Suspected Seizures

The study site interviewed the patient and any witnesses, if possible, regarding the event and completed a Suspected Seizure Event Questionnaire. Suspected seizures were evaluated by a local neurologist using electroencephalograms and magnetic resonance imaging of the brain as soon as possible after the occurrence of the potential seizure event. An Independent Adjudication Committee, consisting of three neurologists with expertise in epilepsy, was responsible for confirming all potential seizure events. For patients experiencing seizure events, an allowable anti-epileptic could be administered on a maintenance basis and enzalutamide treatment continued at the discretion of the investigator.

eAppendix. Institutional Review Boards That Approved the Study

Weill Cornell Medical College Institutional Review Board, 407 East 61st Street, RR110, New York, New York

Quorum IRB, 1501 Fourth Avenue, Suite 800, Seattle, Washington (previously Quorum IRB, 1601 Fifth Avenue, Suite 1000, Seattle, Washington)

Memorial Sloan-Kettering Cancer Center Institutional Review Board, 1275 York Avenue, M302, New York, New York

Duke University Health System Institutional Review Board, Hock Plaza, 2424 Erwin Road, Durham, North Carolina

Western Institutional Review Board (WIRB), 1019 39th Avenue SE, Suite 120, Puyallup, Washington

Biomedical Research Alliance of New York, LLC IRB, 1981 Marcus Avenue, Suite 210, Lake Success, New York

Comite d'ethique de la recherché du CHU de Quebec, CHU de Quebec – Hopital Saint-Francois d'Assise, 10, rue de L'Espinay, local A0-124, Quebec, Quebec

Comité d'Ethique Hôpital Erasme – ULB Cliniques Universitaires de Bruxelles, Route de Lennik nr. 808, Local 3 W 37, Brussels

Comité de Protection des Personnes Sud-Est II, Hôpital Edouard Herriot – Bâtiment 12 – 1er étage, 5 place d'Arsonval, Lyon Cedex

Corporació Sanitària Parc Taulí, Comité Ético de Investigación Clinica, Fundació Parc Taulí, Edificio Santa Fe, ala Izauierda, 2n Planta, Parc Taulí, num. 1, Sabadell, Barcelona

Pohjois-Pohjanmaan sairaanhoitopiirin alueellinen eettinen toimikunta, Kajaanintie 50, Oulu

Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottság, Arany J. u. 6-8, Budapest

Comitato Etico Area Cremona Mantova Lodi, Azienda Ospedaliera Istituti Ospitalieri di Cremona, Viale Concordia, 1, Cremona, Cremona

Comitato Etico Di Area Vasta Sud Est (CEAVSE), Sez. Azienda USL 8 di Arezzo, Via Curtatone, 54, Arezzo, Arezzo

Comitato Etico Centrale IRCCS Lazio, Sezione IFO – Fondazione Bietti, Via Elio Chianesi, 53, Roma, Roma

Comitato Etico IRST IRCCS AVR (CEIIAV), Via Piero Maroncelli, 40, Meldola, Forlì-Cesena

Central and Local Ethics Committee: Eticka komise pri Institutu klinicke a experimentalni mediciny a Thomayerove nemocnici, Videnska 800, Praha 4

NRES Committee London – Harrow, Bristol Research Ethics Committee Centre, Level 3, Block B, Whitefriars, Lewins Mead, Bristol

Regionala Etikprövningsnämnden I Göteborg, Guldhedsgatan 5 A, hus 2, plan 4, Göteborg

Ethik-Kommission des Landes Berlin, Fehrbelliner Platz 1, Berlin

Comité de Ética del Centro de Oncología e Investigación Buenos Aires (CECOIBA), Street 12 Nº 4756, Berazategui, Buenos Aries

Comité Independiente de Ética para Ensayos em Farmacología Clínica (FEFYM), Pte. J.E. Uriburu Nº 774, Floor 1, Ciudad Autónoma de Bs As, Buenos Aires

Comité Institucionalde Ética de al Investigación en Salud (CIEIS), Balcarce 451, Córdoba, Córdoba

Comité Independiente de Ética para Ensayos em Farmacología Clínica (FEFYM), Pte. J.E. Uriburu Nº 774, Floor 1, Ciudad Autónoma de Bs As, Buenos Aires

Comité de Ética en Investigación del Instituto Médico Especializado Alexander Fleming (CEIAF), Av. Cramer 1180, Floor 2, Ciudad Autónoma de Bs As, Buenos Aires

Comité de Evaluación Etica Cientifica, Servicio de Salud Araucanía Sur, Andres Bello 636, Temuco, IX Region

Comité Etico Cientifico Clinica Reñaca, Anabaena 336, Jardin del Mar Reñaca, Viña del Mar, V Region

Comité de Ética de la Investigación, Servicio Salul Metropolitano Norte, San José 1053, Independencia, Santiago, Region Metropolitana

Southern Adelaide Clinical Human Research Ethics Committee, Flinders Medical Centre, The Flats G5, Rooms 3 and 4, Flinders Drive, Bedford Park, South Australia

Macquarie University Human Research Ethics Committee (Medical Sciences), Level 3, Research HUB, C5C East, Macquarie University, New South Wales

Health and Disability Ethics Committee, Ministry of Health, C/-MEDSAFE, Level 6, Deloitte House, 10 Brandon Street, Wellington, Wellington

Domain Specific Review Board (DSRB), 3 Fusionopolis Link, 03-08 Nexus@one-north, Singapore

Institutional Review Board of Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul

Samsung Medical Center Institutional Review Board, 81 Irwon-ro, Gangnam-gu, Seoul

The Catholic University of Korea, Seoul St. Mary's Hospital Institutional Review Board, 222 Banpo-daero, Seocho-gu, Seoul

Seoul National University Bundang Hospital Institutional Review Board, 82 Gumi-ro, 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do

Seoul National University Hospital Institutional Review Board, 101 Dachak-ro, Jongno-gu, Seoul

Kaohsiung Veterans General Hospital Institutional Review Board, No. 386, Dazhong 1st Rd., Zuoying Dist. Kaohsiung

National Taiwan University Hospital Institutional Review Board, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei

Kaohsiung Medical University Chung-Ho Memorial Hospital Institutional Review Board, No. 100, Tzyou 1st Rd., Kaohsiung

Ethics Committee of Assaf Harofeh Medical Center, Zerifin

Ethics Committee of Meir Medical Center, 59 Tcharnichovsky st., Kfar-Saba

Ethics Committee of Soroka University Medical Center, Rager Boulevard, Beer-Sheva

Ethics Committee of Hadassah Medical Center, Ein Kerem, Jerusalem

Ethics Committee of Rambam Medical Center, 8 Ha-Aliya St., Haifa

Ethics Committee of Rabin Medical Center, 39 Jabotinski St., Petah-Tikva

Ethics Committee of Sheba Medical Center, Tel Hashomer, Ramat Gan, Ramat Gan

Ethics Committee of Galilee Medical Center, Sderot HaNassi Ben Tsvi, Naharia

Henry Ford Health System, Institutional Review Board, 2799 West Grand Boulevard, CFP Basement, Room 046, Detroit, Michigan

University Health Network Research Ethics Board, 700 University Avenue, 10th Floor, Suite 1056, Toronto, Ontario

Capital Health Research Ethics Board, 5790 University Avenue, CCR, Room 118, Halifax, Nova Scotia

Health and Disability Ethics Committee, Ministry of Health, C/-MEDSAFE, Level 6, Deloitte House, 10 Brandon Street, Wellington, Wellington

Severance Hospital Institutional Review Board, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul

Asan Medical Center Institutional Review Board, 88, Olympic-ro 43-gil, Songpa-gu, Seoul

Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, 8/F, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin

Chung Gung Medical Foundation IRB, No. 199, Tunghwa North Rd, Taipei

China Medical University Hospital Institutional Review Board, No. 2, YuDe Road, Taichung

eTable 1. List of Medications That May Lower Seizure Threshold

Therapeutic subgroup (ATC 2nd level) Chemical subgroup (ATC 4th level)
All other therapeutic products Antidotes
Analgesics Diphenylpropylamine derivatives Natural opium alkaloids Other opioids Phenylpiperidine derivatives
Anesthetics Opioid anesthetics
Antibacterials for systemic use Beta-lactam antibacterials, penicillins
Anti-emetics and anti-nauseants Other antiemetics
Anti-epileptics Benzodiazepine derivatives
Antihistamines for systemic use Aminoalkyl ethers Other antihistamines for systemic use Phenothiazine derivatives Substituted alkylamines
Anti-inflammatory and anti-rheumatic products Other anti-inflammatory/anti-rheumatic agents in combination with other drugs
Anti-pruritics, including antihistamines, anesthetics, etc Antihistamines for topical use
Cardiac therapy Other cardiac stimulants
Diagnostic agents Tests for gastric secretion
Drugs for functional gastrointestinal disorders Belladonna alkaloids, semisynthetic, quaternary ammonium compounds
Drugs for obstructive airway diseases Anticholinergics

Drugs used in diabetes
Biguanides
Combinations of oral blood glucose-lowering drugs
Dipeptidyl peptidase-4 inhibitors
Insulins and analogs for inhalation
Insulins and analogs for injection, fast-acting
Insulins and analogs for injection, intermediate- or long-acting combined with fast-acting
Insulins and analogs for injection, intermediate-acting
Insulins and analogs for injection, long-acting
Other blood glucose-lowering drugs, excluding insulins
Sulfonamides, urea derivatives
Thiazolidinediones
Nasal preparations
Anti-allergic agents, excluding corticosteroids
Sympathomimetics
Ophthalmologicals
Anticholinergics
Other anti-allergics
Psychoanaleptics
Anticholinesterases
Centrally acting sympathomimetics
Non-selective monoamine reuptake inhibitors
Other antidepressants
Selective serotonin reuptake inhibitors
Xanthine derivatives
Psycholeptics
Benzodiazepine derivatives
Butyrophenone derivatives
Diazepines, oxazepines, thiazepines, and oxepines
Hypnotics and sedatives
Other antipsychotics
Other hypnotics and sedatives
Urologicals
Drugs for urinary frequency and incontinence
Other urologicals

Abbreviation: ATC, anatomical therapeutic chemical.

eTable 2. Demographic and Baseline Characteristics

	Total (N = 423)[a]
Race,[b] n (%)	
White	381 (90.1)
Asian	25 (5.9)
Black or African American	9 (2.1)
Native Hawaiian or other Pacific Islander	1 (0.2)
Other	4 (0.9)
No data	3 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	89 (21.0)
Not Hispanic or Latino	331 (78.3)
No data	3 (0.7)
Age, years	
Mean (SD)	73.2 (8.99)
Median	74.0
Minimum-maximum	48-93
Age category, n (%)	
<65 years	66 (15.6)
≥65 years	357 (84.4)
ECOG performance status at study entry, n (%)	
0	188 (44.4)
1	190 (44.9)
2	45 (10.6)
Prior medication, n (%)	411 (97.2)
Prior chemotherapy	100 (23.6)

[a]All enrolled patients who took ≥1 dose of study drug and for whom any data was reported after the first dose of study drug (safety analysis set).
[b]Race and/or ethnicity was documented as pre-specified in the protocol, in accordance with country-specific regulations.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

eTable 3. Seizure Risk Categories

Category, n (%)	SAF (N = 423)[a]
Current medication that may lower seizure threshold	242 (57.2)
History of traumatic brain/head injury with LOC	112 (26.5)
History of CVA or TIA	94 (22.2)
Alzheimer's disease, meningioma, leptomeningeal disease	15 (3.5)
Unexplained LOC ≤12 months	14 (3.3)
Space-occupying brain lesion[b]	8 (1.9)
Past history of seizure[c]	7 (1.7)
History of brain infection[d]	5 (1.2)
History of brain arteriovenous malformation	3 (0.7)

[a]All enrolled patients who took ≥1 dose of study drug and for whom any data were reported after the first dose of study drug (SAF).
[b]Including previously treated brain metastasis or primary CNS tumor.
[c]Due to any cause except a single febrile seizure in childhood.
[d]i.e. abscess, meningitis, or encephalitis.
Patients may fall into multiple categories; therefore, the total percentage is not 100%.
Abbreviations: CNS, central nervous system; CVA, cerebrovascular accident; LOC, loss of consciousness; SAF, safety analysis set; TIA, transient ischemic attack.

eTable 4. Patients Experiencing a Seizure

Patient age, years/ race	Last dose day	Relevant medical history	Seizure risk category	Confirmed seizure event day	Seizure event(s) – nature and determined cause
Within the 4-month treatment period					
60s/White[a]	72	Use of concomitant medication (fentanyl) and prior stroke	Current use of medication that may lower seizure threshold	12 72	• Loss of consciousness (syncope) was assessed as not related, as heat stroke provided a more plausible alternative etiology • Seizure (tonic clonic): assessed as possibly related to enzalutamide based on temporal association; confounded by concomitant administration of fentanyl and multiple co-morbid conditions
70s/NR	17	History of seizure	Past history of seizure due to any cause except a single febrile seizure in childhood	17	• Loss of consciousness: assessed as possibly related to enzalutamide in agreement with the investigator, based on the implied temporal relationship. Underlying multiple co-morbidities, including orthostatic hypotension, concomitant medications, and elderly age were considered confounders. Sponsor considered loss of consciousness an event of interest
70s/White	79	Use of concomitant medication (not specified) and multiple underlying co-morbidities	History of CVA	62 77	• Suspicion of cerebral seizure (convulsion): assessed as not related to enzalutamide with the confounder of cerebral atherosclerosis • Seizure II (convulsion): in agreement with investigator, assessed as possibly related to enzalutamide • Short seizures: in agreement with investigator, assessed as not related to enzalutamide with the confounder of cerebral atherosclerosis. Short seizures occurred 20 days after permanent discontinuation of enzalutamide
60s/White[a]	65	Parenchymal metastases	Previously treated brain metastasis	65	• In agreement with the investigator, the event of seizure (convulsion) was assessed as not related to enzalutamide since the CNS metastasis provided a more plausible explanation

After the 4-month treatment period					
70s/White	147		History of head injury with loss of consciousness Presence of Alzheimer's disease	147	• Seizure: in agreement with the investigator, determined to be possibly related to enzalutamide
80s/Asian	128		History of traumatic brain injury	128	• Seizure: in agreement with the investigator, assessed as possibly related to enzalutamide, subdural hematoma being a strong confounder. Sponsor considered seizure an event of interest
70s/White	568	Use of medication that may lower seizure threshold (escitalopram)	Current use of medication that may lower seizure threshold and unexpected loss of consciousness within the last 12 months	472 566	• In agreement with the investigator, the event of loss of consciousness was assessed as not related to enzalutamide. Past history of loss of consciousness, syncope, and multiple co-morbid conditions may provide a more plausible explanation • In agreement with the investigator, the event of epileptic seizure was assessed as possibly related to enzalutamide; however, the underlying malignancy and concurrent subdural hematoma may have provided alternative etiologies for the event

[a]Receiving chemotherapy with docetaxel.
Abbreviations: CNS, central nervous system; CVA, cerebrovascular accident; NR, not reported.