A phase 1/2, open-label, randomized, dose-finding and dose expansion study of gedatolisib in combination with darolutamide in metastatic castration-resistant prostate cancer (mCRPC)

Adam Sharp[1], Johann de Bono[1], Begona Mellado Gonzalez[2], Jorge Esteban Villarrubia[3], Sara Perez Ramirez[4], David Lorente Estellés[5], Yohann Loriot[6], Delphine Borchiellini[7], Hakim Mahammedi[8], Gwenaelle Gravis[9], Simon Pacey[10], Simon Crabb[11], Sterling Wu[12], Uzma Ahmed[12], Sarah Mutka[12], Alex Cacovean[12], Igor Gorbatchevsky[12], Josep Maria Piulats Rodriguez[13]

[1]Institute of Cancer Research, Royal Marsden, London, United Kingdom; [2]Hospital Clinic Barcelona, Barcelona, Spain; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [5]Instituto Valenciano de Oncología, Valencia, Spain; [6]Gustave Roussy Cancer Center, Université Paris-Saclay, Villejuif, France; [7]Centre Antoine Lacassagne, Nice, France; [8]Centre Jean Perrin, Clermont-Ferrand, France; [9]Institut Paoli-Calmettes, Marseille, France; [10]Department of Oncology, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [11]University Hospital Southampton NHS Foundation Trust - Southampton General Hospital, Southampton, United Kingdom; [12]Celcuity, Minneapolis, MN, United States; [13]Institut Català d'Oncologia, Barcelona, Spain

FPN# 2237P

Poster presented at ESMO 2026

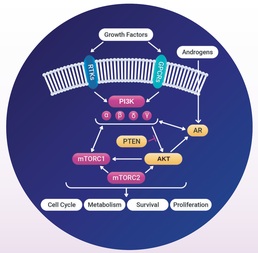
BACKGROUND

Androgen Signaling Is the Key Driver of Prostate Cancer

The PI3K/AKT/mTOR (PAM) pathway helps promote excessive cell proliferation and resistance to apoptosis.

THE AR PATHWAY IS THE PRIMARY THERAPEUTIC TARGET[1,2]

- The androgen receptor (AR) drives the expression of target genes which promote cancer cell survival and growth
- The androgen signaling pathway is the primary therapeutic target for prostate cancer at all stages of disease
- Androgen deprivation therapies (ADT) are used primarily for localized disease
- Second-generation AR inhibitors are used for advanced disease



THE PAM PATHWAY PLAYS A KEY ROLE IN mCRPC[3–5]

- AR and PI3K-AKT-mTOR pathways cross-regulate each other
- 70%–100% of mCRPC tumors have PI3K/AKT/mTOR related pathway alterations
- Mutations are dispersed across PTEN, PI3K, AKT, and mTOR subunits

METHODS

CELC-G-201: Phase 1 Trial Design

13 Sites | **United States • Spain • France • United Kingdom** | **Enrollment and Study Procedures Ongoing**

Key eligibility criteria

- Men ≥18 years
- mCRPC progressing on ADT ± ARPi
- Prior ARPi required; PARPi if BRCA+
- ECOG PS 0–1
- Life expectancy ≥3 months
- Adequate organ function

Key exclusions

- Prior PI3K/AKT/mTOR inhibitor
- Uncontrolled diabetes
- Active HIV/HBV/HCV
- Untreated CNS metastasis

Enroll

Randomized BOIN design (completed)

ARM 1
Gedatolisib 120 mg IV + **Darolutamide** 600 mg PO BID

ARM 2
Gedatolisib 180 mg IV + **Darolutamide** 600 mg PO BID

Non-randomized 3+3 dose escalation

ARM 3 (N=3–6)
Gedatolisib 240 mg IV + **Darolutamide** 600 mg PO BID

ARM 4 (N=3–6)
Gedatolisib 300 mg IV + **Darolutamide** 600 mg PO BID

Intermittent dosing:
3 weeks on / 1 week off
(Days 1, 8, and 15 of each 28-day cycle)

Primary objective
Assess safety and tolerability of gedatolisib + darolutamide in mCRPC

Dose-escalation focus
Evaluate combination dosing and establish the recommended Phase 2 dose

Protocol was amended to allow additional dose escalations; intermittent 3-weeks-on/1-week-off dosing was used.

ADT, androgen deprivation therapy; AKT, protein kinase B; ARPI, androgen receptor pathway inhibitor; BID, twice daily; BOIN, Bayesian optimal interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; mTOR, mechanistic target of rapamycin; PARPI, poly(ADP-ribose) polymerase inhibitor; PI3K, phosphoinositide 3-kinase; PO, orally.

RESULTS

Demographics and Baseline Characteristics

	Geda 120 mg + Daro 600 mg Arm 1 (N=19)	Geda 180 mg + Daro 600 mg Arm 2 (N=19)	Geda 240 mg + Daro 600 mg Arm 3 (N=7)	Overall (N=45)
Median age, years (range)	71 (59,82)	73 (58,85)	70 (57,76)	71 (56,85)
Race, n (%)				
White	15 (78.9)	15 (78.9)	6 (85.7)	36 (80)
Not Reported / Unknown	4 (21.1)	4 (21.1)	1 (14.3)	9 (20)
ECOG Performance Status, n (%)				
0	7 (36.8)	11 (57.9)	3 (42.9)	21 (46.7)
1	12 (63.2)	8 (42.1)	4 (57.1)	24 (53.3)
Areas of disease progression prior to study entry, n (%)				
PSA	15 (78.9)	14 (73.7)	6 (85.7)	35 (77.8)
Nodal disease	6 (31.6)	3 (15.8)	2 (28.6)	11 (24.4)
Bone	12 (63.2)	11 (57.9)	1 (14.3)	24 (53.3)
Visceral disease (lung, liver, adrenal, CNS)	4 (21.1)	5 (26.3)	0	9 (20)
Prior systemic cancer regimens				
1	11 (57.9)	11 (57.9)	4 (57.1)	26 (57.8)
2	5 (26.3)	6 (31.6)	2 (28.6)	13 (28.9)
≥3	3 (15.8)	2 (10.5)	1 (14.3)	6 (13.3)
Prior ARPI[a]				
Abiraterone	10 (52.6)	10 (52.6)	2 (28.6)	22 (48.9)
Enzalutamide	6 (31.6)	8 (42.1)	4 (57.1)	18 (40)
Patients with PTEN loss vs PTEN intact, n (%)				
PTEN loss	9 (47.4)	5 (26.3)	1 (14.3)	15 (33.3)
PTEN intact	10 (52.6)	13 (68.4)	5 (71.4)	28 (62.2)
Missing	0	1 (5.3)	1 (14.3)	2 (4.4)

Baseline characteristics were generally consistent across dose cohorts; over 50% had bone disease, 33% had PTEN loss.

[a]Patients could have received multiple prior ARPIs; therefore, counts and percentages are not mutually exclusive. Only selected prior ARPIs are presented in this table, and patients who received other ARPIs (e.g., darolutamide or apalutamide) are not shown.
Data cutoff date: August 14, 2026
ARPI, androgen receptor pathway inhibitor; CNS, central nervous system; Daro, darolutamide; ECOG, Eastern Cooperative Oncology Group; Geda, gedatolisib; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog.

RESULTS cont.

Treatment-Related Adverse Events (TRAEs) ≥20% by Preferred Term in Any Treatment Arm

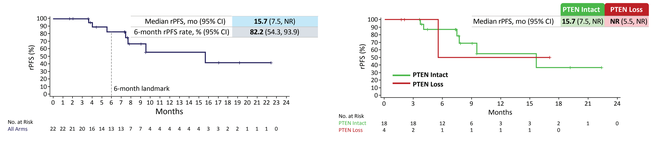
Preferred Term	Geda 120 mg + Daro 600 mg Arm 1 (N=19)				Geda 180 mg + Daro 600 mg Arm 2 (N=19)				Geda 240 mg + Daro 600 mg Arm 3 (N=7)				Overall (N=45)			
	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade
Stomatitis	7 (36.8)	1 (5.3)	0	8 (42.1)	7 (36.8)	2 (10.5)	1 (5.3)	10 (52.6)	2 (28.6)	2 (28.6)	0	4 (57.1)	16 (35.6)	5 (11.1)	1 (2.2)	22 (48.9)
Asthenia	4 (21.1)	3 (15.8)	0	7 (36.8)	5 (26.3)	3 (15.8)	0	8 (42.1)	2 (28.6)	3 (42.9)	0	5 (71.4)	11 (24.4)	9 (20.0)	0	20 (44.4)
Nausea	4 (21.1)	1 (5.3)	0	5 (26.3)	7 (36.8)	0	0	7 (36.8)	3 (42.9)	2 (28.6)	0	5 (71.4)	14 (31.1)	3 (6.7)	0	17 (37.8)
Rash	3 (15.8)	0	1 (5.3)	4 (21.1)	1 (5.3)	2 (10.5)	2 (10.5)	5 (26.3)	2 (28.6)	1 (14.3)	1 (14.3)	4 (57.1)	6 (13.3)	3 (6.7)	4 (8.9)	13 (28.9)
Diarrhea	2 (10.5)	1 (5.3)	0	3 (15.8)	6 (31.6)	1 (5.3)	0	7 (36.8)	1 (14.3)	0	0	1 (14.3)	9 (20.0)	2 (4.4)	0	11 (24.4)
Vomiting	2 (10.5)	0	0	2 (10.5)	3 (15.8)	0	0	3 (15.8)	3 (42.9)	1 (14.3)	0	4 (57.1)	8 (17.8)	1 (2.2)	0	9 (20.0)
AST or ALT increased	1 (5.3)	0	1 (5.3)	2 (10.5)	2 (10.5)	1 (5.3)	0	3 (15.8)	3 (42.9)	0	0	3 (42.9)	6 (13.3)	1 (2.2)	1 (2.2)	8 (17.8)
Pruritus	1 (5.3)	0	0	1 (5.3)	1 (5.3)	1 (5.3)	1 (5.3)	3 (15.8)	3 (42.9)	0	1 (14.3)	4 (57.1)	5 (11.1)	1 (2.2)	2 (4.4)	8 (17.8)
Dysgeusia	0	0	0	0	3 (15.8)	0	0	3 (15.8)	3 (42.9)	0	0	3 (42.9)	6 (13.3)	0	0	6 (13.3)
Mucosal dryness	0	0	0	0	3 (15.8)	1 (5.3)	0	4 (21.1)	1 (14.3)	0	0	1 (14.3)	4 (8.9)	1 (2.2)	0	5 (11.1)

TRAEs were defined as AEs considered related to gedatolisib or darolutamide. Notes: Adverse events are coded based on MedDRA version 26.1. Grades are based on CTCAE version 5.0. Adverse events are sorted by decreasing frequency of system organ class and preferred term in Overall group. Stomatitis is a combination of the following preferred terms (stomatitis, oral mucosal inflammation, mouth ulceration, aphthous ulcer, glossitis, lip ulceration, gingivitis, gingival pain). Mucosal dryness is a combination of the following preferred terms (dry mouth, mucosal dryness, vulvovaginal dryness). Rash is a combination of the following preferred terms (rash, rash pruritic, rash pustular, rash papular, rash erythematous, rash macular, rash morbilliform, rash vesicular, rash maculo-papular). Dysgeusia is a combination of the following preferred terms (dysgeusia, ageusia, hypogeusia). AST or ALT increased is a combination of the following preferred terms (hypertransaminasemia, aspartate aminotransferase increased, alanine aminotransferase increased, transaminases increased).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; Daro, darolutamide; Geda, gedatolisib; MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related adverse event.

Safety Summary

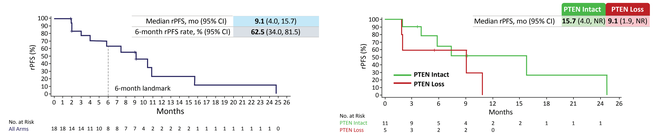
- The combination of gedatolisib and darolutamide was generally well tolerated, with one dose-limiting toxicity (DLT; Grade 3 rash) observed in Arm 3 (240 mg). Dose escalation continues (300 mg).
- 95.6% (43/45) of patients experienced adverse events (AEs) related to gedatolisib (TRAEs); 75.6% (34/45) experienced Grade 1 or 2 TRAEs; Grade 3 TRAEs occurred in 9 (20%) patients with only rash (n=4) and pruritus (n=2) occurring in more than 1 patient; there were no Grade 4 or 5 TRAEs.
- A single treatment-related serious AE (Grade 2 stomatitis) was reported in Arm 3 (240 mg) and resolved within 3 days.
- No treatment discontinuations due to AEs, or treatment-related deaths, were reported in any arm.

Radiographic PFS in All Patients (Arms 1, 2, 3) with Prior Abiraterone Exposure (n=22)



Median rPFS for all patients with prior abiraterone was 15.7 months (rPFS6 = 82%) and 15.7 months for the PTEN-intact subgroup and not reached for the PTEN-loss subgroup

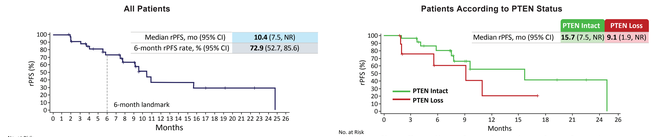
Radiographic PFS in All Patients (Arms 1, 2, 3) with Prior Enzalutamide Exposure (n=18)



Two of 18 patients had missing PTEN status and were excluded from the PTEN subgroup analysis.

Median rPFS for all patients with prior enzalutamide was 9.1 months (rPFS6 = 63%) and 15.7 months for the PTEN-intact subgroup and 9.1 months for the PTEN-loss subgroup

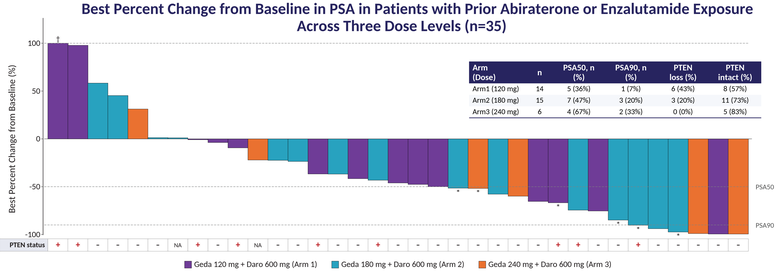
Radiographic PFS in Patients with Prior Abiraterone and/or Enzalutamide Exposure (n=35)



Two of 35 patients had missing PTEN status and were excluded from the PTEN subgroup analysis.

Median rPFS for all patients with prior abiraterone and/or enzalutamide was 10.4 months (rPFS6 = 73%) and 15.7 months for the PTEN-intact subgroup and 9.1 months for the PTEN-loss subgroup

Best Percent Change from Baseline in PSA in Patients with Prior Abiraterone or Enzalutamide Exposure Across Three Dose Levels (n=35)



Arm (Dose)	n	PSA50, n (%)	PSA90, n (%)	PTEN loss (%)	PTEN intact (%)
Arm1 (120 mg)	14	5 (36%)	1 (7%)	6 (43%)	8 (57%)
Arm2 (180 mg)	15	7 (47%)	3 (20%)	3 (20%)	11 (73%)
Arm3 (240 mg)	6	4 (67%)	2 (33%)	0 (0%)	5 (83%)

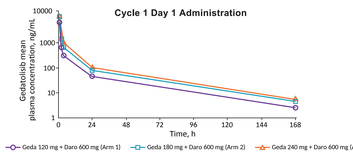
PSA50 indicates ≥50% decrease from baseline. PSA90 indicates ≥90% decrease from baseline.
PSA Response Analysis Set includes subjects in the Safety Analysis Set with a valid baseline PSA value and at least one post-baseline PSA assessment.
+, PTEN loss; –, PTEN intact; NA, no record of PTEN status. PTEN status was not available for 2 patients. †Denotes >100% increase in PSA.
*Patients achieving PSA50 or PSA90 without a corresponding confirmed PSA response. PSA50 and PSA90 responses were considered confirmed if maintained for ≥21 days.
Data cutoff date: August 14, 2026.
Daro, darolutamide; Geda, gedatolisib; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog.

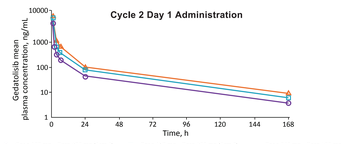
rPFS and PSA Response by Prior ARPi and PTEN Status

Subgroups	n	Median rPFS (months)	PSA50[c]	PSA90[c]
Prior abiraterone exposure[a]	22	15.7	55%	27%
PTEN loss	4	NR	50%	25%
PTEN intact	18	15.7	56%	28%
Prior enzalutamide exposure[a]	18[b]	9.1	39%	6%
PTEN loss	5	9.1	20%	0%
PTEN intact	11	15.7	55%	9%
Prior abiraterone and/or enzalutamide exposure[a]	35[b]	10.4	46%	17%
PTEN loss	9	9.1	33%	11%
PTEN intact	24	15.7	54%	21%
No prior abiraterone or enzalutamide exposure	10	7.4	10%	0%
PTEN loss	6	7.4	0%	0%
PTEN intact	4	4.9	25%	0%

[a]5 patients received both abiraterone and enzalutamide (4 received abiraterone and enzalutamide; 1 patient received abiraterone, enzalutamide, and apalutamide).
[b]2 patients had missing PTEN status and were excluded from the PTEN subgroup analysis.
[c]Includes patients with either confirmed or unconfirmed PSA50 and PSA90.
ARPI, androgen receptor pathway inhibitor; NR, not reached; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival.

Gedatolisib Mean Plasma Concentration–Time Profiles (CELC-G-201)





	Geda 120 mg + Daro 600 mg Arm 1	Geda 180 mg + Daro 600 mg Arm 2	Geda 240 mg + Daro 600 mg Arm 3
n	12	14	3
Gedatolisib C2D1:C1D1 ratio, mean (%CV)			
C_{max}	0.95 (32%)	0.98 (39%)	0.99 (22%)
$AUC_{tau\text{-}ss}$	0.95 (27%)	0.96 (17%)	1.00 (4%)

$AUC_{tau\text{-}ss}$, area under the plasma concentration–time curve from 0 to 168 hours; C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; C_{max}, maximum plasma concentration; CV, coefficient of variation; Daro, darolutamide; Geda, gedatolisib.

CONCLUSIONS

- Gedatolisib plus darolutamide demonstrated a manageable safety profile across the evaluated dose levels (120 mg, 180 mg, 240 mg), with one DLT (Grade 3 rash), no Grade 4/5 TRAEs, and no TRAEs leading to treatment discontinuation or death.
- Preliminary antitumor activity was observed in patients with mCRPC previously treated with ARPis.
  - Among patients with prior abiraterone exposure (n=22), median rPFS was 15.7 months with an rPFS6 rate of 82.2%.
  - Among patients with prior enzalutamide exposure (n=18), median rPFS was 9.1 months with an rPFS6 rate of 62.5%.
  - PSA50 responses were observed across all dose levels; response rates were 36%, 47%, and 67% at the 120-, 180-, and 240-mg dose levels, respectively.
  - Exploratory analyses of patients according to their PTEN status suggest activity is independent of PTEN status. The limited sample sizes and overlapping confidence intervals preclude definitive conclusions regarding differential treatment effect.
  - Given the small sample sizes and limited number of events, subgroup and dose-level analyses should be interpreted with caution.
- Preliminary pharmacokinetic (PK) analyses demonstrated slightly more than dose-proportional increases in gedatolisib exposure across the 120–240 mg dose range, with no evidence of exposure plateauing, no evidence of PK interaction with darolutamide, and no evidence of gedatolisib accumulation with repeated dosing.
- These early, descriptive findings support continued dose optimization and further evaluation of gedatolisib plus darolutamide.

REFERENCES: 1. Beer TM, et al. *N Engl J Med*. 2014;371(5):424-433. **2.** Carver BS, et al. *Cancer Cell*. 2011;19(5):575-586. **3.** Mulholland DJ, et al. *Cancer Cell*. 2011;19(6):792-804. **4.** Robinson D, et al. *Cell*. 2015;161(5):1215-1228. **5.** Tortorella E, et al. *Int J Mol Sci*. 2023;24(3):2046.

DISCLOSURES: Study sponsored by Celcuity, Inc. COI for Adam Sharp: A.S. has received travel support from Celcuity, Sanofi, Roche-Genentech and Nurix, and speaker honoraria from Astellas Pharma and Merck Sharp & Dohme. He has served as an advisor to AbbVie, Monte Rosa Therapeutics, Delphia Therapeutics, DE Shaw Research, CHARM Therapeutics, Ellipses Pharma and Droia Ventures. He serves as a member of the Independent Data Monitoring Committee for the ProBio Trial. A.S. has been an investigator on multiple industry-sponsored clinical trials. Email address for Adam Sharp: adam.sharp@icr.ac.uk

Copies of this poster obtained through QR codes are for personal use only and may not be reproduced without written permission of the authors.