Phase 1/2 Study of Gedatolisib in Combination with Darolutamide in Metastatic Castration-Resistant Prostate Cancer

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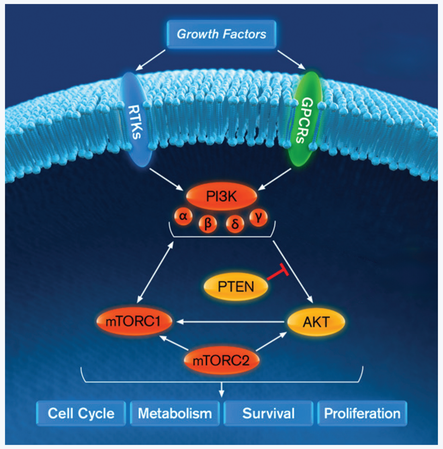
BACKGROUND

- Preclinical studies demonstrated interaction between the androgen receptor (AR) and phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mechanistic target of rapamycin (mTOR) pathway through reciprocal negative feedback, whereby inhibition of one pathway cross-activates the other.[1]
- Elevated androgen levels upregulate the PI3K-AKT-mTOR (PAM) pathway; oncogenic PAM activation is linked with resistance to androgen deprivation therapy, disease progression, and poor outcomes in prostate cancer.[2]
- Dual targeting with a PAM inhibitor plus an AR pathway inhibitor (ARPi) may produce synergistic antitumor effects in metastatic castration-resistant prostate cancer (mCRPC), including in patients with prior ARPi progression.[3,4] Preliminary clinical data further support this hypothesis.[5]
- Gedatolisib, a potent pan-PI3K, mTOR complex 1/2 inhibitor that comprehensively blocks the PAM pathway, is being studied in combination with the ARPi darolutamide in an ongoing Phase 1/2 clinical trial (CELC-G-201; NCT06190899).



AKT, protein kinase B; GPCR, G protein-coupled receptor; mTORC, mechanistic target of rapamycin complex; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

STUDY DESIGN

CELC-G-201: Phase 1 Trial Design

Patients with mCRPC who received an AR inhibitor and have not received docetaxel for mCRPC

Dose Escalation[a]
Assess safety and tolerability
Determine RP2D

Arm 1
Gedatolisib 120 mg[b] IV +
Darolutamide 600 mg PO BID

Arm 2
Gedatolisib 180 mg[b] IV +
Darolutamide 600 mg PO BID

Multicenter study across 13 sites in 4 countries: United States, Spain, France, and the United Kingdom. Enrollment and study procedures are ongoing.

Primary Objective

- To assess the safety and tolerability of gedatolisib in combination with darolutamide in mCRPC

Key Eligibility Criteria

Inclusion:
- Men ≥18 years
- Adenocarcinoma (<10% neuroendocrine)
- mCRPC, progression on ADT ± ARPi (prior ARPi required; PARPi if BRCA+)
- Measurable disease (RECIST v1.1 / PCWG3)
- ECOG PS 0–1
- Life expectancy ≥3 months
- Adequate organ function

Exclusion:
- Small cell/neuroendocrine ≥10%
- Prior PI3K/AKT/mTOR, chemotherapy, or radiopharmaceutical for mCRPC
- Uncontrolled diabetes
- Active HIV/HBV/HCV
- Untreated CNS metastasis

[a]Protocol was amended to allow additional dose escalations; [b]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle).
ADT, androgen deprivation therapy; AR, androgen receptor; ARPi, androgen receptor pathway inhibitor; BID, twice daily; 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; PARPi, poly(ADP-ribose) polymerase inhibitors; PO, by mouth; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose.

RESULTS

Demographics and Baseline Characteristics

	Geda 120 mg[a] + Daro 600 mg BID (n=19)	Geda 180 mg[a] + Daro 600 mg BID (n=19)	Overall (N=38)
Median age, years (range)	71.0 (59, 82)	73.0 (58, 85)	72.0 (58, 85)
Race, n (%)			
White	15 (78.9)	15 (78.9)	30 (78.9)
Not Reported / Unknown	4 (21.1)	4 (21.1)	8 (21.1)
ECOG Performance Status, n (%)			
0	7 (36.8)	11 (57.9)	18 (47.4)
1	12 (63.2)	8 (42.1)	20 (52.6)
Median PSA, ug/L (range)	10 (0.1, 290)	13 (2.7, 260)	11 (0.1, 290)
Total prior systemic cancer regimens			
0	0	0	0
1	11 (57.9)	12 (63.2)	23 (60.5)
2	6 (31.6)	5 (26.3)	11 (28.9)
≥3	2 (10.5)	2 (10.5)	4 (10.5)
Patterns of progression prior to study entry, n (%)			
Bone	12 (63.2)	11 (57.9)	23 (60.5)
Nodal disease	6 (31.6)	3 (15.8)	9 (23.7)
PSA	15 (78.9)	14 (73.7)	29 (76.3)
Visceral disease (lung, liver, adrenal, CNS)	4 (21.1)	5 (26.3)	9 (23.7)

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle).
BID, twice daily; CNS, central nervous system; Daro, darolutamide; ECOG, Eastern Cooperative Oncology Group; Geda, gedatolisib; PSA, prostate-specific antigen.

Patient Disposition

	Geda 120 mg[a] + Daro 600 mg BID (n=19)	Geda 180 mg[a] + Daro 600 mg BID (n=19)	Overall (N=38)
Gedatolisib median duration of treatment, weeks (range)	27 (8, 65)	27 (4, 67)	27 (4, 67)
Darolutamide median duration of treatment, weeks (range)	29 (8, 64)	25 (4, 61)	26 (4, 64)
Treatment discontinuation,[b] n (%)	15 (78.9)	18 (94.7)	33 (86.8)
Primary reason			
Radiological disease progression[c]	6 (31.6)	8 (42.1)	14 (36.8)
Adverse event	0	0	0
Death	0	1 (5.3)	1 (2.6)
Withdrawal by patient from treatment	2 (10.5)	2 (10.5)	4 (10.5)
Physician decision	7 (36.8)	7 (36.8)	14 (36.8)

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle). [b]Discontinuation of both gedatolisib and darolutamide; [c]Per RECIST v1.1 with PCWG3 modifications as assessed by Investigator.
BID, twice daily; Daro, darolutamide; Geda, gedatolisib.

Safety Summary

- Stomatitis was the most frequent treatment-related adverse event, mostly Grade 1, with only one (n=1) Grade 3. Prophylactic use of a steroid-containing "swish and spit" regimen[6] was mandated, and oral nonsedating antihistamine therapy was recommended for patients in the gedatolisib arm.

Adverse Event, n (%)	Geda 120 mg[a] + Daro 600 mg BID (n=19)	Geda 180 mg[a] + Daro 600 mg BID (n=19)	Overall (N=38)
TEAEs	19 (100)	19 (100)	38 (100)
Grade ≥3 TEAEs	5 (26.3)	10 (52.6)	15 (39.5)
Serious TEAEs	4 (21.1)	5 (26.3)	9 (23.7)
TEAE leading to death	0	1 (5.3)[b]	1 (2.6)[b]
Gedatolisib-related TEAEs	17 (89.5)	18 (94.7)	35 (92.1)
Gedatolisib-related serious TEAEs	0	0	0
Darolutamide-related TEAEs	13 (68.4)	13 (68.4)	26 (68.4)
Darolutamide-related serious TEAEs	0	0	0
Dose-limiting toxicities	0	0	0
Discontinued darolutamide due to adverse event	0	1 (5.3)	1 (2.6)
Dose reduced due to gedatolisib-related OR darolutamide-related adverse event	4 (21.1)	5 (26.3)	9 (23.7)

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle). [b]Patient experienced grade 5 acute cholecystitis not related to gedatolisib or to darolutamide 313 days after initiating study treatment.
BID, twice daily; Daro, darolutamide; Geda, gedatolisib; TEAE, treatment-emergent adverse event.

Summary of Treatment-Related Adverse Events (TRAEs) >15% in Any Treatment Arm

	Geda 120 mg[a] + Daro 600 mg BID (n=19)		Geda 180 mg[a] + Daro 600 mg BID (n=19)		Overall (N=38)	
Preferred Term, n (%)	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
At least one TRAE	18 (94.7)	2 (10.5)	18 (94.7)	4 (21.1)	36 (94.7)	6 (15.8)
Stomatitis	7 (36.8)	0	10 (52.6)	1 (5.3)	17 (44.7)	1 (2.6)
Asthenia	6 (31.6)	0	8 (42.1)	0	14 (36.8)	0
Nausea	5 (26.3)	0	7 (36.8)	0	12 (31.6)	0
Diarrhea	3 (15.8)	0	7 (36.8)	0	10 (26.3)	0
Anemia	3 (15.8)	0	3 (15.8)	0	6 (15.8)	0
Decreased appetite	2 (10.5)	0	3 (15.8)	0	5 (13.2)	0
Rash maculo-papular	2 (10.5)	1 (5.3)	3 (15.8)	1 (5.3)	5 (13.2)	2 (5.3)
Dry mouth	0	0	4 (21.1)	0	4 (10.5)	0
Pruritus	1 (5.3)	0	3 (15.8)	1 (5.3)	4 (10.5)	1 (2.6)
Dysgeusia	0	0	3 (15.8)	0	3 (7.9)	0

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle).
BID, twice daily; Daro, darolutamide; Geda, gedatolisib.

No Grade 4 or 5 TRAEs were observed.

Summary of Treatment-Emergent Serious Adverse Events (TESAEs)

Adverse Event, n (%)	Geda 120 mg[a] + Daro 600 mg BID (n=19)	Geda 180 mg[a] + Daro 600 mg BID (n=19)	Overall (N=38)
At least one TESAE	4 (21.1)	5 (26.3)	9 (23.7)
Pneumonia	0	1 (5.3)	1 (2.6)
Spinal cord infection	1 (5.3)	0	1 (2.6)
Urosepsis	1 (5.3)	0	1 (2.6)
Febrile neutropenia	0	1 (5.3)	1 (2.6)
Myocardial infarction	0	1 (5.3)	1 (2.6)
Cholecystitis acute	0	1 (5.3)	1 (2.6)
Lumbar vertebral fracture	1 (5.3)	0	1 (2.6)
Intervertebral disc protrusion	0	1 (5.3)	1 (2.6)
Cerebral amyloid angiopathy	1 (5.3)	0	1 (2.6)
Disorientation	0	1 (5.3)	1 (2.6)
Hematuria	0	1 (5.3)	1 (2.6)
Hypoxia	0	1 (5.3)	1 (2.6)

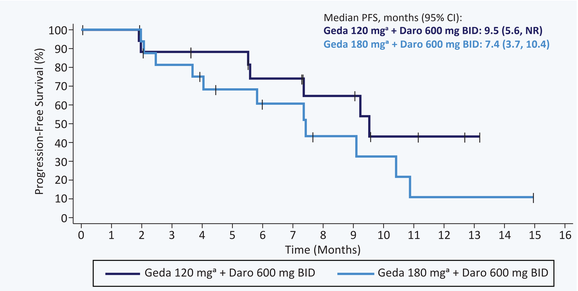
Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle).
BID, twice daily; Daro, darolutamide; Geda, gedatolisib.

Radiological Progression-Free Survival

	Geda 120 mg[a] + Daro 600 mg BID (n=19)	Geda 180 mg[a] + Daro 600 mg BID (n=19)	Overall (N=38)
Patients with event, n (%)	7 (36.8)	11 (57.9)	18 (47.4)
Type of event			
Radiological progression	7	9	16
Death without radiological progression	0	2	2
Probability of being event-free at month 6, % (95% CI)[b]	74.0 (44.3, 89.5)	60.6 (32.1, 80.2)	67.1 (47.2, 80.9)
Median radiological PFS, months (1Q, 3Q)[b]	9.5 (5.6, NR)	7.4 (3.9, 10.4)	9.1 (5.5, NR)
Median radiological PFS follow-up, months (1Q, 3Q)[c]	9.0 (5.5, 11.1)	7.7 (4.4, 14.9)	9.0 (4.4, 12.7)

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle). [b]Calculated from Kaplan-Meier estimates using Greenwood; [c]Calculated from reverse Kaplan-Meier method.
BID, twice daily; Daro, darolutamide; Geda, gedatolisib; NR, not reached; PFS, progression-free survival; Q, quartile.

Median Radiological Progression-Free Survival By Investigator Assessment



Patients at Risk:

Geda 120 mg[a] + Daro 600 mg BID	19	17	15	14	13	13	10	10	7	7	3	3	2	1	0
Geda 180 mg[a] + Daro 600 mg BID	19	17	15	13	11	9	7	7	4	4	3	1	1	1	1	0

Note: For one patient, the last nontarget lesions status was entered as "Unequivocal Progression," while the corresponding overall response was entered as NE, which resulted in PFS being censored as the patient discontinued gedatolisib due to Physician Reason.

Data cutoff date: August 15, 2025
[a]Intermittent 3-weeks-on/1-week-off dosing schedule was used (Days 1, 8, and 15 of each 28-day cycle).
BID, twice daily; Daro, darolutamide; Geda, gedatolisib; NE, not evaluable; NR, not reached; PFS, progression-free survival.

CONCLUSIONS

- The combination of gedatolisib and darolutamide was safe and well tolerated across both dose levels evaluated.
  - No dose-limiting toxicities were observed.
  - No Grade 4 or 5 treatment-related adverse events were reported.
  - No treatment-related serious adverse events occurred.
  - No treatment-related adverse events led to treatment discontinuation of the combination regimen.
- Preliminary efficacy was favorable, with a median progression-free survival of 9.1 months and a 6-month radiographic progression-free survival rate of 67.1%.
- The favorable safety profile supports evaluation of higher gedatolisib and darolutamide dose levels to determine the optimal biologic dose.
- The study protocol has been amended to include two additional dose levels and a randomized Phase 1b expansion to inform the recommended Phase 2 dose.

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