

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)

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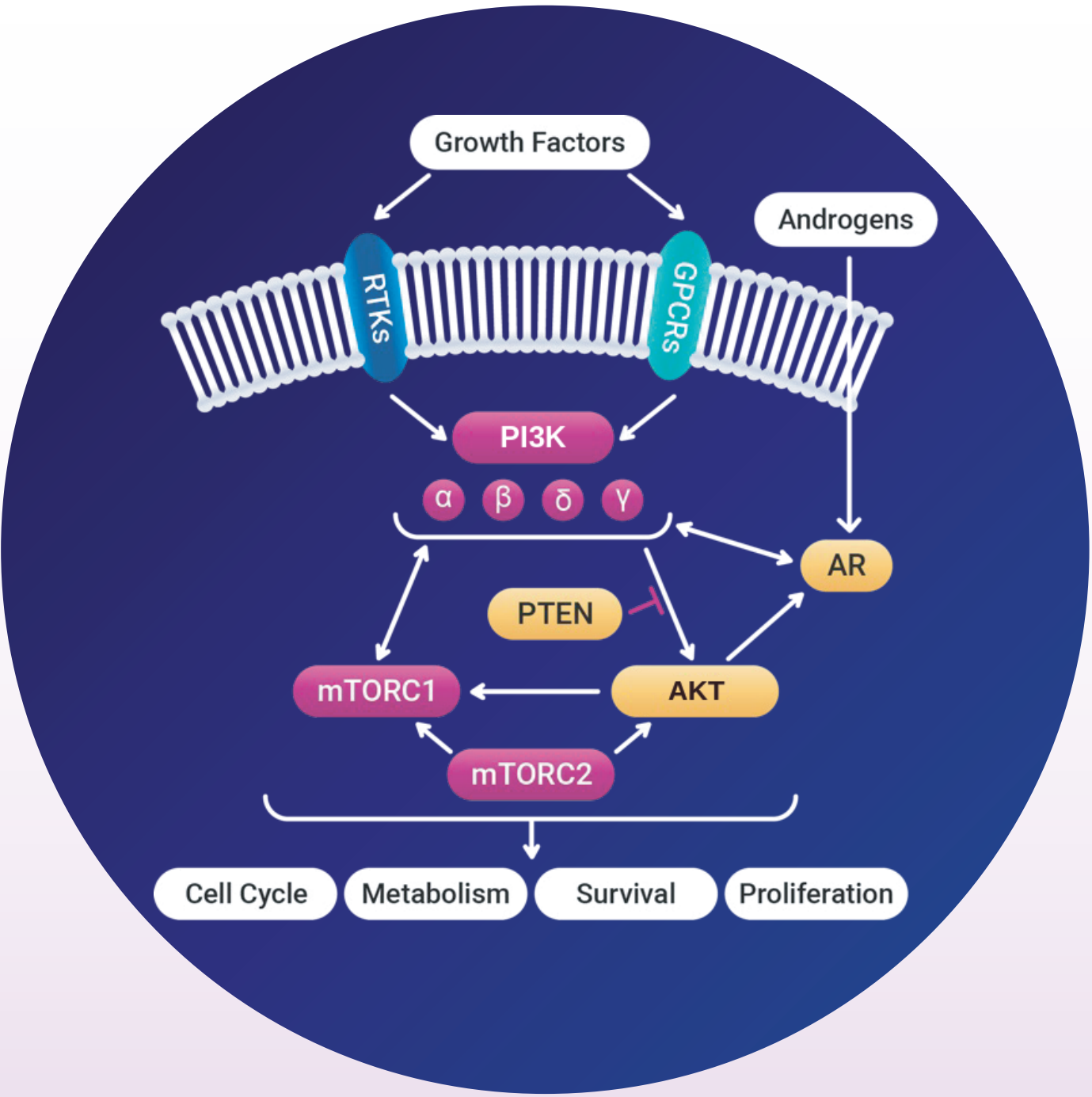
BACKGROUND

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 mCRPC³⁻⁵

- 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

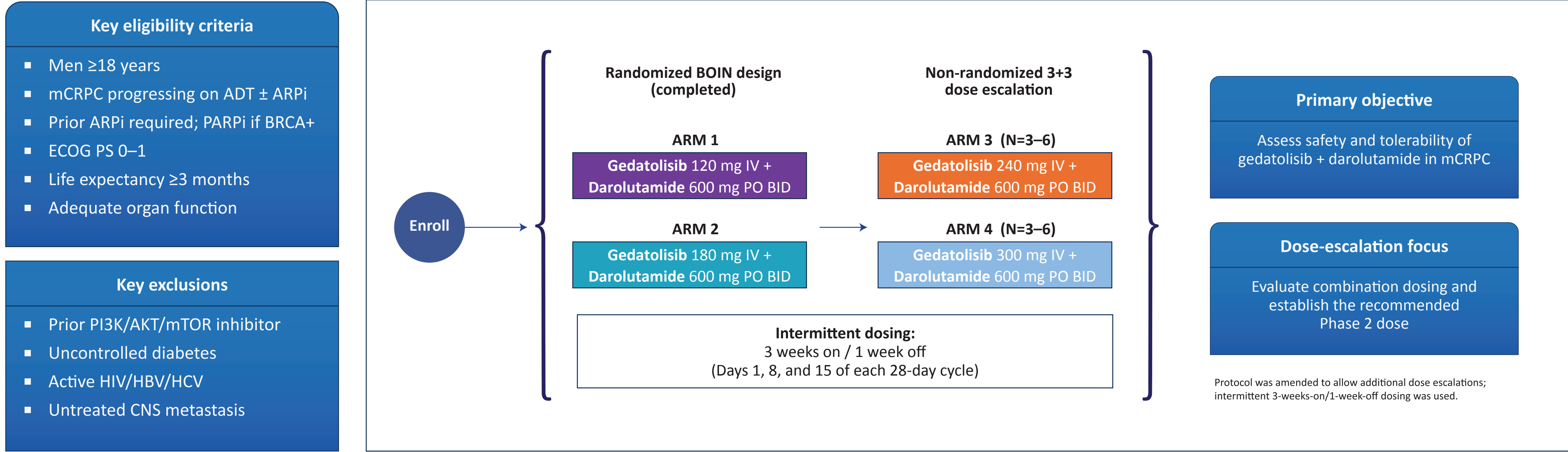
METHODS

CELIC-G-201: Phase 1 Trial Design

United States • Spain • France • United Kingdom

Enrollment and Study Procedures Ongoing

13 Sites



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)	5 (71.4)	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.

^aPatients 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.

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

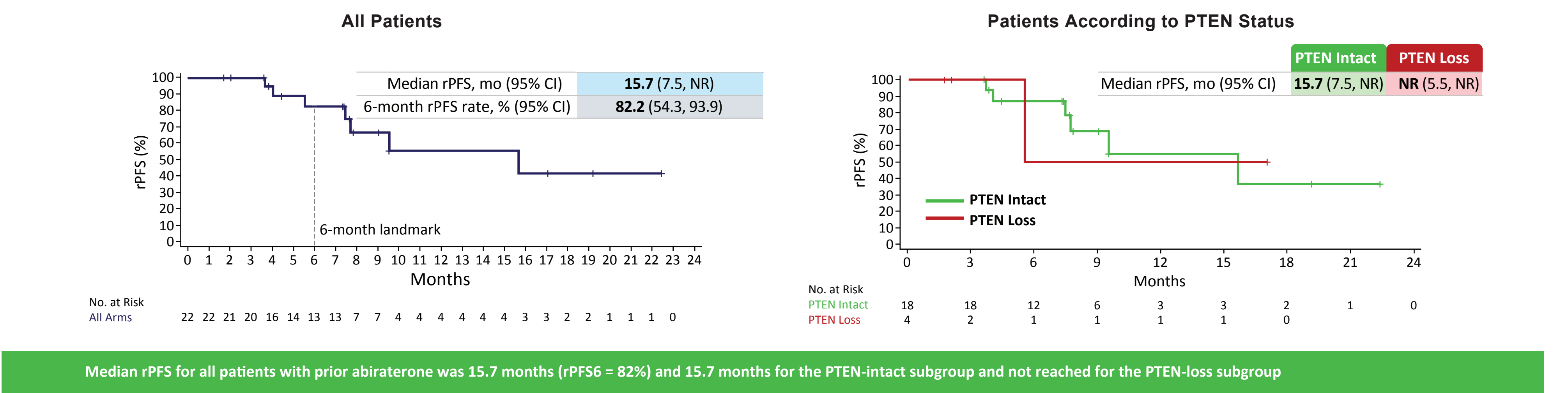
Preferred Term	Geda 120 mg + Daro 600 mg Arm 1 (N=19)				Geda 180 mg + Daro 600 mg Arm 2 (N=19)				Geda 240 mg + Daro 600 mg Arm 3 (N=7)				Overall (N=45)			
	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade
Stomatitis	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)	3 (15.8)	0	0	3 (15.8)	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)	3 (15.8)	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 papular, rash erythematous, rash macular, rash maculopapular, 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 (hypertansaminemia, 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.

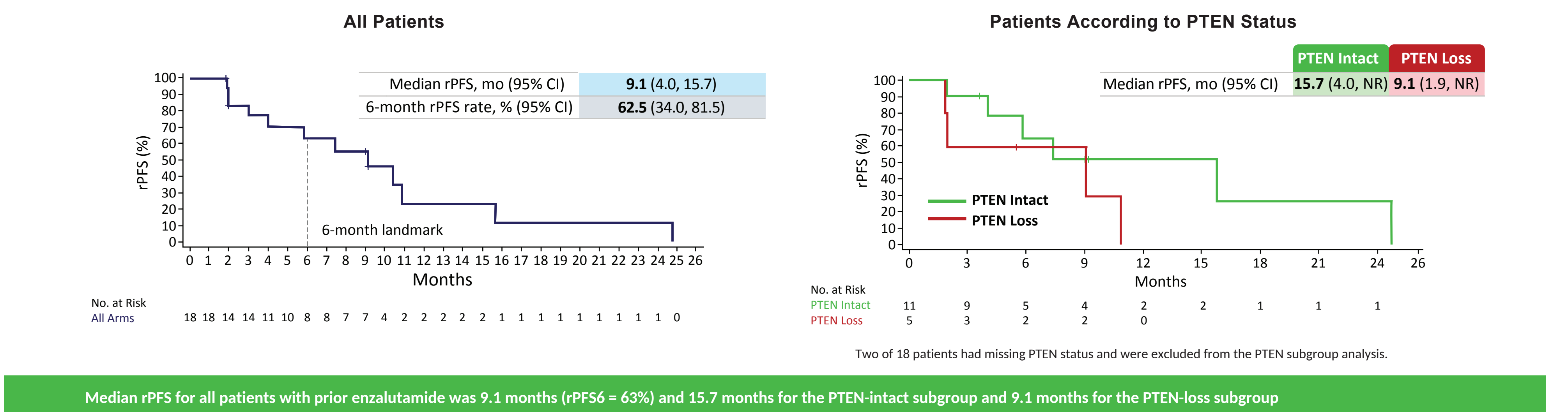
Safety Summary

- 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.

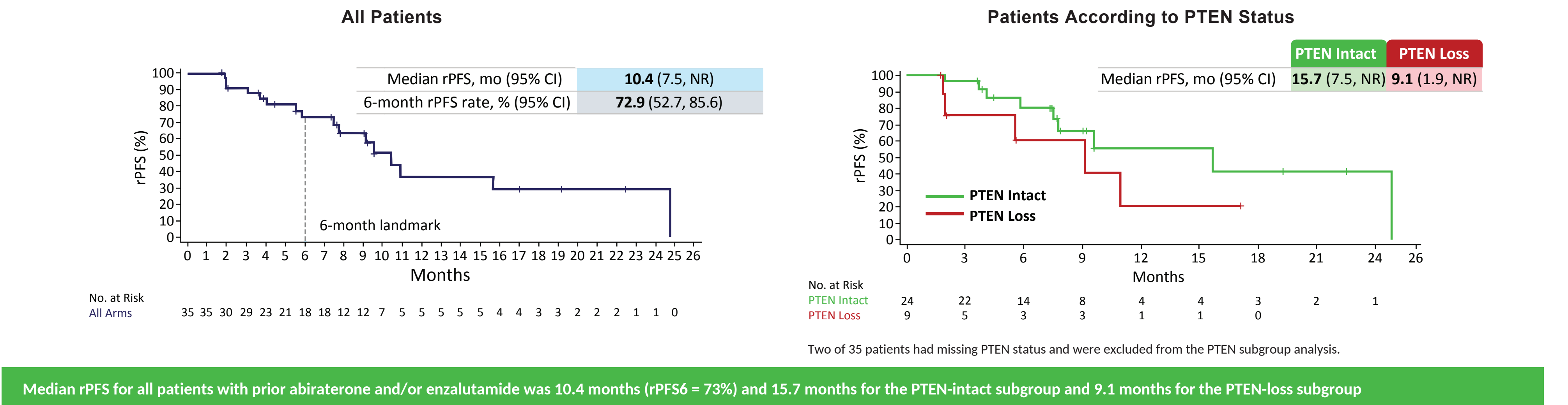
Radiographic PFS in All Patients (Arms 1, 2, 3) with Prior Abiraterone Exposure (n=22)



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

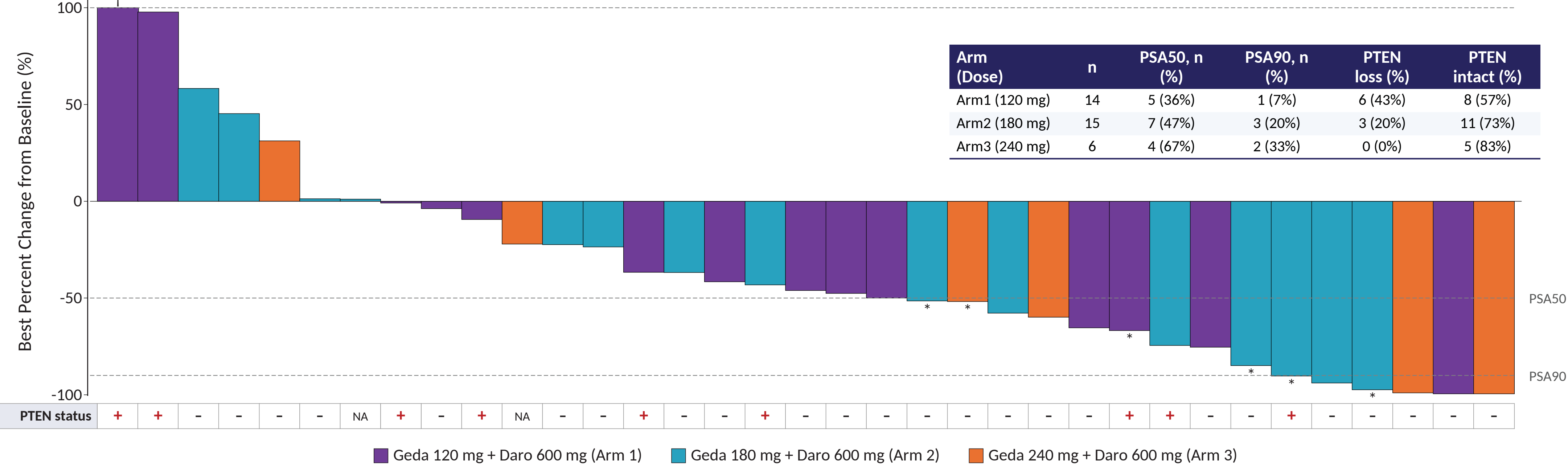


Radiographic PFS in Patients with Prior Abiraterone and/or Enzalutamide Exposure (n=35)



RESULTS cont.

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



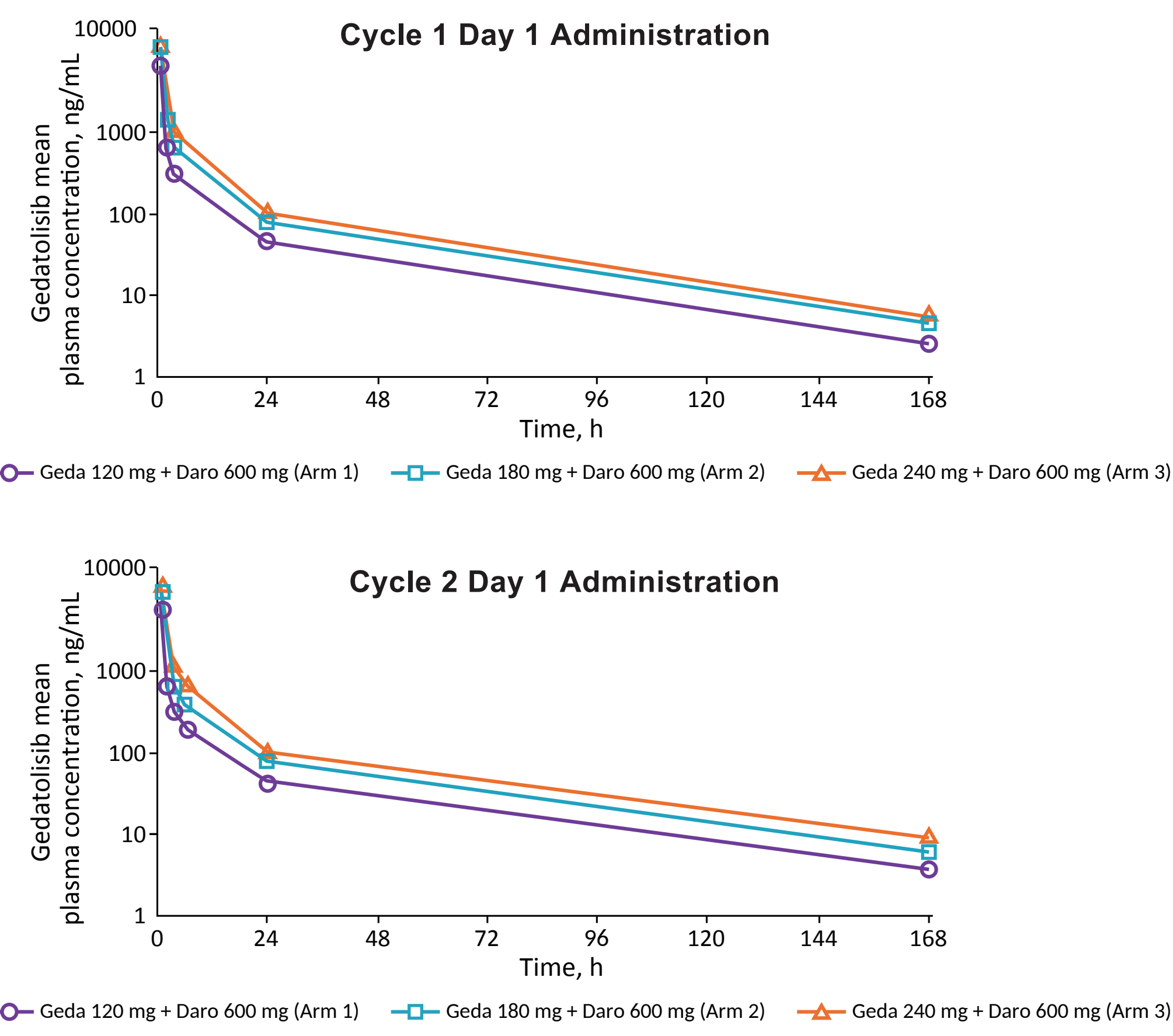
PSA50 indicates ≥50% decrease from baseline. PSA90 indicates ≥90% decrease from baseline. PSA Response Analysis Set includes subjects in the safety analysis set with a valid baseline PSA value and at least one post-baseline PSA assessment. +, PTEN loss; -, PTEN intact; NA, no record of PTEN status. PTEN 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 ^a	PSA90 ^a
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%

^a5 patients received both abiraterone and enzalutamide (4 received abiraterone and enzalutamide; 1 patient received abiraterone, enzalutamide, and apalutamide).
^b2 patients had missing PTEN status and were excluded from the PTEN subgroup analysis.
^cIncludes 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 (CELIC-G-201)



n	12	14	3
Gedatolisib C2D1:C1D1 ratio, mean (%CV)			
C _{max}	0.95 (32%)	0.98 (39%)	0.99 (22%)
AUC _{0-168h}	0.95 (27%)	0.96 (17%)	1.00 (4%)

AUC_{0-168h}, 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.

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