5067

Phase 1 Study Of Gotistobart (BNT316/ONC-392) In Combination With Lutetium 177 Vipivotide Tetraxetan (Lu 177) In Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC)

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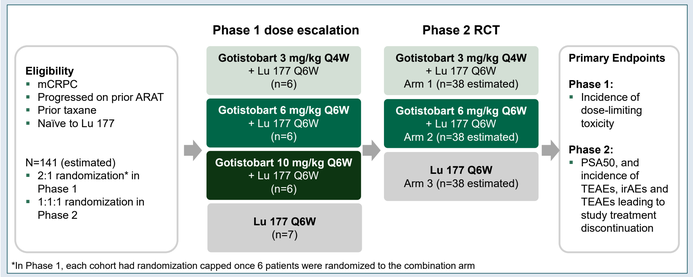
Background

- When used in combination with physician's choice of care, Lutetium-177 (Lu 177) PSMA-617 radioligand therapy showed significant PFS and OS improvements in patients with mCRPC who had progressed on prior lines of therapy.[1]
- Combinations with other PSMA-targeted radionuclides, ARPIs, chemotherapy, PARP inhibitors, and immune checkpoint inhibitors are being explored to extend the therapeutic benefit.[2]
- Preclinical prostate cancer models and early phase clinical trials demonstrated that radiotherapy increases T-cell infiltration and Treg expansion in the tumor microenvironment (TME) and may enhance response to PD-1 and CTLA-4 inhibitors.[3]
- Given the role of gotistobart (a unique pH-sensitive anti-CTLA-4 antibody that preserves CTLA-4 recycling and avoids lysosomal degradation) in selective depletion of Tregs in the TME,[4–7] this study will initially test the safety and toxicity of gotistobart plus Lu 177 in mCRPC.

Study design and objectives

- PRESERVE-006 (NCT05682443) is an open-label, randomized, active control, multi-center, phase 1/2 study of gotistobart in combination with Lu 177 in patients with mCRPC who have progressed after androgen receptor pathway inhibition.
- Patients were randomized (2:1*) to receive gotistobart at 3 mg/kg Q4W, 6 mg/kg Q6W, or 10 mg/kg Q6W for up to 13 doses plus Lu 177 7.4 GBq (200 mCi) Q6W for up to 6 doses, or to the control arm to receive Lu 177 7.4 GBq (200 mCi), Q6W for up to 6 doses.
- Here we report results from the dose escalation phase (Phase 1) that aims to assess safety and select two dose regimens for the Phase 2 dose optimization study.

Figure 1. Randomized study of gotistobart + Lu 177 versus Lu 177 for mCRPC



*In Phase 1, each cohort had randomization capped once 6 patients were randomized to the combination arm

Clinical activity

- At data cut-off (6 May 2025), median follow-up in the gotistobart combination arm was 14.7 months for 3 mg/kg Q4W (n=6), 6.1 for 6 mg/kg Q6W (n=6) and 9.3 months for 10 mg/kg Q6W (n=6) regimens and 10.4 months for the Lu 177 control arm (n=7). One patient had baseline PSA < 1 ng/mL (protocol deviation) and was excluded from efficacy analyses.

Table 2. PSA response rate

	Gotistobart + Lu 177			
	3 mg/kg Q4W (n=6)	6 mg/kg Q6W (n=6)	10 mg/kg Q6W (n=5)	Lu 177 Q6W (n=7)
PSA50 response Rate, n (%)	4 (66.7)	3 (50.0)	3 (60.0)	2 (28.6)
95% CI	(22.3–95.7)	(11.8–88.2)	(14.7–94.7)	(3.7–71.0)

Figure 2. PSA best percent change from baseline

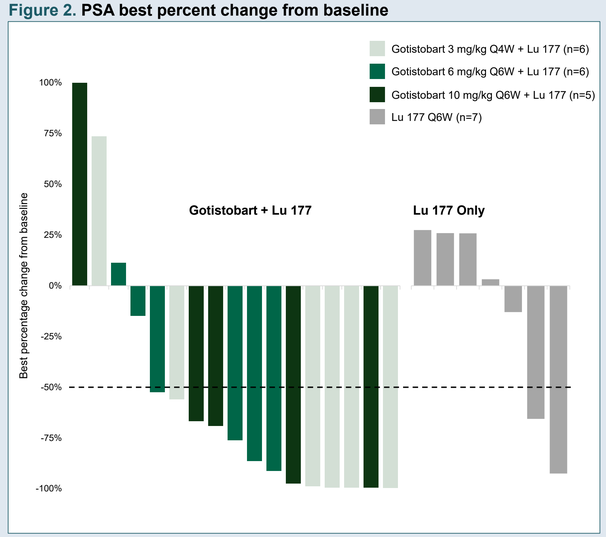
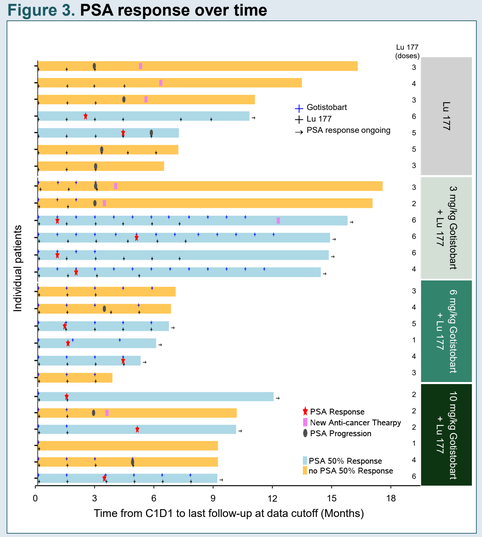


Figure 3. PSA response over time



Safety

Table 3. Adverse events

	Gotistobart + Lu 177			
	3 mg/kg Q4W (n=6)	6 mg/kg Q6W (n=6)	10 mg/kg Q6W (n=6)	Lu 177 Q6W (n=7)
Any TEAEs, n (%)	6 (100.0)	6 (100.0)	6 (100.0)	6 (85.7)
TEAEs of grades 3/4, n (%)	0	3 (50.0)	5 (83.3)	1 (14.3)
Colitis	0	0	2 (33.3)	0
Abdominal pain	0	0	1 (16.7)	0
Diarrhea	0	0	1 (16.7)	0
Nausea	0	0	1 (16.7)	0
Upper gastrointestinal hemorrhage	0	1 (16.7)	0	0
Anemia	0	2 (33.3)	0	1 (14.3)
Clostridium difficile infection	0	0	1 (16.7)	0
Pneumonia	0	0	1 (16.7)	0
Sepsis	0	0	1 (16.7)	0
Neutrophil count decreased	0	1 (16.7)	0	0
Platelet count decreased	0	1 (16.7)	0	0
Weight decreased	0	0	1 (16.7)	0
Decreased appetite	0	0	1 (16.7)	0
Hyperglycemia	0	0	1 (16.7)	0
Hypocalcemia	0	0	1 (16.7)	0
Hypokalemia	0	1 (16.7)	0	0
Fatigue	0	0	1 (16.7)	0
Muscular weakness	0	0	1 (16.7)	0
Acute kidney injury	0	1 (16.7)	0	0
Embolism	0	0	0	1 (14.3)
Any serious TEAEs, n (%)	1 (16.7)	1 (16.7)	5 (83.3)	0
TEAEs leading to:				
Dose reduction	0	1 (16.7)	1 (16.7)	0
Treatment discontinuation†	0	0	3 (50.0)	0
Death	0	0	0	0

†Treatment discontinuation of both drugs.

- No deaths, dose-limiting toxicity, or Gr 4–5 TRAEs were observed at any gotistobart dose during the DLT period.
  - At gotistobart 3 mg/kg, one patient discontinued gotistobart after cycle 4 due to Gr 2 colitis; one patient discontinued Lu 177 after 4 cycles due to Gr 2 anemia.
  - At gotistobart 6 mg/kg, one patient had Gr 3 acute kidney injury with Gr 4 hypokalemia and Gr 3 upper GI hemorrage with Gr 3 anemia. All events occurred after cycle 2, were assessed as unrelated to study drugs, recovered and didn't lead to dose change.
  - At gotistobart 10 mg/kg, three patients discontinued gotistobart, two due to Gr 3 colitis and one due to intermittent fever; all three continued with Lu 177. Five patients had Gr 1-2 IRR.

Patient characteristics

Table 1. Baseline patient and disease characteristics

	Gotistobart + Lu 177			
	3 mg/kg Q4W (n=6)	6 mg/kg Q6W (n=6)	10 mg/kg Q6W (n=6)	Lu 177 Q6W (n=7)
Median age, years (range)	71.0 (58–79)	69.0 (57–78)	67.5 (54–81)	69.0 (52–86)
Race, n (%)				
White	1 (16.7)	4 (66.7)	5 (83.3)	6 (85.7)
Black	3 (50.0)	2 (33.3)	0	1 (14.3)
Asian	0	0	1 (16.7)	0
Other	2 (33.3)	0	0	0
ECOG score, n (%)				
0	6 (100.0)	5 (83.3)	6 (100.0)	2 (28.6)
1	0	1 (16.7)	0	5 (71.4)
Mean PSA Level, ug/L (SD)	31.2 (30.2)	68.6 (148.3)	60.5 (61.1)	62.6 (87.9)
Mean duration since diagnosis, years (SD)	6.9 (2.0)	5.9 (5.5)	7.2 (5.8)	5.1 (2.9)
Patients with metastasis, n (%)	6 (100)	6 (100)	6 (100)	7 (100)
Bone metastasis	6 (100)	5 (83)	6 (100)	7 (100)
Lymph node metastasis	3 (50)	3 (50)	2 (33)	1 (17)
Visceral organs	3 (50)	2 (33)	2 (33)	0
At least one tumor lesion with PSMA-PET ≥ 20 SUV	5 (83)	4 (67)	1 (17)	3 (43)
Prior taxane treatment	6 (100)	6 (100)	6 (100)	7 (100)
Prior 1 line of taxane	4 (67)	6 (100)	6 (100)	7 (100)
Prior ≥ 2 lines of taxane	2 (33)	0	0	0
Prior ARPI treatment	6 (100)	6 (100)	6 (100)	7 (100)
Prior 1 line of ARPI	4 (33)	4 (67)	3 (50)	4 (57)
Prior 2 lines of ARPI	4 (67)	2 (33)	3 (50)	3 (43)

Figure 4. PSA change over time

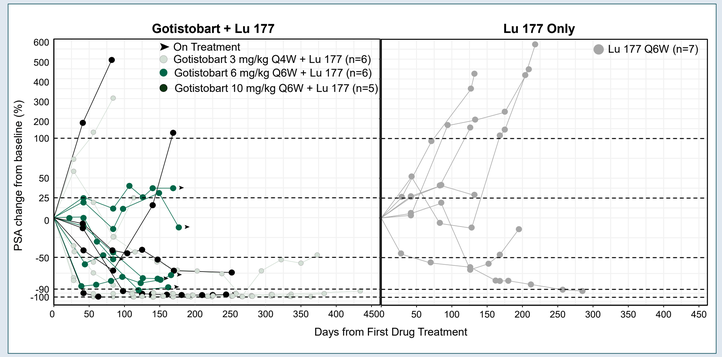
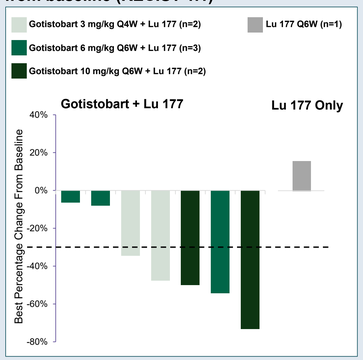


Figure 5. Target lesion best percent change from baseline (RECIST 1.1)



Conclusions

- Overall findings support combination regimens with gotistobart doses less than 10 mg/kg.
- The combination of gotistobart + Lu 177 was well tolerated and associated with durable PSA50 responses at doses of 3 mg/kg Q4W and 6 mg/kg Q6W compared with Lu 177 alone, supporting these doses for the ongoing Phase 2 study.
- The Phase 2 study is expected to complete enrollment by end of 2025.

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Trial registration: NCT05682443

ARPIs, androgen Receptor Pathway Inhibitors; ARAT, androgen receptor-axis-targeted therapies; ASCO, American Society of Clinical Oncology; CTLA-4, cytotoxic T-Lymphocyte-Associated Protein 4; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; GBq, gigabecquerel; Gr, grade; IRR, infusion-related reaction; Lu 177, Lutetium-177; mCi, millicurie; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death-1; PFS, progression-free survival; PSA, prostate-specific antigen; PSA50, prostate-specific antigen 50% Response; PSMA-617, prostate-specific membrane antigen-617; PSMA-PET, prostate-specific membrane antigen positron emission tomography; Q4W, every 4 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TEAEs, treatment-emergent adverse events; TME, tumor microenvironment; TRAEs, treatment-related adverse events; Tregs, regulatory T cells.

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