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Efficacy and safety of ^{177}Lu-PNT2002 prostate-specific membrane antigen (PSMA) therapy in metastatic castration-resistant prostate cancer (mCRPC): initial results from SPLASH

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BACKGROUND

^{177}Lu-PNT2002 ([Lu-177]-PSMA-I&T) is a prostate-specific membrane antigen (PSMA)-targeted small molecule radioligand which contains a glutamate-urea-based pharmacophore that is connected to a 1,4,7,10-tetraazacyclododecane,1-(glutaric acid)-4,7,10-triacetic acid (DOTAGA) radiometal chelator through a linker (**Figure 1**)

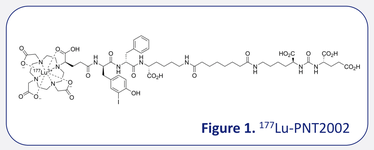


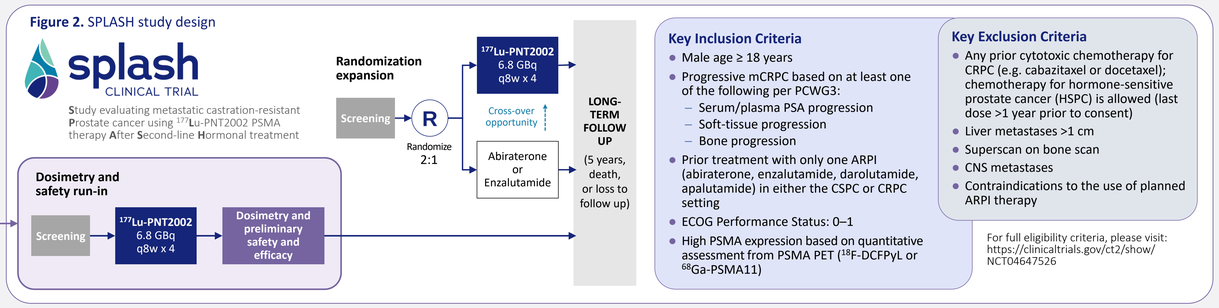
Figure 1. ^{177}Lu-PNT2002

SPLASH (NCT04647526) is a multinational, phase III, open-label, randomized study to evaluate efficacy and safety of ^{177}Lu-PNT2002 in metastatic castration-resistant prostate cancer (mCRPC) after androgen receptor pathway inhibitor (ARPI) therapy

- SPLASH is designed to evaluate radioligand therapy earlier in the treatment pathway and using fewer and lower doses, as compared to the currently approved indication for radioligand treatment in prostate cancer
- SPLASH dosimetry results were presented previously[1]:
  - The average dose to red marrow was 0.034 Gy/GBq, well below critical thresholds, enabling a potential opportunity for combination therapy
  - Organs receiving the largest absorbed doses were the lacrimal glands at 1.2 Gy/GBq, followed by the kidneys at 0.73 Gy/GBq
- Here we present **preliminary safety and efficacy results** from the **dosimetry lead-in sub-study of SPLASH**

METHODS

Figure 2. SPLASH study design



Key Inclusion Criteria

- Male age ≥ 18 years
- Progressive mCRPC based on at least one of the following per PCWG3:
  - Serum/plasma PSA progression
  - Soft-tissue progression
  - Bone progression
- Prior treatment with only one ARPI (abiraterone, enzalutamide, darolutamide, apalutamide) in either the CSPC or CRPC setting
- ECOG Performance Status: 0–1
- High PSMA expression based on quantitative assessment from PSMA PET (^{18}F-DCFPyL or ^{68}Ga-PSMA11)

Key Exclusion Criteria

- Any prior cytotoxic chemotherapy for CRPC (e.g. cabazitaxel or docetaxel); chemotherapy for hormone-sensitive prostate cancer (HSPC) is allowed (last dose >1 year prior to consent)
- Liver metastases >1 cm
- Superscan on bone scan
- CNS metastases
- Contraindications to the use of planned ARPI therapy

For full eligibility criteria, please visit: https://clinicaltrials.gov/ct2/show/NCT04647526

- The SPLASH study commenced with a 27-participant dosimetry and safety lead-in phase prior to randomization expansion (**Figure 2**)
- Participants were enrolled with tumours exhibiting high PSMA uptake on PET/CT per blinded independent central review, chemotherapy-naïve for CRPC, progressing on an ARPI, and adequate bone marrow and end organ reserve; fluorodeoxyglucose (FDG) PET concordance was not assessed
- All participants received up to four cycles of ^{177}Lu-PNT2002 at 6.8 GBq per cycle every 8 weeks
  - This dose was selected to minimize long-term risk while providing a dose found to be efficacious in previous studies with ^{177}Lu-PSMA-I&T[2,3]

PARTICIPANTS

- Of 35 participants screened, 33 underwent PSMA PET/CT; of those, 27 (81.8%) were eligible for treatment; 5 (15.2%) did not meet PSMA-avidity criteria, 1 was excluded based on other eligibility criteria

Table 1. Demographics and baseline characteristics

		Safety Population (n=27)
Age at informed consent (years)	Mean (SD)	71.4 (8.53)
	Median (range)	72.0 (57–86)
Age group, n (%)	< 65 years	7 (25.9)
	≥ 65 years	20 (74.1)
Race, n (%)	Black or African American	4 (14.8)
	White	23 (85.2)
Country, n (%)	Canada	12 (44.4)
	United States	15 (55.6)
PSA at baseline, median (range)		22 (0.3–701.0)
ECOG performance status, n (%)	0	16 (59.3)
	1	11 (40.7)
Prior taxane treatment for HSPC, n (%)	Yes	6 (22.2)
	No	21 (77.8)
Prior bisphosphonate treatment, n (%)	Yes	14 (51.9)
	No	13 (48.1)
Receiving opioids for cancer-related pain, n (%)	No	27 (100.0)
Progressed on prior ARPI therapy, n (%)	Yes	27 (100.0)
	- Enzalutamide	12 (44.4)
	- Abiraterone	12 (44.4)
	- Apalutamide	2 (7.4)
	- Darolutamide	1 (3.7)
Metastatic status on prior ARPI therapy, n (%)	M0	11 (40.7)
	M1	16 (59.3)

Table 2. Treatment exposure

	Safety Population (n=27)
Number (%) of participants by number of ^{177}Lu-PNT2002 cycles	
1 cycle	3 (11.1)
2 cycles	3 (11.1)
3 cycles	2 (7.4)
4 cycles	19 (70.4)
Number of cycles of ^{177}Lu-PNT2002 out of the 4 planned	(n=27)
Mean (SD)	3.37 (1.079)
Median (range)	4.00 (1.0–4.0)
Dose per cycle (GBq) of ^{177}Lu-PNT2002	(n=91)
Mean (SD)	6.88 (0.268)
Median (range)	6.89 (6.2–7.5)

RESULTS

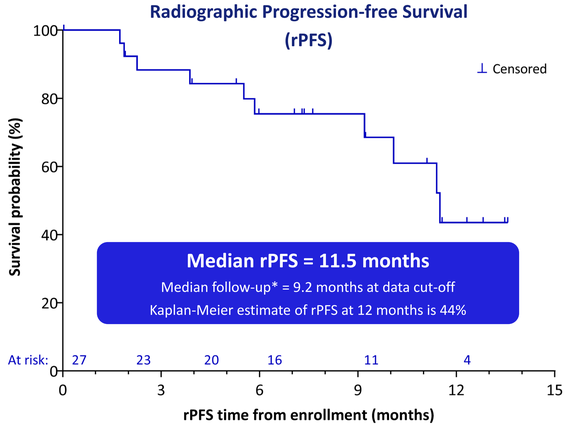


Figure 3. Kaplan-Meier curve for radiographic progression-free survival.
*rPFS follow-up calculated as time in months from date of enrollment to date of last available imaging (conventional) prior to the data cut-off for all enrolled participants.

Median overall survival has not been reached based on a 11.7-month median duration of follow-up

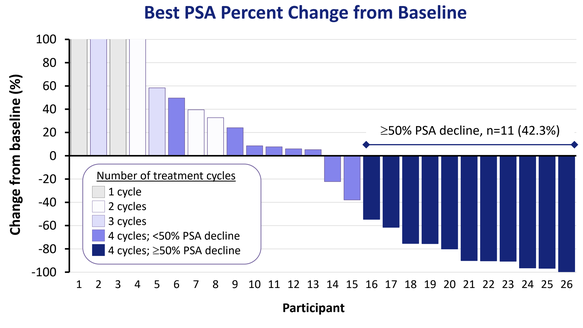


Figure 4. Best PSA percent change from baseline. One participant is excluded due to absence of post-baseline PSA data; this participant received 1 cycle.

Table 3. Radiographic objective response rate

	Objective Responses, n (%) (n=10*)
Complete response (CR)	2 (20%)
Partial response (PR)	4 (40%)
Stable disease	3 (30%)
Progressive disease	1 (10%)

*Participants with evaluable disease at baseline (target and/or non-target lesions).

Radiographic objective response rate = 60%
among evaluable participants (n=10)

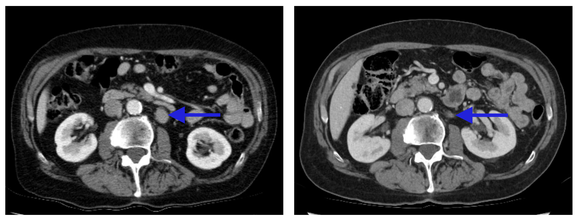


Figure 5. Complete response participant vignette. Retroperitoneal lymph node target lesion (indicated by blue arrows) with a short axis measurement of 2.1 cm at baseline, and the complete response of the lesion imaged at month 11.

- Grade ≥3 treatment-emergent adverse events occurred in 8 (29.6%) participants, of which anaemia (4, 14.8%) and haematuria (3, 11.1%) occurred in >10%
- Treatment-related adverse events (AEs) in >10% of participants included dry mouth (7, 25.9%), fatigue (6, 22.2%), nausea (5, 18.5%), and anaemia (4, 14.8%)

Table 4. Overall incidence of treatment-emergent adverse events (TEAEs), all grades

	Any		Treatment-related*	
	# of pts	%	# of pts	%
TEAEs	25	92.6	14	51.9
TEAEs of CTCAE Grade 3 or higher	8	29.6	3	11.1
Serious adverse events (SAEs)	6	22.2	1	3.7
TEAEs leading to discontinuation of ^{177}Lu-PNT2002	1	3.7	0	0.0
TEAEs leading to dose delay of ^{177}Lu-PNT2002†	3	11.1	1	3.7
TEAEs leading to death‡	1	3.7	0	0.0

*Includes events assessed by the investigator as definitely, probably, or possibly related to treatment. †Reflects intended action at time of AE. ‡Fatal event of disseminated intravascular coagulation likely due to underlying malignancy, deemed unrelated to treatment by the investigator.

Table 5. Incidence of treatment-related AEs by preferred term and maximum grade

	Grade 1		Grade 2		Grade 3		Grade 4/5	
	# of pts	%	# of pts	%	# of pts	%	# of pts	%
Treatment-related AEs that occurred in >10%								
Dry mouth	7	25.9	0	0.0	0	0.0	0	0.0
Fatigue*	3	11.1	3	11.1	0	0.0	0	0.0
Nausea	3	11.1	2	7.4	0	0.0	0	0.0
Anaemia	1	3.7	1	3.7	2	7.4	0	0.0
Additional treatment-related AEs of interest								
Thrombocytopenia	1	3.7	0	0.0	1	3.7	0	0.0
Neutropenia	0	0.0	1	3.7	1	3.7	0	0.0
Lymphopenia	0	0.0	0	0.0	0	0.0	0	0.0
Leukopenia	0	0.0	0	0.0	0	0.0	0	0.0
Acute kidney injury	0	0.0	0	0.0	1†	3.7	0	0.0
Vomiting	0	0.0	0	0.0	0	0.0	0	0.0
Laboratory abnormalities								
Lymphocyte count decreased	1	3.7	0	0.0	0	0.0	0	0.0
Neutrophil count decreased	0	0.0	1	3.7	0	0.0	0	0.0
Red blood cell count decreased	1	3.7	0	0.0	0	0.0	0	0.0
Blood creatinine increased	0	0.0	0	0.0	0	0.0	0	0.0

*Includes fatigue and asthenia. †Acute kidney injury leading to hospitalization resolved the following day; this event was attributed to several factors including dehydration as definitely related and ^{177}Lu-PNT2002 deemed possibly related.

CONCLUSIONS

- In the SPLASH lead-in cohort, median rPFS time was 11.5 months, as compared to the control arm benchmarks of 3.5–4.2 months for individuals with progressive mCRPC post-ARPI failure receiving similar treatment[4,5]
- A radiographic objective response (CR, PR) was achieved in 60% of the 10 participants with evaluable disease at baseline
- ^{177}Lu-PNT2002 was well tolerated with no treatment-related deaths and few treatment-related AEs of grade 3 or higher
- SPLASH has successfully completed the lead-in treatment phase and the randomization phase is currently enrolling

REFERENCES 1. Beauregard J-M, Probst S, Hansen AR, et al. Abstract MWMA2244, presentation at: SNMMI Mid-Winter Annual Meeting 2022. 2. Baum RP, Kulkarni HR, Schuchardt C, et al. J Nucl Med 2016;57:1006–13. 3. Okamoto S, Thieme A, Allman J, et al. J Nucl Med 2017;58:445–50. 4. Powles T, Yuen KC, Gillessen S, et al. Nature 2022;28:144–53. 5. de Bono J, Mateo J, Fizazi K, et al. N Engl J Med 2020; 382:2091–102. **ABBREVIATIONS** AE, adverse event; ARPI, androgen receptor pathway inhibitor; CNS; central nervous system; CR, complete response; CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer; CTCAE, common terminology criteria for adverse events; ECOG, Eastern Cooperative Oncology Group; GBq, gigabecquerel radioactivity units; Gy/GBq, grays per gigabecquerel (absorbed dose per unit of administered radioactivity); HSPC, hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Working Group 3; PET/CT, positron emission tomography–computed tomography; PR, partial response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; pts, participants; q8w, every 8 weeks; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event. **DISCLOSURES** A.R. Hansen reports grants and other support from Merck and GSK; other support from Eisai; and grants from Genentech, Roche, BMS, Astellas, AstraZeneca, Janssen, Bayer, and Boehringer Ingelheim. **ACKNOWLEDGEMENTS** We thank the study participants and study site personnel. The SPLASH study is sponsored by POINT Biopharma. Medical writing and editorial support were provided by Sara Hawley, MSc and Chantal Trieu, PharmD, RPh of POINT Biopharma; editorial and graphical support was provided by Joanne Fitz-Gerald, BPharm and Jonathan A C Lee, PhD of FourWave Medical Communications, funded by POINT Biopharma.

Presented at the European Society for Medical Oncology (ESMO) Congress, September 9–13, 2022 Paris, France. Corresponding author: Aaron.R.Hansen@health.qld.gov.au