Supplemental Table 1: The 3TMPO investigators and collaborators

Five centres were activated for enrolling and imaging patients. Principal investigators are identified with *.

Participating site	Investigator(s)	Collaborator(s)	Included patients
Centre Hospitalier Universitaire de Québec – Université Laval Québec, QC, Canada	BEAUREGARD, Jean-Mathieu* POULIOT, Frédéric*	CASTONGUAY, Vincent FRADET, Yves LACOMBE, Louis LEVESQUE, Éric LODDE, Michele MARCOUX, Nicolas TOREN, Paul	66
Centre Hospitalier Universitaire de Sherbrooke Sherbrooke, QC, Canada	GUÉRIN, Brigitte* RICHARD, Patrick ROUSSEAU, Etienne TURCOTTE, Éric	BOISJOLY, Josie-Anne CARMEL, Michel CASTILLOUX, Jean-François EKINDI-NDONGO, Nadia JELDRES, Claudio LACROIX-POISSON, Frédéric NOËL-LAMY, Maxime PAVIC, Michel SABBAGH, Robert TÉTREAULT-LAFLAMME, Audrey	14
Jewish General Hospital Montreal, QC, Canada	PROBST, Stephan ANIDJAR, Maurice	ABIKHZER, Gad FERRARIO, Cristiano	2
Centre Hospitalier de l'Université de Montréal Montreal, QC, Canada	SAAD, Fred TRUDEL, Dominique	ALBADINE, Roula HAMILOU, Zineb KARAKIEWICZ, Pierre I. JUNEAU, Daniel LATOUR, Mathieu LATTOUF, Jean-Baptiste	16
McGill University Health Center Montreal, QC, Canada	KASSOUF, Wassim	APRIKIAN, Armen HICKESON, Marc	0
Total			**98**

Supplemental Table 2: Inclusion and Exclusion criteria

Inclusion criteria

1. Male ≥ 18 years old
2. Histologically or cytologically proven adenocarcinoma of the prostate cancer with or without neuroendocrine carcinoma features at initial diagnosis
3. Castration-resistant prostate cancer defined by progression under continuous castration (measured serum testosterone ≤ 50 ng/dL [1.73 nM]) anytime while on androgen deprivation therapy
4. Metastatic disease documented by at least three metastatic active lesions on whole body bone scan* and/or measurable soft tissue on CT-scan.** Metastatic lesions on imaging are defined by RECIST 1.1
5. Evidence of disease progression (biochemical or radiographic) on prior therapy or watchful waiting
6. Able and willing to provide signed informed consent in French or English and to comply with protocol requirements

Exclusion criteria

1. Another non-cutaneous malignancy or melanoma diagnosed in the past 5 years
2. Currently under a randomized controlled trial with unknown allocation
3. Limited survival prognosis (ECOG ≥3)
4. Patients under dialysis
5. Any disease or condition limiting the patient's capacity to execute the study procedures, based on the investigators' opinion

*A bone lesion that has been treated with site-directed radiation therapy is excluded from the target lesion count to fulfil the criteria of at least three metastatic lesions on conventional imaging.

**The reference conventional imaging (confirming the presence of at least three active metastases) must be done either: a) after biochemical progression on treatment or b) at least 90 days after last treatment has begun if imaging was performed while the patient was still responding (to avoid disappearance of metastasis due to treatment response).

Supplemental Table 3: Adverse events

Adverse events observed in the 3TMPO cohort (n=98), their severity (graded according to the Common Terminology Criteria for Adverse Events, version 5), their causality as assessed by the qualified doctor of the corresponding centre and their seriousness.

Event	Severity	Causality	Seriousness	Occurrence
Headache	Grade 1	Possibly related	Not serious	1
Nausea	Grade 1	Possibly related	Not serious	1
Hyperthermia	Grade 1	Possibly related	Not serious	1
Fall	Grade 1	Unrelated	Not serious	1
Urosepsis	Grade 3	Unrelated	Serious	1
Total				5

Supplemental Table 4: Systemic treatment categories received before accrual (excluding androgen deprivation therapy)

Type of treatment	Total (n=98)	No IIH (n=16)	With IIH (n=81)
Taxanes*			
None	31 (31.6%)	6 (37.5%)	25 (30.9%)
Docetaxel only	13 (13.3%)	2 (12.5%)	11 (13.6%)
Cabazitaxel only	2 (2.0%)	0 (0.0%)	2 (2.5%)
Both	52 (53.1%)	8 (50.0%)	43 (53.1%)
ARPI			
None	11 (11.2%)	3 (18.7%)	8 (9.9%)
1	73 (74.5%)	12 (75.0%)	60 (74.1%)
2	13 (13.3%)	0 (0.0%)	13 (16.0%)
3	1 (1.0%)	1 (6.3%)	0 (0.0%)
Radium-223	16 (16.3%)	1 (6.3%)	15 (18.5%)
PARP-I	6 (6.1%)	1 (6.3%)	5 (6.2%)
Other	11 (11.2%)	3 (18.7%)	8 (9.9%)

ARPI : Androgen-receptor pathway inhibitor
IIH : intra-patient inter-metastatic heterogeneity
PARP-I : PolyADP-ribose polymerase inhibitor
*Taxanes received as either hormone-sensitive or castration-resistant prostate cancer