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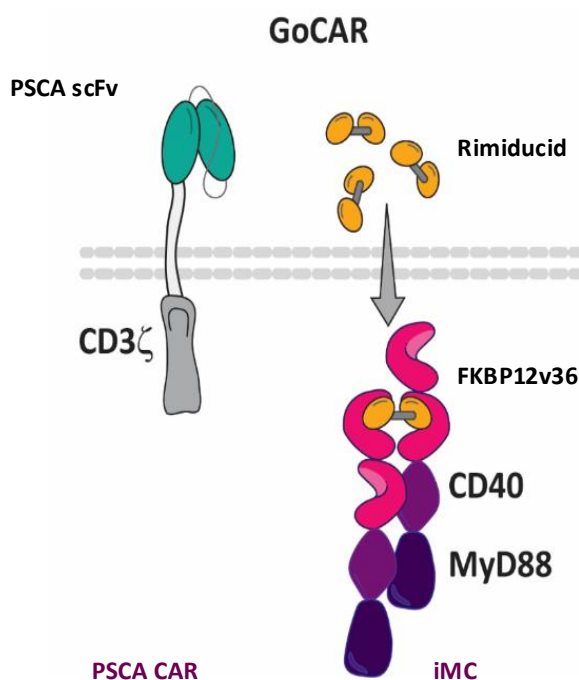
### **BP-012 Clinical Study Protocol**

## Supplementary Figure 1

A



B



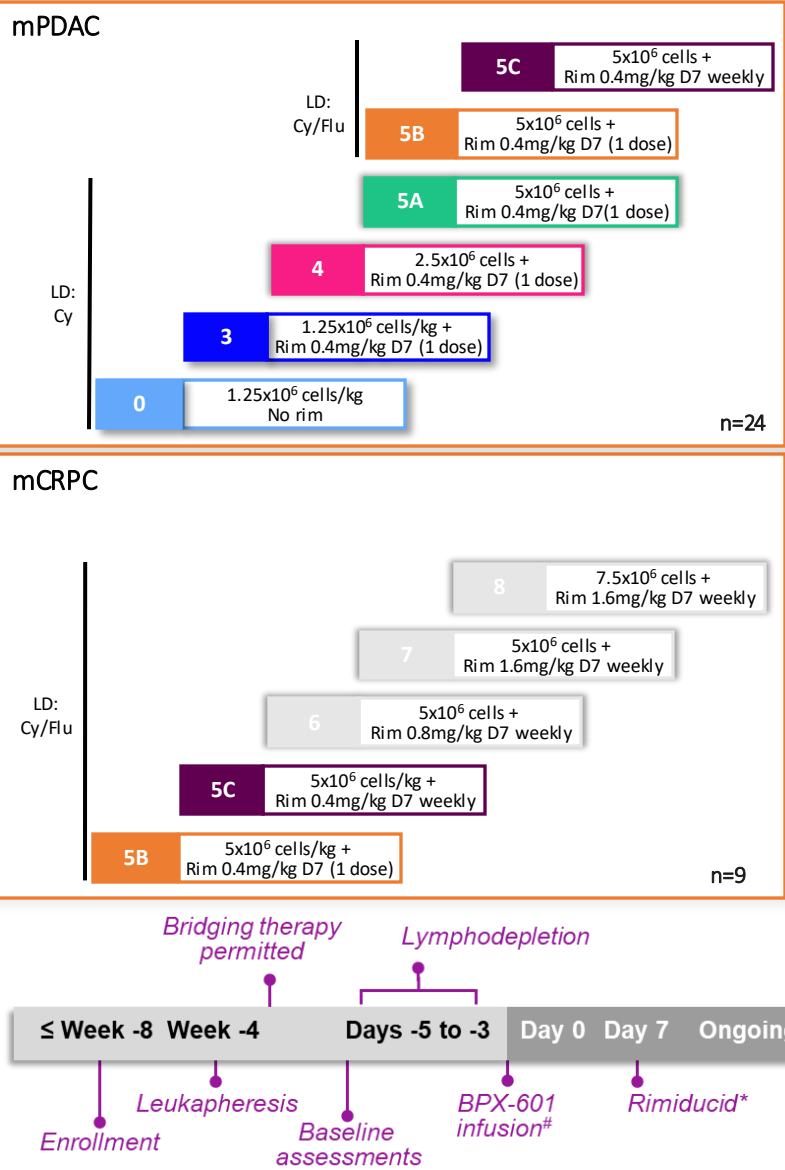
### Supplementary Figure 1. BPX-601 GoCAR-T® cells.

**A.** BPX-601 retroviral GoCAR-T® cell gamma-retroviral vector construct. BPX-601 is a PSCA-directed, genetically modified, autologous GoCAR-T® cell product candidate that binds to PSCA-expressing cells. BPX-601 T cells target PSCA with a first-generation CAR construct containing a traditional cluster of differentiation 3 zeta chain (CD3ζ) cytoplasmic signaling domain together with a single-chain variable domain fragment of the humanized PSCA A.11 antibody. In addition to the anti-PSCA CAR, BPX-601 T cell therapy is engineered to express an inducible dual co-stimulatory domain comprised of 2 FKBP12v36 binding proteins (FKBP) in-frame with the signaling domains from MyD88 and CD40 (inducible MyD88/CD40 or iMC).

**B.** Mechanism of action of BXP-601 and rimiducid. The small molecule rimiducid leads to the dimerization of the FKBP binding domains and CD40 and MyD88 signaling domains, triggering the downstream NFκB, AP1, and IRF7 signaling pathways and activation of pro-inflammatory cytokines and type I IFN production, and T cell proliferation and persistence.

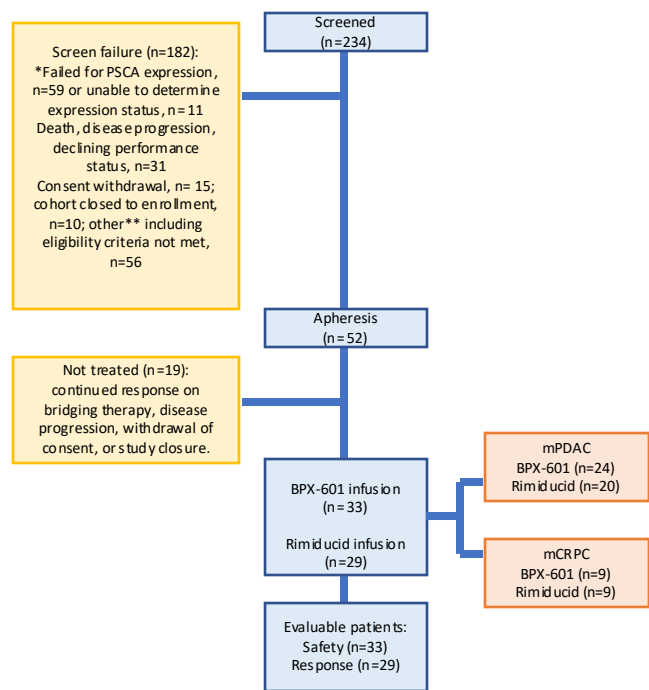
Supplementary Figure 2

A



Supplementary Figure 2

B



\*pancreatic only

\*\* additional reasons may have included: insurance, return to primary oncologist, started another line of therapy, lost to follow up, and other not otherwise specified. Change in protocol to limit to second-line for mPDAC resulted in several subjects not meeting inclusion criteria; other reasons for screen failure included lack of measurable disease, organ function disqualification and unwillingness to comply with protocol mandated contraception measures.

**Supplementary Figure 2. Protocol 3 + 3 design and consort diagram.**

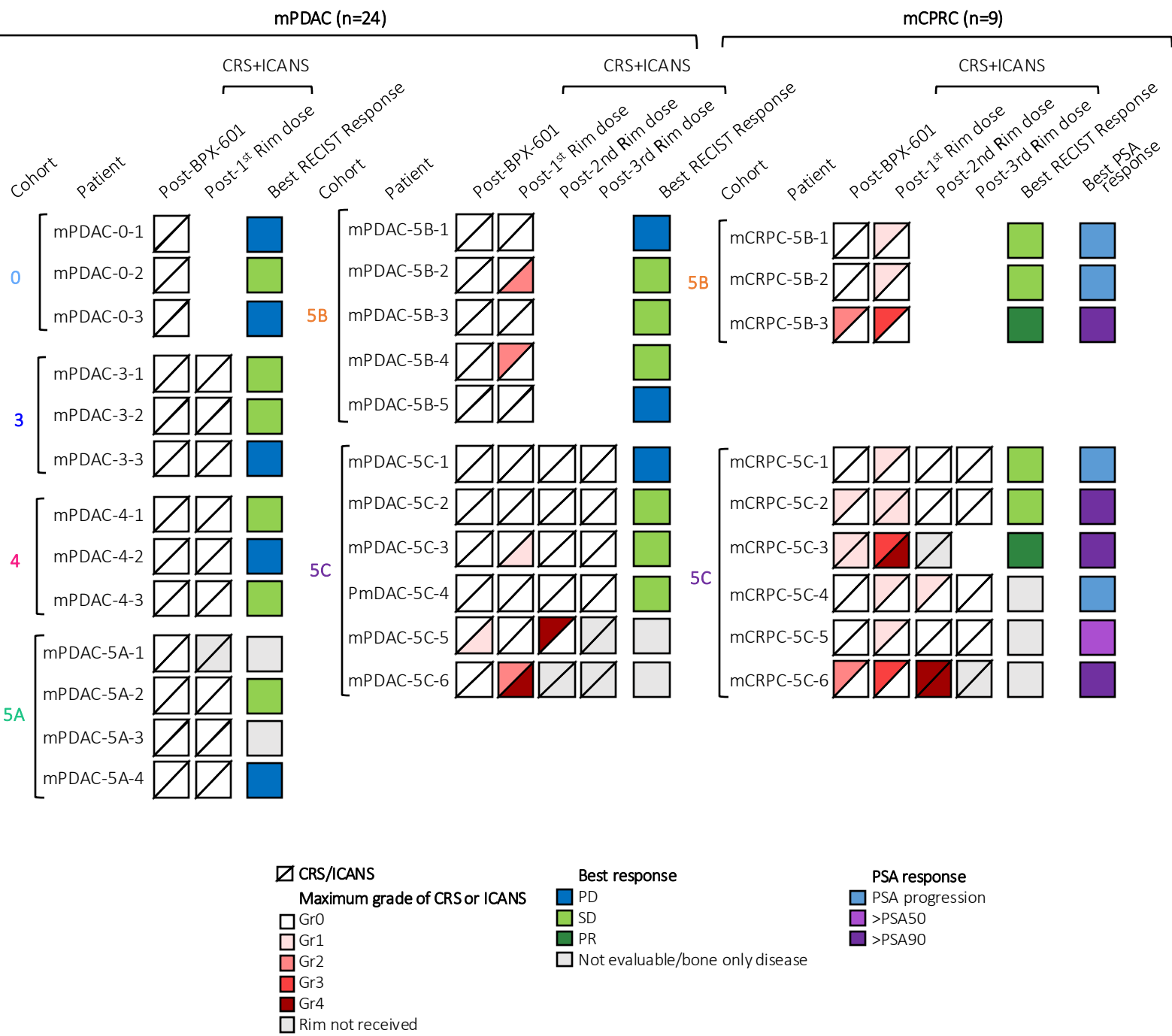
**A.** Protocol 3+3 design for dose-escalation cohorts; study timeline for screening, apheresis, T cell manufacture, treatment with BPX-601 cells and rimiducid, response assessment, and follow up. mCRPC cohorts shown in gray were planned but not initiated prior to study closure.

# patients received a single infusion of BPX-601 cells/kg; \*doses of 0.4 mg/kg rimiducid were infused beginning 7 days following cell infusion

**B.** CONSORT diagram indicating the number of patients screened, enrolled in the study and infused with BPX-601 and rimiducid. Screen failure reasons are provided.



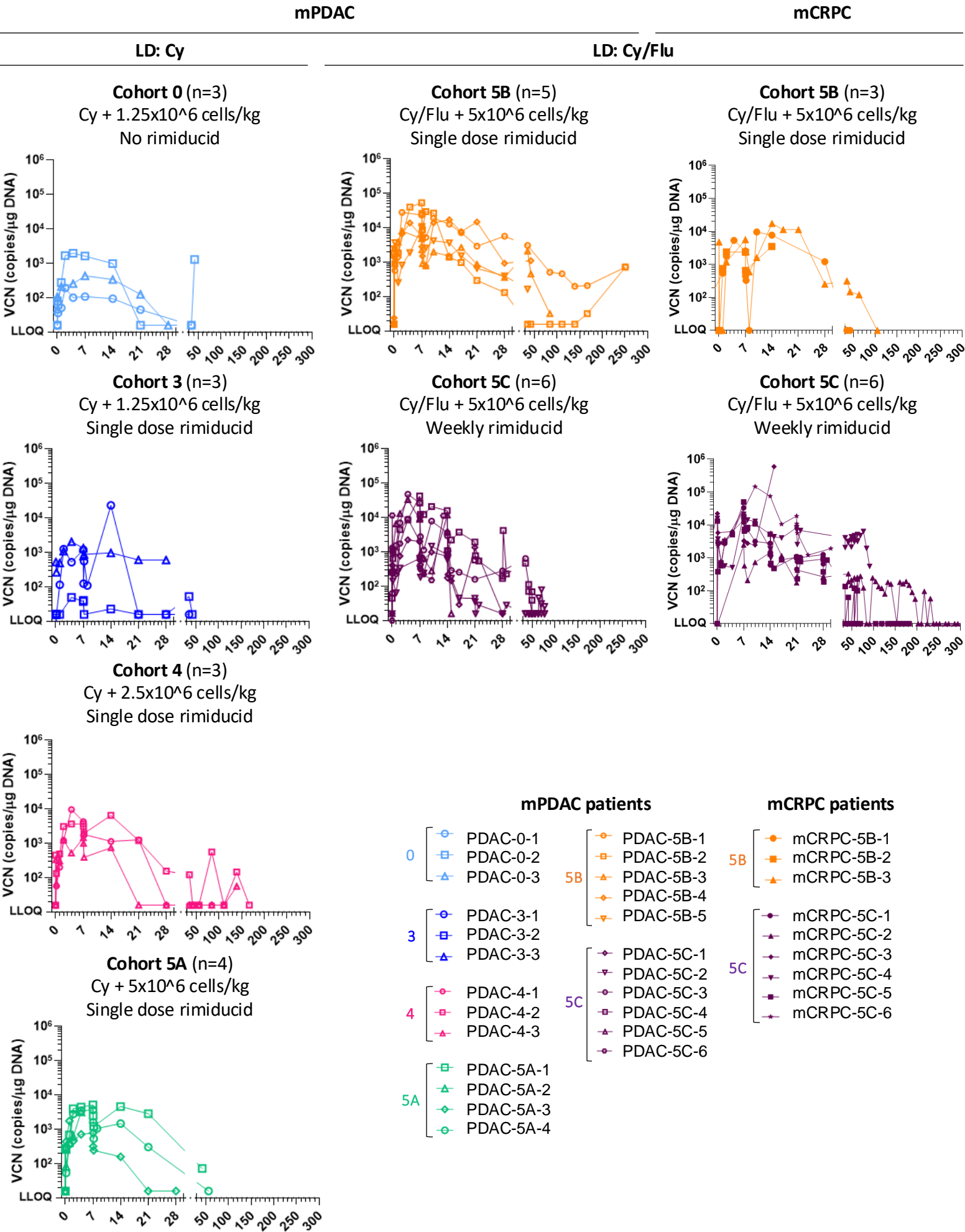
Supplementary Figure 3



**Supplementary Figure 3. Summary of per-patient cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) related to study drugs and best response by RECIST and PSA (mCRPC patients) after BPX-601 and first three rimiducid infusions.** Patients are organized by indication and cohort. Occurrence of CRS and ICANS related to study drugs, graded according to Lee grading scale, is shown for period of time (approximately 1 week) between respective BPX-601 or rimiducid and the following infusion, up to third rimiducid infusion, as applicable for the respective cohort. Best response by RECIST is shown for evaluable mPDAC and mCRPC patients with soft tissue disease; best biochemical response (PSA response) is shown for all mCRPC patients.

Rim, rimiducid

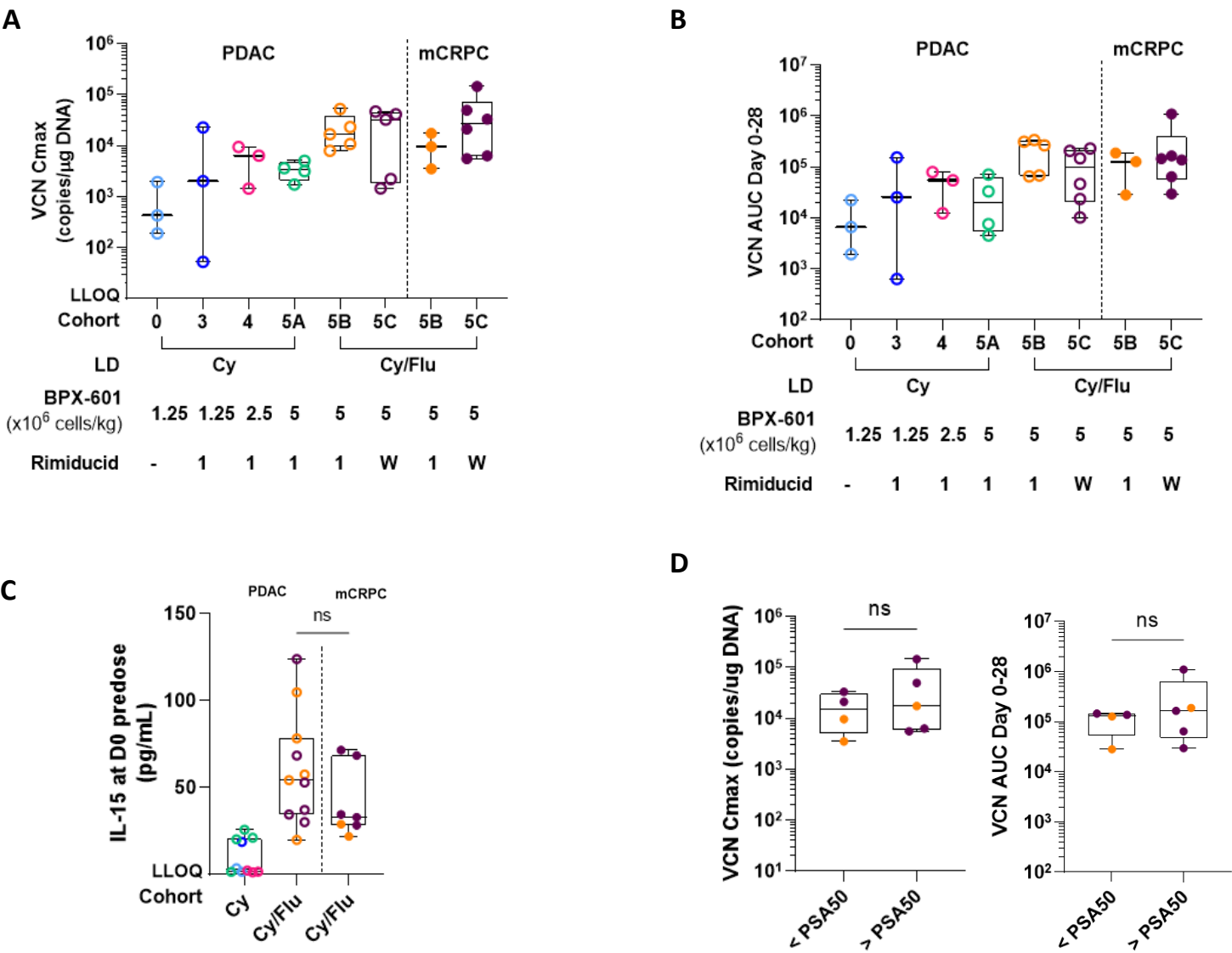
Supplementary Figure 4



***Supplementary Figure 4. CAR T cell expansion and persistence per cohort.***

BPX-601 cell expansion and persistence in peripheral blood shown per patient and cohort in mPDAC and mCRPC patients, measured by qPCR-based detection of vector copy number (VCN) in genomic DNA. LLOQ, lower limit of quantitation

Supplementary Figure 5



**Supplementary Figure 5. BPX-601 early expansion and persistence and relationship with activity and LD.**

**A.** VCN Cmax in peripheral blood of patients with mPDAC (n=23) or mCRPC (n=9).

**B.** Area under the curve (AUC) day 0-28 in peripheral blood of patients with mPDAC (n=24) or mCRPC (n=9).

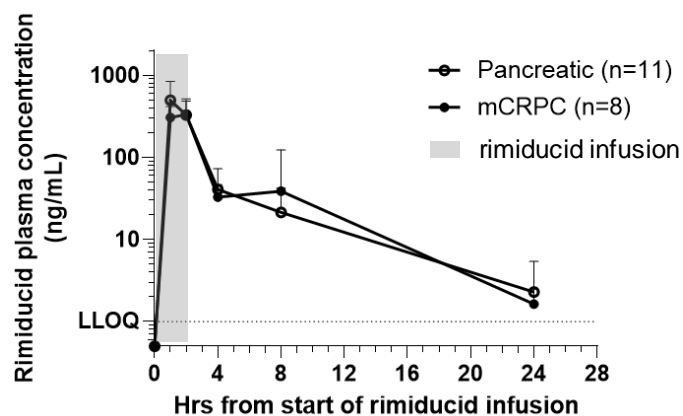
**C.** IL-15 at day 0 in patients with mPDAC or mCRPC, as a function of LD regimen received: mPDAC patients treated with Cy (n=10) or Cy/flu (n=11) and mCRPC patients treated with Cy/flu (n=7). Box plots show minimum, lower quartile, median, upper quartile, and maximum.

**D.** Non-significant association (one-tail unpaired t test) between higher VCN Cmax and AUC in peripheral blood and PSA response (PSA50) in patients with mCRPC. n=4 patients with PSA response < PSA50; n=5 patients with PSA response > PSA50.

W, weekly

Box plots show minimum, lower quartile, median, upper quartile, and maximum.

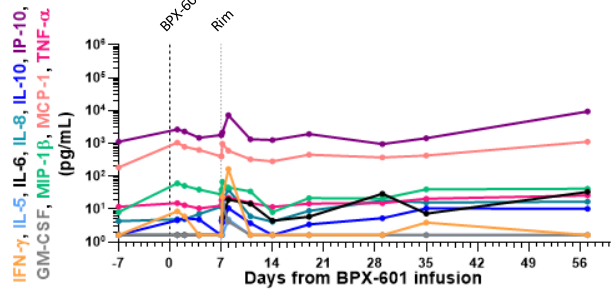
Supplementary Figure 6



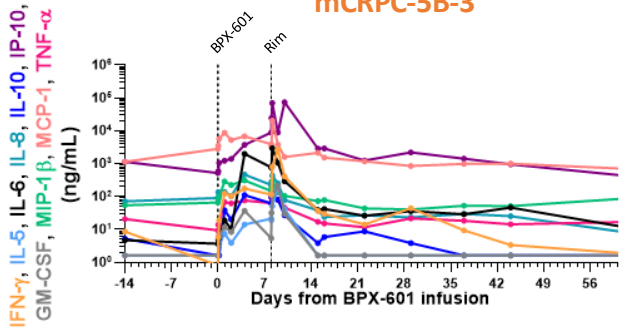
**Supplementary Figure 6. Rimiducid pharmacokinetics after first dose in patients with mPDAC or mCRPC from cohorts 5B and 5C.** Rimiducid mean plasma concentrations versus time semi-logarithmic curves (mean  $\pm$  SD) after first rimiducid infusion in patients with mPDAC and mCRPC enrolled in cohorts 5B and 5C.

Supplementary Figure 7

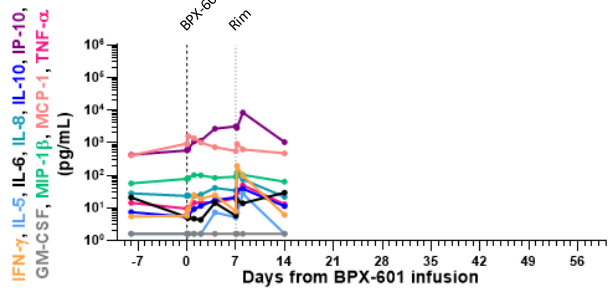
mCRPC-5B-1



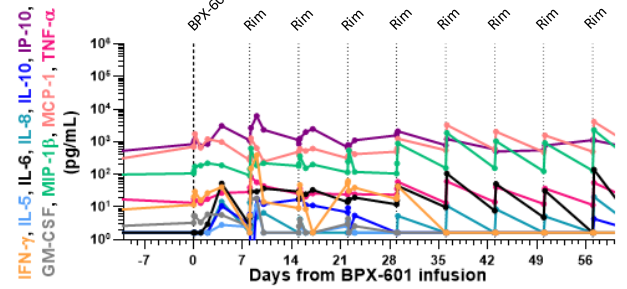
mCRPC-5B-3



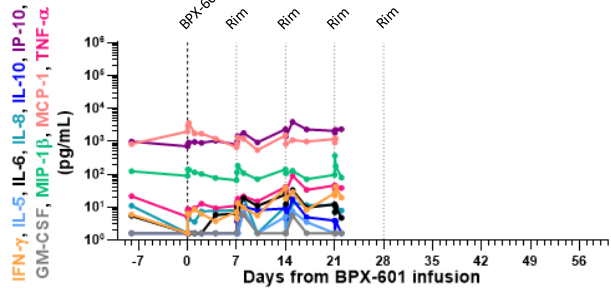
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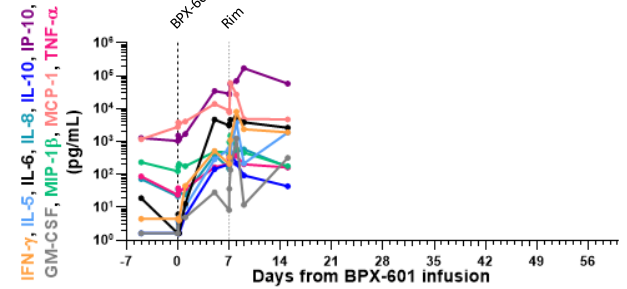
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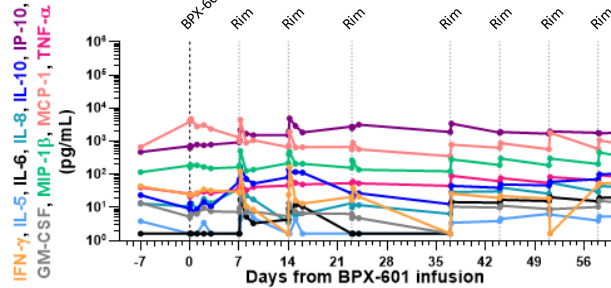
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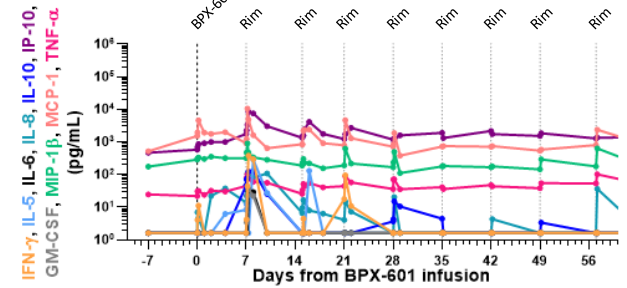
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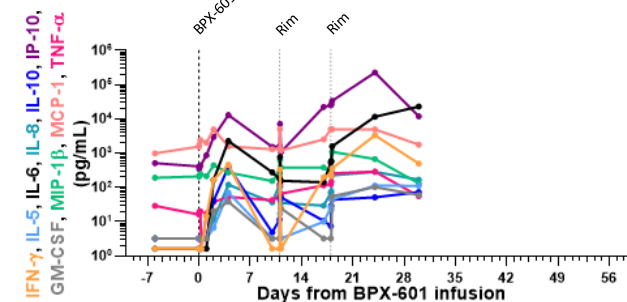
mCRPC-5C-4



mCRPC-5C-5

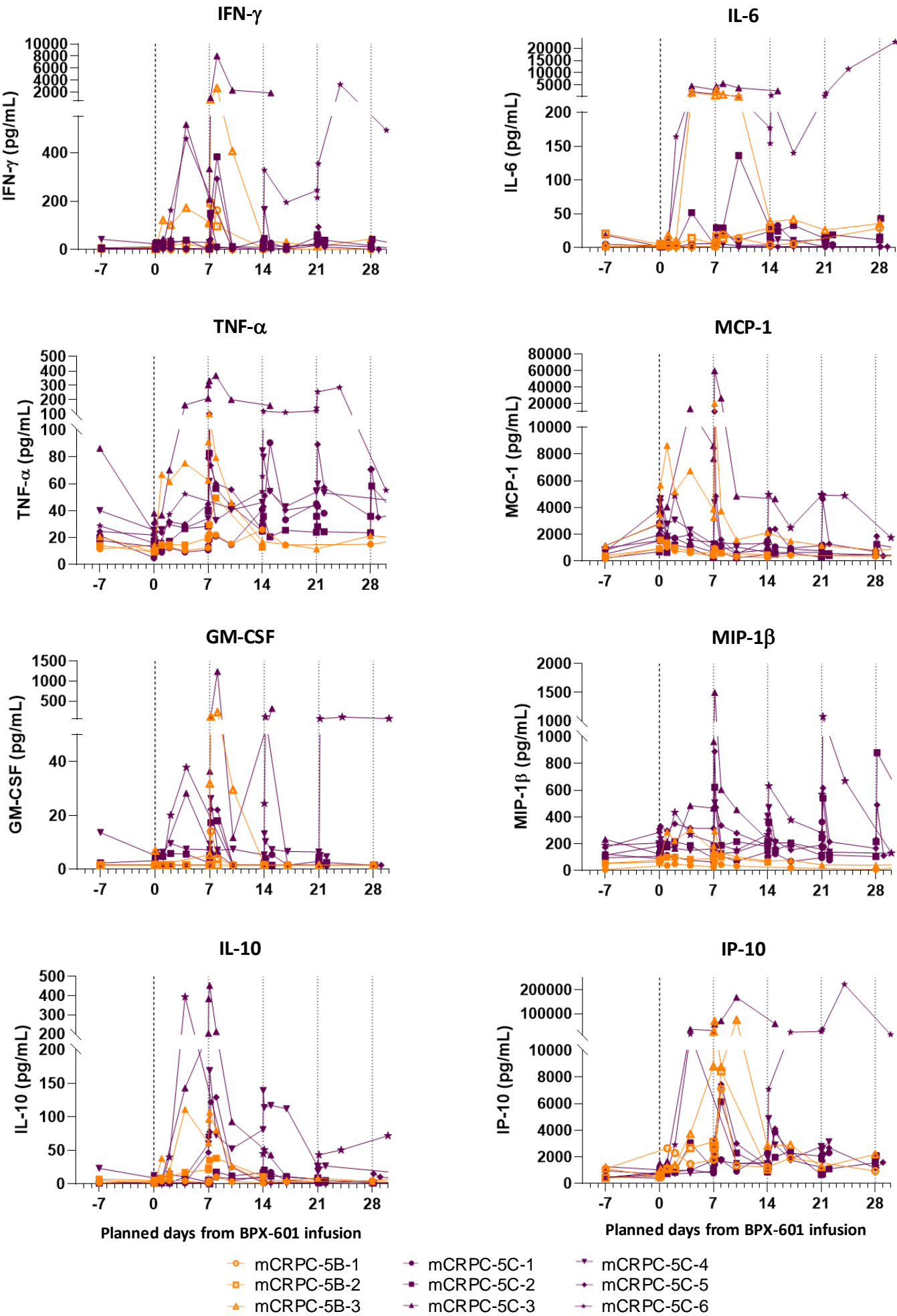


mCRPC-5C-6



**Supplementary Figure 7. Select cytokines and chemokines pharmacodynamics during the first 60 days of treatment for nine patients with mCRPC.** Serum levels (pg/mL) of IFN- $\gamma$ , IL-5, IL-6, IL-8, IL-10, IP-10, GM-CSF, MIP-1 $\beta$ , MCP-1, and TNF- $\alpha$  are shown for each individual patient with mCRPC enrolled in cohorts 5B and 5C. Vertical dashed lines indicate BPX-601 and rimiducid infusions.

Supplementary Figure 8

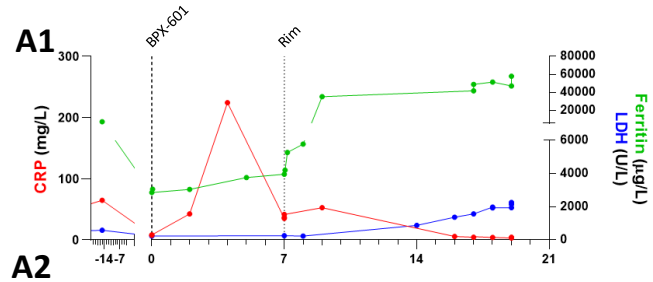




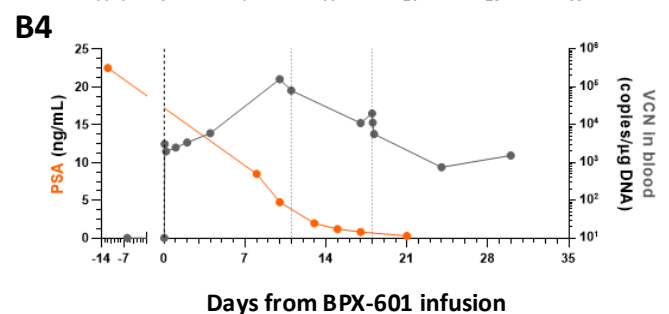
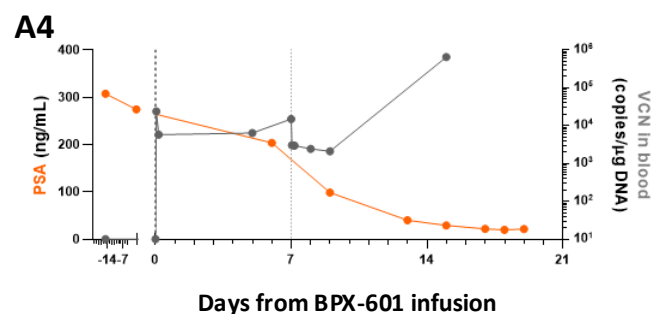
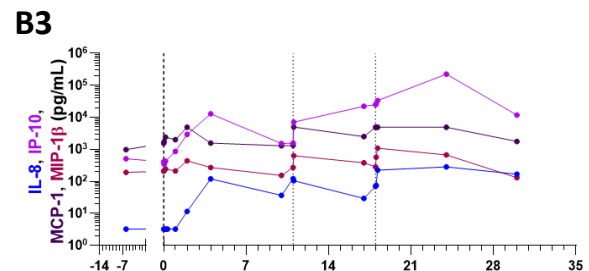
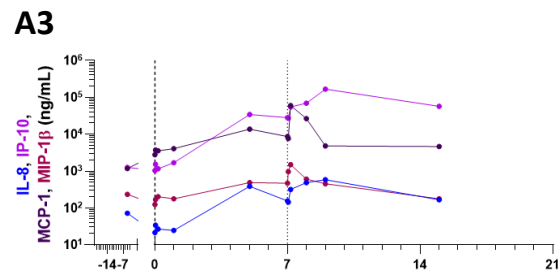
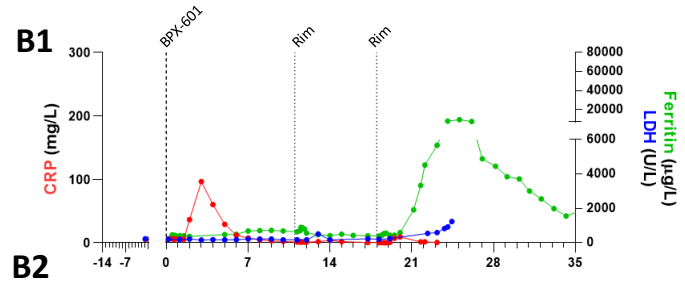
***Supplementary Figure 8. Comparative analysis of select cytokines and chemokines pharmacodynamics during the first 30 days of treatment for patients with mCRPC.*** Serum levels (pg/mL) of IFN- $\gamma$ , IL-6, IL-10, IP-10, GM-CSF, MIP-1 $\beta$ , MCP-1, and TNF- $\alpha$  are shown for all patients with mCRPC. Timeline (days) has been adjusted to align BP-601 and rimiducid infusions across the nine patients.

Supplementary Figure 9

mCRPC-5C-3



mCRPC-5C-6



**Supplementary Figure 9. Exploratory pharmacodynamic evaluation of two cases of high-grade CRS, ICANS and HLH in mCRPC cohort 5C.**

Pharmacodynamic responses of inflammation markers (CRP, Ferritin, LDH) (**A1** and **B1**), IFN- $\gamma$ , TNF- $\alpha$ , IL-5, IL-6 (**A2** and **B2**), IL-8, IP-10, MCP-1, MIP-1b (**A3** and **B3**), PSA, and VCN (**A4** and **B4**) in subjects mCRPC-5C-3 (**A**) and mCRPC-5C-5 (**B**).

**Supplementary Table 1. Summary of patient characteristics**

	<b>mPDAC cohorts</b>	<b>mCRPC cohorts</b>
No. patients	24	9
Median age (range), years	62.5 (48-78)	66.0 (56-75)
Male sex, n (%)	14 (58.3%)	9 (100%)
Ethnicity		
Hispanic or Latino	2 (8.3%)	1 (11.1%)
Not Hispanic or Latino	21 (87.5%)	8 (89.9%)
Not reported	1 (4.2%)	0
Race		
White	22 (91.7%)	8 (88.9%)
Other <sup>‡</sup>	1 (4.2%)	1 (11.1%)
Not reported	1 (4.2%)	0
ECOG score at baseline, n (%)		
0	8 (33.3%)	4 (44.4%)
1	6 (25.0%)	5 (55.6%)
Missing	10 (41.7%)	0
Prior anticancer therapy regimens, n (%)		
Median (range)	2 (1-6)	8 (5-9)
Site of metastatic disease, n (%)		
Liver	13	1
Lung	6	1
Lymph nodes	4	5

Bone	0	6
Bone only	0	3
Prior prostatectomy	n/a	3 (33.3%)
PSA level (ng/ml), median (range)	n/a	130 (22.5-318.0)
Previous systemic regimens, n (%)		
Platinum	20 (83.3%)	0
Gemcitabine	14 (58.3%)	0
Antiandrogen	n/a	9 (100%)
Taxanes	6 (25%)	9 (100%)
Anti-PD-1/PD-L1 antibody	2 (8%)	4 (44.4%)
Other immunotherapy	2 (8%)*	4 (44.4%)**

¥Other was not specified but excluded: White, Black, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander; \* Dendritic cell vaccine; \*\* Included: sipuleucel-T (n=3) and investigational PSMA bispecifics (n=2).

**Supplementary Table 2. Treatment-emergent adverse events occurring in ≥ 20% of patients\***

	mPDAC (n=24)		mCRPC (n=9)		Total (N=33)	
	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4	Any
<b>Hematologic</b>						
Anemia	5 (20.8%)	6 (25.0%)	7 (77.8%)	7 (77.8%)	12 (36.4%)	13 (39.4%)
Leukopenia	9 (37.5%)	9 (37.5%)	4 (44.4%)	4 (44.4%)	13 (39.4%)	13 (39.4%)
Febrile neutropenia	8 (33.3%)	8 (33.3%)	1 (11.1%)	1 (11.1%)	9 (27.3%)	9 (27.3%)
Neutropenia	11 (45.8%)	12 (50.0%)	5 (55.6%)	5 (55.6%)	16 (48.5%)	17 (51.5%)
Platelet count decreased	1 (4.2%)	1 (4.2%)	2 (22.2%)	6 (66.7%)	3 (9.1%)	7 (21.2%)
<b>Non-Hematologic</b>						
Back pain	2 (8.3%)	4 (16.7%)	1 (11.1%)	3 (33.3%)	3 (9.1%)	7 (21.2%)
Blood bilirubin increased	5 (20.8%)	5 (20.8%)	2 (22.2%)	2 (22.2%)	7 (21.2%)	7 (21.2%)
Diarrhea	0	4 (16.7%)	0	3 (33.3%)	0	7 (21.2%)
Fatigue	0	5 (20.8%)	1 (11.1%)	4 (44.4%)	1 (3.0%)	9 (27.3%)
Hypotension	1 (4.2%)	5 (20.8%)	2 (22.2%)	2 (22.2%)	3 (9.1%)	7 (21.2%)
Nausea	1 (4.2%)	5 (20.8%)	0	2 (22.2%)	1 (3.0%)	7 (21.2%)
Pyrexia**	0	8 (33.3%)	0	9 (100%)	0	17 (51.5%)

\*Excluding CRS and ICANS which are reported separately in Table 1B. \*\*Pyrexia was reported separately and may not have been associated with cytokine release syndrome. Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; mPDAC, pancreatic ductal adenocarcinoma.

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one treatment-emergent adverse event are counted only once.

Adverse events are coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities, version 25.1.

**Supplementary Table 3. Safety Summary by Cohort**

<b>Tumor Type</b>	<b>mPDAC</b>						<b>mCRPC</b>	
<b>Cohort</b>	<b>0</b>	<b>3</b>	<b>4</b>	<b>5A</b>	<b>5B</b>	<b>5C</b>	<b>5B</b>	<b>5C</b>
<b>BPX-601 Dose (x 10<sup>6</sup> cells/kg)</b>	<b>1.25</b>	<b>1.25</b>	<b>2.5</b>	<b>5</b>	<b>5</b>	<b>5</b>	<b>5</b>	<b>5</b>
<b>Rimiducid Dose Exposure</b>	<b>None</b>	<b>Single</b>	<b>Single</b>	<b>Single</b>	<b>Single</b>	<b>Weekly</b>	<b>Single</b>	<b>Weekly</b>
<i>Subjects Exposed to BPX-601</i>	3	3	3	4	5	6	3	6
<i>Subjects Exposed to Rimiducid</i>	0	3	3	3	5	6	3	6
Total Number of TEAEs*	16	14	12	49	74	141	85	305
Subjects Reporting at Least One TEAE, n (%)	3 (100%)	3 (100%)	3 (100%)	4 (100%)	5 (100%)	6 (100%)	3 (100%)	6 (100%)
Grade 1	0	1 (33.3%)	1 (33.3%)	1 (25.0%)	0	0	0	0
Grade 2	1 (33.3%)	0	1 (33.3%)	0	1 (20.0%)	0	0	1 (16.7%)
Grade 3	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (25.0%)	0	0	0	1 (16.7%)
Grade 4	0	0	0	2 (50.0%)	4 (80.0%)	4 (66.7%)	3 (100%)	2 (33.3%)
Grade 5	1 (33.3%)	1 (33.3%)	0	0	0	2 (33.3%)	0	2 (33.3%)
Total Number of TESAEs*	5	3	0	9	7	17	4	11
Subjects Reporting at Least One SAE, n (%)	2 (66.7%)	1 (33.3%)	0	3 (75.0%)	4 (80.0%)	4 (66.7%)	1 (33.3%)	5 (83.3%)

Subjects Reporting at Least One SAE Grade $\geq 3$ , n (%)	2 (66.7%)	1 (33.3%)	0	3 (75.0%)	4 (80.0%)	4 (66.7%)	1 (33.3%)	5 (83.3%)
CRS toxicity grade, n (%)								
Grade 1	0	0	0	0	0	0	2 (66.7%)	4 (66.7%)
Grade 2	0	0	0	0	1 (20.0%)	1 (16.7%)	0	0
Grade 3	0	0	0	0	0	0	1 (33.3%)	1 (16.7%)
Grade 4	0	0	0	0	0	1 (16.7%)	0	1 (16.7%)
Grade 5	0	0	0	0	0	0	0	0
ICANS severity, n (%)								
Grade 1	0	0	0	0	0	3 (50.0%)	0	1 (16.7%)
Grade 2	0	0	0	0	1 (20.0%)	0	0	0
Grade 3	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	1 (16.7%)	0	2 (33.3%)
Grade 5	0	0	0	0	0	0	0	0
Subjects Reporting at Least One DLT, n (%)	0	0	0	0	0	2 (33.3%)	0	2 (33.3%)

DLT = dose-limiting toxicity; TEAE = Treatment-emergent adverse event. TESAE = Treatment-emergent serious adverse event. CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; mCRPC, metastatic castration-resistant prostate cancer; mPDAC, pancreatic ductal adenocarcinoma.

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NOTES:

- For summary presentation by CTCAE grade, subjects reporting more than one adverse event are counted only once using the highest CTCAE severity.
- Total number for TEAEs and TESAEs does not include adverse events of CRS and neurotoxicity (except for DLTs) as they are presented separately in the table.
- CTCAE grades are scored as: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant; Grade 4 = Life-threatening; Grade 5 = Death related to AE

CRS was graded based on the modified Lee criteria (44). Subjects reporting more than one event are counted once using the highest severity. Neurotoxicity events were graded based on ASTCT (American Society for Transplantation and Cellular Therapy) consensus grading (44).



**Supplementary Table 4. Summary of cases for patients experiencing dose-limiting toxicities in highest dose cohorts with weekly rimiducid**

<b>Cohort 5C: <math>5 \times 10^6</math> cells/kg with weekly rimiducid</b>	
<b>Patient ID</b>	<b>Time course of key events**</b>
Patient: mPDAC-5C-5	<ul style="list-style-type: none"> <li>• Day 0: BPX-601 infusion; decline in performance status to ECOG score of 1 from baseline of ECOG score of 0</li> <li>• Day 4: ECOG score of 2</li> <li>• Day 7: Rimiducid infusion (first dose); ANC nadir of <math>0.2 \times 10^9/L</math></li> <li>• Day 8: Grade 3 febrile neutropenia; G-CSF was given.</li> <li>• Day 9: Afebrile</li> <li>• Day 10: ECOG score of 3</li> <li>• Day 16: Rimiducid infusion (second dose); grade 3 CRS</li> <li>• Day 19: Grade 4 CRS*. He was observed choking on thin liquids and a swallow evaluation confirmed mild oral dysphagia and suspected mild pharyngeal dysphagia. Other adverse events included grade 4 atrial fibrillation with rapid ventricular response. Aspiration pneumonia was confirmed by chest x-ray.</li> <li>• Day 20: Family elected for comfort care only; he died on this day due to sepsis; an autopsy was not performed</li> </ul>
Patient: mPDAC-5C-6	<ul style="list-style-type: none"> <li>• Day 0: BPX-601 infusion; elevations in total and direct bilirubin (2.2 and 1.1 mg/dL)</li> <li>• Day 8: Rimiducid infusion (first dose); grade 2 ICANS; ICE score = 4</li> <li>• Day 9: Grade 3 ICANS*; ICE score = 0. Electroencephalogram and head CT performed with no clinically significant findings.</li> <li>• Day 10: Grade 2 CRS</li> <li>• Day 11: ICANS evolved to grade 4 for a 2-hour period, patient unarousable</li> <li>• Day 12: Improvement in ICANS to grade 3</li> <li>• Day 14: Disease progression confirmed by CT; new bilateral pleural effusions, increase in size and number of the cirrhotic morphology hypodense hepatic masses, and mild dilation of the pancreatic duct</li> <li>• Day 15: Total bilirubin 3.7 mg/dL and direct bilirubin 2.7 mg/dL</li> <li>• Day 18: Total bilirubin 9.3 mg/dL</li> <li>• Day 25: Grade 2 CRS persisted, ICANS improved to grade 2</li> <li>• Day 26: ICANS grade 1</li> <li>• Day 29: Total bilirubin 15.8 mg/dL and direct bilirubin 10.8 mg/dL</li> <li>• Day 33: Total and direct bilirubin peaked at 25.2 and 15 mg/dL</li> </ul>

<p>Patient: mCRPC-5C-3</p>	<ul style="list-style-type: none"> <li>• Baseline: elevated ferritin and serum creatinine (secondary to underlying disease); PSA 307.5 ng/mL</li> <li>• Day -5: Fever</li> <li>• Day -3: CMV reactivation with antivirals modified</li> <li>• Day 0: BPX-601 infusion</li> <li>• Day 1: Grade 1 CRS, resolving 3 days later</li> <li>• Day 7: Rimiducid infusion (first dose)</li> <li>• Day 8: One day following the first dose of rimiducid grade 3 CRS was reported</li> <li>• Day 13: Grade 3 retroperitoneal hemorrhage* in the setting of disseminated intravascular coagulation (DIC) (likely secondary to carHLH). CT for safety evaluation showed tumor shrinkage meeting a RECIST partial response; PSA 39.9 ng/mL</li> <li>• Day 14: Grade 4 ICANS* (7 days following rimiducid administration) with grade 3 carHLH* were reported (bone marrow was not evaluated for confirmation of carHLH); the CRS resolved completely and ICANS resolved to grade 1</li> <li>• Day 15: Last ANC obtained was <math>0.79 \times 10^9/L</math> and absolute lymphocyte count was <math>0.05 \times 10^9/L</math></li> <li>• Day 20: Rapid onset of hypoxia and hypotension developed requiring intubation. The patient experienced cardiac arrest and could not be resuscitated.</li> </ul> <p>Autopsy findings: postmortem blood and bilateral lung cultures were positive for <i>Stenotrophomonas maltophilia</i>; cause of death was overwhelming gram-negative sepsis*; a near complete absence of white pulp in spleen was noted. There was no concern for active CRS or ICANS at the time of death.</p>
<p>Patient: mCRPC-5C-6</p>	<ul style="list-style-type: none"> <li>• Day 0: BPX-601 infusion</li> <li>• Day 1: Grade 1 CRS 1 day following BPX-601 administration, evolving to grade 2 one day later which resolved 3 days following initial CRS symptoms.</li> <li>• Day 11: Rimiducid infusion (first dose)</li> <li>• Day 13: Grade 3 CRS occurred 2 days following the first dose rimiducid administration, manifested by fever, hypoxia and hypotension, resolving within 2 days.</li> <li>• Day 18: Rimiducid infusion (second dose)</li> <li>• Day 19: 1 day following the second dose of rimiducid, the patient once again experienced fever, hypoxia and hypotension and was assessed as having grade 3 CRS</li> <li>• Day 21: Grade 4 CRS*</li> <li>• Day 22: Grade 3 cholecystitis</li> <li>• Day 23: Grade 4 DIC*</li> </ul>

	<ul style="list-style-type: none"><li>• Day 25: Grade 3 carHLH*</li><li>• Day 28: Grade 3 ICANS</li><li>• Day 33: Grade 4 ICANS*; fever; grade 4 sepsis*: a blood culture was positive for <i>Enterococcus faecium</i> and van A/B (vancomycin-resistance gene)</li><li>• Day 39: Family elected comfort measures</li><li>• Day 41: Death; an autopsy was not performed</li></ul> <p>The CRS event was considered resolved 10 days following administration of rimiducid; however, this assessment is confounded due to the patient's experiencing grade 4 DIC on day 23 and grade 3 carHLH on day 25.</p>
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NOTE: \*Adverse events meeting protocol defined DLT-criteria. \*\*All patients received standard-of-care treatment for immune-mediated adverse events. Subject mCRPC-5C-6 was administered emapalumab and ruxolitinib for the management of car-HLH. Anakinra was administered to all patients with ICANS except for subject mPDAC-5C-2.

**Supplementary Table 5. List of Sites, Investigators and IRBs**

The final study protocol and subject informed consent documentation was approved by the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the 15 institutions listed below. Approval from each applicable committee was received in writing before initiation of the study. Below lists the institutional review boards and ethics committees.

Site: Duke University Medical Center  
Investigator: Christopher Hoimes, MD  
Institutional review board or ethics committee: Duke University Health System  
Institutional Review Board, 2200 West Main Street, Suite 900 Erwin Square, Durham, NC 27705

Site: The University of Texas MD Anderson Cancer Center  
Investigator: E. Caterina Dumbrava, MD  
Institutional review board or ethics committee: The University of Texas MD Anderson Cancer Center, Office of Human Subject Protection 7007 Bertner Avenue, Unit 1637, Houston, TX 77030

Site: H. Lee Moffitt Cancer Center and Research Institute  
Investigator: Monica Chatwal, MD  
Institutional review board or ethics committee: Advarra IRB, 6940 Columbia Gateway Drive Suite 110, Columbia MD 21046

Site: The Sarah Cannon Research Institute  
Investigator: Johanna Bendell, MD  
Institutional review board or ethics committee: Western Institutional Review Board, 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

Site: Roswell Park Cancer Institute  
Investigator: Gurkumal Chatta MD  
Institutional review board or ethics committee: Roswell Park Institute Institutional Review Board, Elm & Carlton Streets, Buffalo, New York 14263

Site: Baylor Charles A. Sammons Cancer Center.  
Investigator: Carlos Becerra, MD  
Institutional review board or ethics committee: Baylor Scott & White Research IRB One Baylor Plaza, Houston, Texas 77030

Site: Winship Cancer Institute at Emory University.

Investigator: Mehmet Asim Bilen

Institutional review board or ethics committee: Western Institutional Review Board (WCG IRB), 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

Site: Columbia University Medical Center

Investigator: Mark Stein (formerly Gulam Manji), MD

Institutional review board or ethics committee: CUIMC 154 Haven Avenue, 2nd Floor  
New York, NY 10032

Site: University of Chicago

Investigator: Walter Stadler, MD

Institutional review board or ethics committee: Biological Sciences Division/University of Chicago Medical Center IRB Committee C. 5841 S. Maryland Ave., MC7132, I-625, Chicago, IL 60637

Site: Thomas Jefferson University Investigator: Usama Gergis, MD

Institutional review board or ethics committee: Western Institutional Review Board, 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

Site: John Theurer Cancer Center at Hackensack University Medical Center

Investigator: Martin Gutierrez, MD

Institutional review board or ethics committee: Western Institutional Review Board, 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

Site: Karmanos Cancer Institute

Investigator: Elisabeth Heath, MD

Institutional review board or ethics committee: Western Institutional Review Board (WCG IRB), 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

Site: University of Nebraska Medical Center

Investigator: Benjamin Teply, MD

Institutional review board or ethics committee: University of Nebraska Medical Center, Office of Regulatory Affairs (ORA) Institutional Review Board (IRB) Academic and Research Services Building 3000, 987830  
Nebraska Medical Center, Omaha, NE 68198-7830

Site: Rush University

Investigator: Timothy Kuzel, MD

Institutional review board or ethics committee: Rush University's Office of Research Affairs

Site: Hospital of the University of Pennsylvania

BP-012: Phase 1 Manuscript

Target Journal: Nature Communications – *3 September 2024*

Investigator: Mark O'Hara, MD

Institutional review board or ethics committee: Western Institutional Review Board (WCG IRB), 1019 39th Avenue SE Suite 120, Puyallup, WA 98374

## **A PHASE 1/2 FEASIBILITY, SAFETY, AND ACTIVITY STUDY OF PSCA-SPECIFIC CHIMERIC ANTIGEN RECEPTOR ENGINEERED T CELLS (BPX-601) IN SUBJECTS WITH PREVIOUSLY TREATED ADVANCED SOLID TUMORS**

**Protocol Number:** BP-012

**Investigational Products:** **BPX-601** – Autologous T cells genetically modified with retrovirus vector containing PSCA-specific chimeric antigen receptor (PSCA-CAR) and an inducible MyD88/CD40 (iMC) costimulatory domain.

**Rimiducid** – dimerizer utilized to activate the iMC of the BPX-601 T cells for improved persistence.

**Trial Sponsor:** **Bellicum Pharmaceuticals, Inc.**  
3730 Kirby Dr. Suite 1200,  
Houston, TX 77098

**ClinicalTrials.Gov Number:** NCT02744287

**Version Number:** Amendment 9

**Date:** 09 November 2021

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This document contains information confidential to Bellicum Pharmaceuticals, Inc. and it may not be disclosed to anyone other than recipient study staff and members of Institutional Review Board and Ethical Committees. This information cannot be used for any purpose other than either evaluation or conduct of the clinical study described here without prior written consent from Bellicum Pharmaceuticals, Inc.

## INVESTIGATOR'S AGREEMENT

I have read this protocol and agree to comply with all provisions set forth in this protocol, including all statements regarding confidentiality, and to complete the study within the time designated.

I assume responsibility for the conduct of this study at my study site. I will ensure that I have sufficient resources allocated to this project such that the safety of my subjects is protected at all times and that I complete my obligations to the Sponsor according to the agreed timelines. I will delegate responsibilities only to those who are qualified by training and experience. I will ensure the integrity of the data generated by my team and that all team members are familiar with the study protocol and the study medication.

I agree that I will grant access to the applicable records, my staff allocated to the conduct of this protocol and my facilities for the purposes of monitoring, auditing and any required inspections associated with the conduct of this clinical trial.

I agree to comply with the International Conference on Harmonisation Guideline on Good Clinical Practices, applicable European Medicines Agency regulations and applicable FDA guidelines set forth in 21 Code of Federal Regulations Parts 11, 50, 54, 56, and 312.

Confidential information contained in the protocol document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

\_\_\_\_\_  
Investigator Printed Name

\_\_\_\_\_  
Investigator Signature

\_\_\_\_\_  
Date



## **SPONSOR'S AGREEMENT**

### **Protocol Title:**

A Phase 1/2 Feasibility, Safety, And Activity Study of PSCA-Specific Chimeric Antigen Receptor Engineered T Cells (BPX-601) In Subjects with Previously Treated Advanced Solid Tumors

### **Sponsor Approval:**

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The signature of the Sponsor personnel below constitutes his/her/their agreement and approval of this document.

\_\_\_\_\_  
Sponsor Printed Name

\_\_\_\_\_  
Sponsor Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Sponsor Title

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## PROTOCOL SYNOPSIS

<b>Protocol No.:</b>	BP-012
<b>Protocol Title:</b>	A Phase 1/2 Feasibility, Safety, and Activity Study of PSCA-Specific Chimeric Antigen Receptor Engineered T Cells (BPX-601) in Subjects with Previously Treated Advanced Solid Tumors
<b>Study Phase:</b>	Phase 1/2
<b>Duration of Study:</b>	<p><b>Subject Accrual:</b> Up to 5 years.</p> <p><b>Prescreening:</b> Anytime during routine standard of care.</p> <p><b>Screening:</b> Within 28 days before enrollment.</p> <p><b>Enrollment:</b> At the time of apheresis.</p> <p><b>Baseline:</b> Within 14 days before BPX-601 T cell infusion (includes lymphodepletion [LD]).</p> <p><b>Treatment:</b> Up to 12 Months following BPX-601 T cell infusion on Day 0.</p> <p><b>Post-treatment Follow-Up:</b> Up to 15 Years following BPX-601 T cell infusion.</p>
<b>Number of Subjects:</b>	Up to 160 subjects depending on safety and efficacy results
<b>Number of Sites:</b>	Up to 12
<b>Study Design:</b>	<p>This is a Phase 1/2, multicenter, open-label, nonrandomized study to characterize the feasibility, safety, and clinical activity of BPX-601 T cells with or without rimiducid administered to subjects with previously treated: 1) metastatic advanced solid tumors of the pancreas that express high levels of prostate stem cell antigen (PSCA) and 2) metastatic advanced solid tumors of the prostate. This study will be comprised of multiple parts, beginning initially with Phase 1 (Part 1). Treatment will be administered in an outpatient or inpatient setting, as deemed appropriate by the Investigator and/or per discussion with the Sponsor. Subject safety will be monitored throughout all parts of the study by a safety review team established by the Sponsor.</p> <p><b>Phase 1 (Part 1) is a cell and rimiducid dose/schedule escalation</b> to identify the optimal dose of BPX-601 T cells (escalating doses from <math>1.25 \times 10^6</math> cells/kg up to <math>10 \times 10^6</math> cells/kg) administered by intravenous (IV) infusion on Day 0 with subsequent IV rimiducid either as a single (0.4 mg/kg infused over 2 hours) or weekly (0.4 mg/kg infused over 2 hours, 0.8 mg/kg infused over 4 hours, or 1.6 mg/kg infused over 6 hours) dose starting on Day 7 until disease progression or other treatment discontinuation criteria are met. A lead-in cohort (Cohort 0) was previously completed whereby 3 subjects received BPX-601 T cells (<math>1.25 \times 10^6</math> cells/kg by IV infusion) only. Available safety and biomarker data were reviewed and discussed with FDA prior to proceeding with BPX-601 T cell dose escalation with the addition of rimiducid.</p> <p>Part 1 is designed to identify the recommended phase 2 dose of BPX-601 T cells and the rimiducid dose and infusion duration (RP2D) using a 3+3 dose-escalation design. Dose escalation for BPX-601 T cells and the rimiducid dose and infusion duration will proceed in cohorts of <math>\geq 3</math> and up to 6 subjects until the RP2D is defined. RP2D is represented by the dose of BPX-601 T cells and rimiducid dose and infusion duration that provides adequate T cell persistence and biological activity while not exceeding the maximum tolerated dose (MTD).</p>

	<p>The evaluation period for defining dose-limiting toxicity (DLT) and informing dose escalation decisions is from the start of the BPX-601 T cell infusion (Day 0) through 4 weeks after the first planned rimiducid infusion (ie, Day 35). Dose-limiting toxicity is defined as any of the following unless clearly due to disease progression or extraneous causes:</p> <ul style="list-style-type: none"> <li>• Any treatment-emergent Grade 4 or 5 cytokine release syndrome (CRS)</li> <li>• Any treatment-emergent Grade 3 CRS that does not resolve to Grade <math>\leq 2</math> within 7 days</li> <li>• Grade <math>\geq 3</math> infusion reaction that does not resolve within 7 days</li> <li>• Grade <math>\geq 3</math> organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, neurologic, or autoimmune) not pre-existing or due to the underlying malignancy that does not resolve to Grade <math>\leq 2</math> within 7 days.</li> </ul> <p><b>Phase 2 (Parts 2 and 3) is an indication-specific dose expansion</b> to further assess safety, pharmacodynamics (including BPX-601 T cell persistence), and clinical activity of BPX-601 T cells administered at the RP2D with rimiducid. Part 2 will begin once a RP2D is determined in Part 1. Ten subjects, including those treated at the RP2D in Part 1, will be enrolled based on tumor type (pancreas and prostate; Part 2). Within each group, subjects will be monitored for clinical response to enable early stopping for futility if sufficient antitumor activity is not demonstrated. If no responses are observed in the first 10 subjects for a given indication, no further subjects with that tumor type will be enrolled.</p> <p>For subjects with pancreatic cancer, response will be defined according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For subjects with prostate cancer, response will be defined according to RECIST v1.1 or Prostate Cancer Working Group 3 (PCWG3), or a prostate specific antigen (PSA) decline <math>\geq 50\%</math> from baseline measured twice <math>\geq 3</math> to 4 weeks apart. If 1 or more responses are observed, the Sponsor may elect to open Part 3 of study to enroll up to an additional 30 subjects with the tumor type of interest. For each indication, up to 40 total subjects may be enrolled (Parts 2 and 3 combined).</p>
<b>Study Objectives</b>	<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>• <b>Phase 1:</b> To determine the safety, tolerability, and MTD and/or recommended Phase 2 dose/schedule (RP2D) of BPX-601 T cells and rimiducid to subjects with advanced solid tumors</li> <li>• <b>Phase 2:</b> To evaluate the antitumor activity of BPX-601 T cells administered with rimiducid in select solid tumor</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>• To characterize the safety and tolerability of BPX-601 T cells administered with rimiducid at the RP2D</li> <li>• To characterize the pharmacokinetics (PK) of rimiducid</li> <li>• To evaluate the clinical efficacy of BPX-601 T cells administered with rimiducid in select solid tumor types</li> <li>• To assess the long-term safety of BPX-601 T cells</li> </ul> <p><b>Exploratory Objectives:</b></p> <ul style="list-style-type: none"> <li>• To assess the immunogenicity of BPX-601 T cells</li> </ul>



	<ul style="list-style-type: none"> <li>• To characterize the pharmacodynamics of BPX-601 T cells administered with and without rimiducid (eg, expansion and persistence of peripheral BPX-601 T cells over time)</li> <li>• To explore the relationship between rimiducid PK and BPX-601 T cell pharmacodynamic biomarkers as applicable (eg, BPX-601 T cell persistence, phenotyping, functional activity, tumor infiltration) and genetic and/or protein profiles in tumor tissue and peripheral blood</li> <li>• To explore the relationship between tumor tissue/blood-based immune biomarkers, including serum cytokines, and clinical response or resistance to BPX-601 T cells</li> <li>• To describe the PSCA expression level on tumor cells before chimeric antigen receptor (CAR) T cell infusion, and the relationship it may have with disease response and observed toxicities.</li> </ul>
<b>Inclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Each subject must sign and date an informed consent form (ICF) approved by the Institutional Review Board/Ethics Committee, as appropriate, indicating that he/she understands the purpose of and procedures required for the study and are willing to comply. Consent is to be obtained prior to the performance of any study-specific procedures or tests that are not part of the standard of care for the subject's disease.</li> <li>2. Histologically or cytologically confirmed diagnosis of 1 of the following: <ul style="list-style-type: none"> <li>• Metastatic pancreatic ductal adenocarcinoma (PDAC) with disease progression during or within 6 months of the most recent anti-cancer treatment <ul style="list-style-type: none"> <li>– Prior treatment with first or second-line therapy including targeted immunotherapy. Subjects eligible for approved targeted therapy based on microsatellite instability high/deficient mismatch repair status and/or gene profiling should have received such therapy as appropriate unless contraindicated. Subjects with mixed histology may be included if the predominant component is adenocarcinoma.</li> <li>– Measurable disease (<math>\geq 1</math> target lesion) per RECIST v1.1 at Baseline (<a href="#">Eisenhauer 2009</a>).</li> <li>– Documented positive tumor expression of PSCA as determined by central testing of an available, representative tissue specimen (formalin-fixed paraffin-embedded tissue, either from an archived sample or fresh biopsy).</li> </ul> </li> <li>• Metastatic castration-resistant adenocarcinoma of the prostate (CRPC) defined as serum testosterone level <math>\leq 50</math> ng/dL with prior surgical castration or ongoing androgen deprivation, with progressive disease: <ul style="list-style-type: none"> <li>– Progressive disease is defined by rising PSA or radiographic imaging according to the PCWG3 criteria (<a href="#">Scher 2016</a>) during or following the direct prior line of therapy in the setting of medical or surgical castration</li> <li>– At least 2 prior therapies including a standard <math>17\alpha</math> lyase inhibitor or second-generation anti-androgen therapy for the treatment of castrate resistant prostate cancer</li> <li>– Must have measurable disease by RECIST v1.1 or bone only metastases with measurable PSA (<math>\geq 1</math> ng/mL) at Baseline</li> </ul> </li> </ul> </li> </ol>

	<ol style="list-style-type: none"> <li>3. Age <math>\geq 18</math> years.</li> <li>4. Life expectancy <math>&gt; 12</math> weeks.</li> <li>5. Agreement to consent to a pretreatment as well as on treatment, fresh tumor biopsy where tissue collection is clinically feasible.</li> <li>6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (<a href="#">Appendix 2</a>).</li> <li>7. Subjects must have adequate venous access for apheresis or agree to use of a central line for apheresis collection.</li> <li>8. Subject has adequate organ function: <ul style="list-style-type: none"> <li><b>Cardiac:</b> Left ventricular ejection fraction at rest must be <math>\geq</math> lower limit of institutional normal</li> <li><b>Coagulation:</b> International normalized ratio <math>\leq 1.5</math></li> <li><b>Hematologic:</b> <ul style="list-style-type: none"> <li>• White blood cell count <math>\geq 2 \times 10^3/\mu\text{L}</math></li> <li>• Absolute neutrophil count <math>\geq 1 \times 10^3/\mu\text{L}</math> without granulocyte colony stimulating factor support</li> <li>• Platelets <math>\geq 100 \times 10^3/\mu\text{L}</math></li> <li>• Hemoglobin <math>\geq 9</math> g/dL</li> </ul> </li> <li><b>Hepatic:</b> <ul style="list-style-type: none"> <li>• Direct bilirubin <math>\leq 1.5 \times</math> upper limit of normal (ULN), or <math>\leq 3 \times \text{ULN}</math> if due to Gilbert's disease</li> <li>• Aspartate aminotransferase and alanine aminotransferase <math>\leq 2.5 \times \text{ULN}</math>, or <math>\leq 5 \times \text{ULN}</math> if liver metastases are present</li> </ul> </li> <li><b>Renal:</b> Creatinine <math>\leq 1.5 \times \text{ULN}</math> or a calculated glomerular filtration rate <math>&gt; 50</math> mL/min/1.73mm<sup>2</sup></li> </ul> </li> <li>9. From the time of Screening/Study Treatment ICF signature, a female subject must be either: <ul style="list-style-type: none"> <li>• Not of childbearing potential defined as: <ol style="list-style-type: none"> <li>(1) Premenarchal</li> <li>(2) Postmenopausal (<math>&gt; 45</math> years of age with amenorrhea <math>\geq 12</math> months)</li> <li>(3) Permanently sterilized</li> <li>(4) Otherwise incapable of pregnancy.</li> </ol> </li> <li>• Of childbearing potential and agrees to use 2 highly effective methods of birth control (<a href="#">Effectiveness of Contraception Methods, Centers for Disease Control and Prevention [CDC] 2018</a>) for <math>\geq 12</math> months after LD.</li> </ul> </li> <li>10. From the time of Screening/Study Treatment ICF signature, male subjects with female partners of childbearing potential must agree to use 2 highly effective methods of birth control (<a href="#">Effectiveness of Contraception Methods, CDC 2018</a>) from the time of Screening/Study Treatment ICF signature until <math>\geq 12</math> months after LD.</li> </ol>
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<p><b>Exclusion Criteria:</b></p>	<ol style="list-style-type: none"> <li>1. Pancreatic cancer subjects with: <ul style="list-style-type: none"> <li>• Islet cell neoplasms</li> <li>• Clinical or radiographic evidence of deep vein thrombosis, pulmonary embolism, or other known thromboembolic event that has not been definitely treated. Subjects with prior history of coagulopathy must be asymptomatic within 4 weeks of enrollment.</li> </ul> </li> <li>2. Prostate cancer subjects with: <ul style="list-style-type: none"> <li>• Structurally unstable bone lesions suggesting impending fracture</li> <li>• Clinical or radiographic evidence of deep vein thrombosis, pulmonary embolism, or other known thromboembolic event that has not been definitely treated. Subjects with prior history of coagulopathy must be asymptomatic within 4 weeks of enrollment.</li> <li>• History of Grade <math>\geq 2</math> hematuria within the previous 6 months.</li> </ul> </li> <li>3. Symptomatic, untreated, or actively progressing central nervous system metastases. Subjects with prior brain metastases treated <math>\geq 2</math> weeks before the planned infusion who are clinically stable and do not require chronic corticosteroid treatment are allowed.</li> <li>4. History or presence of clinically relevant central nervous system pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or leptomeningeal disease.</li> <li>5. Ongoing toxicities related to prior anticancer therapy that have not resolved to Grade <math>\leq 1</math>. Current unresolved Grade <math>\geq 2</math> nonhematologic toxicity may be allowed following discussion with and approval by the Sponsor.</li> <li>6. Participation in any investigational drug study within 4 weeks before enrollment.</li> <li>7. Chemotherapy, targeted therapy, or radiotherapy (excluding palliative radiation) within 2 weeks or 5 half-lives, whichever is shorter, or immunotherapy within 4 weeks before enrollment (Note, salvage chemotherapy as clinically indicated may be administered following apheresis and before LD as described in <a href="#">Section 7.7</a>).</li> <li>8. Prior CAR T cell or other genetically-modified T cell therapy. Prior treatment with an immune-based therapy for the treatment of prostate cancer, including cancer vaccine therapies (such as Sipuleucel-T, PROSTVAC) are allowable. Immune checkpoint inhibitors, radium-223 and immunoconjugate therapies are also allowable pending discussion with the Sponsor.</li> <li>9. Any disease requiring chronic immunosuppressive therapy.</li> <li>10. Impaired cardiac function or clinically significant cardiac disease, including any of the following: <ul style="list-style-type: none"> <li>• Symptomatic congestive heart failure requiring treatment</li> <li>• Clinically significant cardiac arrhythmia</li> <li>• Uncontrolled hypertension</li> </ul> </li> </ol>
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	<ul style="list-style-type: none"> <li>• Acute myocardial infarction or unstable angina pectoris within 3 months before enrollment</li> <li>• QT interval corrected for heart rate using Fredericia's formula (QTcF) &gt;480 msec</li> <li>• Marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort (ie, New York Heart Association Functional Class III-IV; <a href="#">Appendix 3</a>).</li> </ul> <ol style="list-style-type: none"> <li>11. Major surgical procedure, other than for diagnosis, within 4 weeks prior enrollment, or anticipation of the need for a major surgical procedure during the study.</li> <li>12. Received a vaccine containing live virus within 4 weeks before enrollment. Seasonal flu vaccines that do not contain live virus are permitted.</li> <li>13. Treatment with systemic chronic steroid therapy (prednisone of <math>\geq 10</math> mg/day or equivalent) within 7 days or 7 half-lives of the prescribed corticosteroid, whichever is shorter, before the planned apheresis date (refer to <a href="#">Appendix 4</a> on half-lives of common corticosteroids).</li> <li>14. Uncontrolled intercurrent illness including but not limited to poorly controlled hypertension or diabetes, or any medical condition determined by the Investigator to be a risk for enrolling on the protocol.</li> <li>15. Untreated or active infection at the time of initial Screening, at the time of leukapheresis, or within 72 hours before LD. Prior oral or IV antibiotics, antifungals, or antiviral medications must be discontinued <math>\geq 2</math> weeks before BPX-601 T cell infusion except for use of prophylactic antimicrobial agents.</li> <li>16. Active hepatitis B, active hepatitis C, or any human immunodeficiency virus (HIV) infection at the time of Screening: <ul style="list-style-type: none"> <li>• Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen test during Screening. Subjects with a past or resolved HBV infection, defined as having a negative hepatitis B surface antigen test and a positive total hepatitis B core antibody test at screening are eligible for the study if HBV DNA test is negative. If a subject has a negative hepatitis B surface antigen test and a positive total hepatitis B core antibody test at screening, an HBV DNA test should be performed.</li> <li>• Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test during Screening. The HCV RNA test will be performed only for subjects who have a positive HCV test.</li> </ul> </li> <li>17. Subject is a woman of child-bearing potential and is pregnant (positive serum <math>\beta</math>-human chorionic gonadotropin test at Baseline), planning to become pregnant within 12 months after LD, or is breastfeeding.</li> <li>18. Subject is a man who plans to donate sperm or father a child within 12 months after LD.</li> <li>19. Known bovine product allergy.</li> <li>20. Malignant disease other than that being treated in this study. Exceptions to this exclusion are:</li> </ol>
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	<ul style="list-style-type: none"><li>• Malignancies that were treated curatively and have not recurred within 2 years before Screening</li><li>• Completely resected basal cell or squamous cell skin cancers</li><li>• Any malignancy considered to be indolent and that has never required therapy</li></ul> <p>21. Any other clinically significant disease or co-morbidity which may adversely affect the safe delivery of treatment within this trial.</p>
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## LIST OF ABBREVIATIONS AND TERMS

<b>Abbreviation</b>	<b>Definition</b>
$\alpha$	alpha chain of TCR
ACTB	actin beta
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP-1	activator protein-1
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
$\beta$	beta chain of TCR
CAR	chimeric antigen receptor
CD3 $\zeta$	CD3 zeta chain
CEA	carcinoembryonic antigen
CDC	Centers for Disease Control and Prevention
CID	chemical inducer of dimerization, rimiducid
C <sub>max</sub>	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	electroencephalogram
EOT	end-of-treatment
FDA	Food and Drug Administration
FKBP	FK binding protein
Flu/Cy	fludarabine plus cyclophosphamide
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HIV	human immunodeficiency virus
hr	hour(s)
HTLV	human t-lymphotropic virus
HUS	hemolytic-uremic syndrome
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	Informed Consent Form
IEC	immune effector cells
ICH	International Conference on Harmonisation

<b>Abbreviation</b>	<b>Definition</b>
ICU	intensive care unit
IFN	interferon
IL	interleukin
iMC	inducible MyD88/CD40
IND	Investigation New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRF-7	interferon regulatory factor 7
IV	intravenous(ly)
kg	kilogram
LD	lymphodepletion
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LTR	long terminal repeat
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute(s)
mm	millimeter
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
MyD88	myeloid differentiation primary response 88
NCI	National Cancer Institute
NFATc	nuclear factor of activated t cells cytoplasmic-1
NF- $\kappa$ B	nuclear factor kappa-light-chain-enhancer of activated b cells
ng	nanogram
NOAEL	no observed adverse effect level
NT	nontransduced T cells
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCWG	prostate cancer working group
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PK	pharmacokinetics
PR	partial response
PSA	prostate specific antigen
PSCA	prostate stem cell antigen
PT	prothrombin time
PTT	partial thromboplastin time
qPCR	quantitative polymerase chain reaction
QTcF	qt interval corrected for heart rate using Fredericia's formula
QW	once weekly
RCR	replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
Rim	rimiducid
RP2D	recommended phase 2 dose
scFv	single-chain variable fragment

<b>Abbreviation</b>	<b>Definition</b>
SAE	serious adverse event
SBP	systolic blood pressure
SD	stable disease
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TCR	T cell receptor
TNF	tumor necrosis factor
TTP	thrombotic thrombocytopenic purpura
μL	microliter
ULN	upper limit of normal

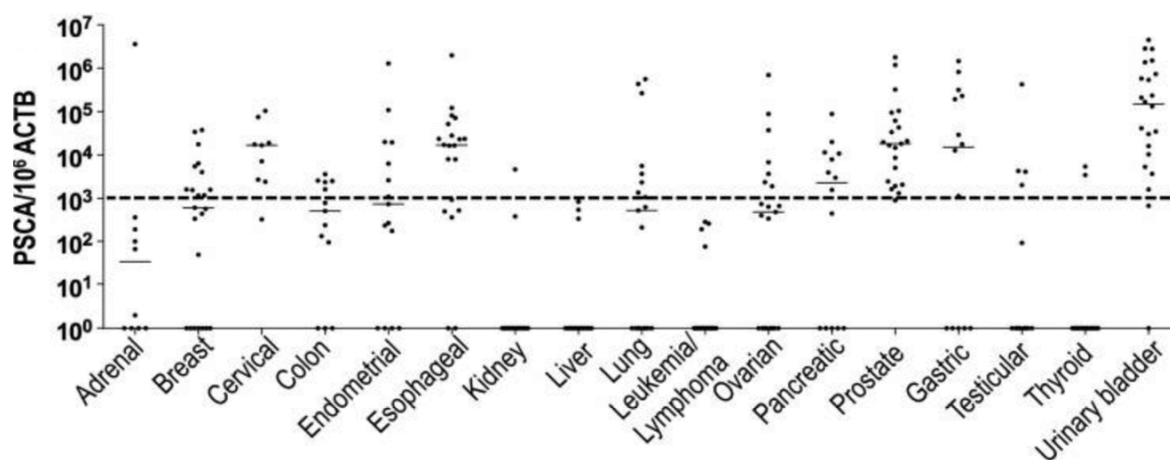


## 1 INTRODUCTION

### 1.1 Prostate Stem Cell Antigen (PSCA) as a Therapeutic Target

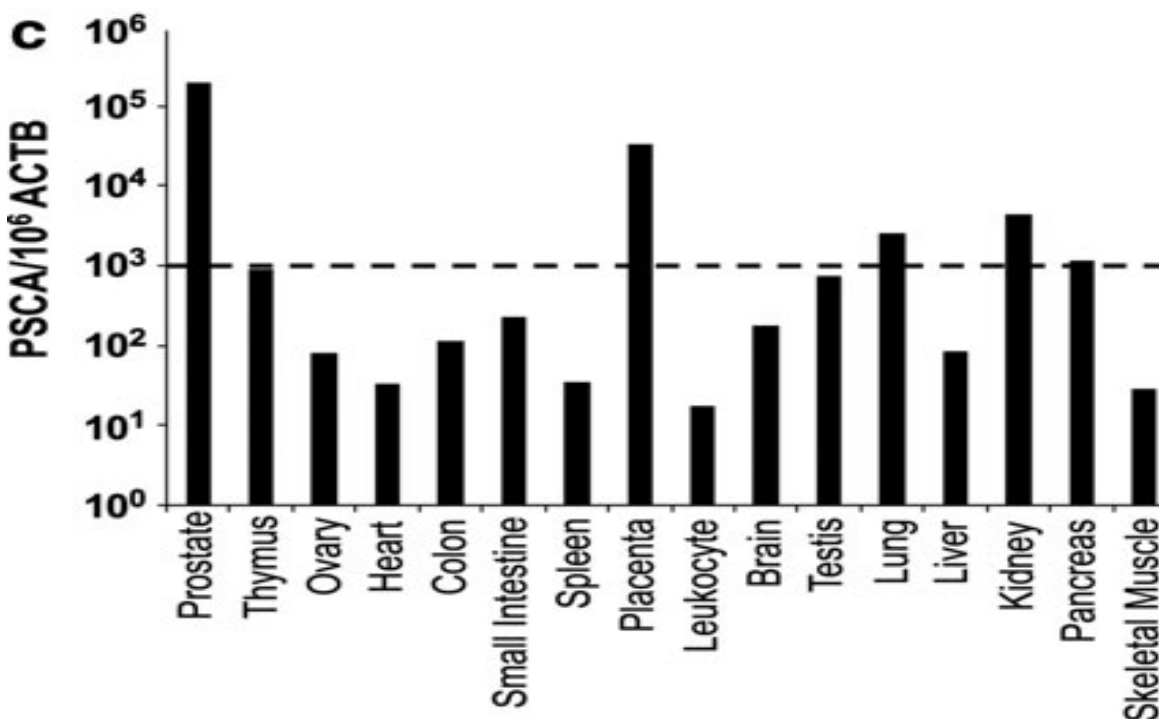
Prostate stem cell antigen (PSCA) is a glycosylphosphatidylinositol-anchored cell surface protein with 123 amino acids. PSCA has low expression in normal epithelial cells of prostate, urinary bladder, kidney, skin, esophagus, stomach, and placenta. Conversely, PSCA is upregulated in cancers of the pancreas, prostate, stomach, ovary, and bladder and expression is positively correlated with advanced clinical stage and metastasis in prostate cancers (Figure 1; Abate-Daga 2014; Kim 2017; Saeki 2010).

**Figure 1 PSCA RNA Expression in Tumor Tissues**



There are normal tissues that have low to moderate levels of PSCA RNA expression that are well-differentiated from tumors in those tissues with high levels of PSCA RNA (eg: pancreatic and ovarian cancers). Alternatively, there are tumor tissues noted to have a high prevalence of PSCA expression (>80%) with a high level of PSCA RNA, such as prostate, where normal cells also have a moderate to high levels of PSCA RNA (Figure 2; Abate-Daga 2014). Current RNA-based assays (eg, in situ hybridization, polymerase chain reaction [PCR]) have not been successful in delineating PSCA expression in normal versus tumor cells, making prospective selection of subjects who may benefit from therapies targeting PSCA a challenge. In this study, due to the high prevalence of PSCA expression in prostate tumors, subjects will not be selected using prospective prescreening for PSCA RNA expression. Tumor samples from enrolled subjects with prostate cancer will be analyzed for PSCA expression retrospectively with PSCA levels correlated to clinical outcome and any relevant observed toxicities. The goal will be to establish a selection algorithm based upon PSCA expression for subjects with PSCA plus prostate cancer.

**Figure 2 PSCA RNA Expression in Normal Tissues**



Abbreviations: ACTB = actin beta; PSCA = prostate stem cell antigen.

Therefore, PSCA represents a potential target for anticancer immunotherapy. The safety and clinical activity of PSCA-directed monoclonal antibodies (AGS-1C4D4 or AGS-PSCA) has been previously evaluated in Phase I and II clinical trials for the treatment of advanced pancreatic ([NCT00902291](#)) and prostate cancers ([Antonarakis 2012](#); [Morris 2012](#)), respectively. In about 200 subjects, treatment with an anti-PSCA antibody showed low toxicity at doses up to 48 mg/kg and modest efficacy. This favorable safety profile was attributed to the limited expression of PSCA on normal tissue, which may help to reduce on-target, off-tumor side effects. Together, these data provide clinical evidence that PSCA is a relevant target of interest for therapeutic intervention.

## 1.2 PSCA-Expressing Solid Tumors with Significant Unmet Medical Need

Current data show that the PSCA is expressed in over 50% of pancreatic ductal adenocarcinomas (PDAC) and in >80% of prostate cancers ([Abate-Daga 2014](#); [Shaw 2020](#)). The increased level of expression in prostate cancer patients is associated with a higher Gleason score, higher tumor state, and progression to androgen independent disease ([Gu 2000](#)).

### 1.2.1 Pancreatic Cancer

Pancreatic ductal adenocarcinoma is the fourth most common cause of cancer-related death in the United States (Siegel 2017). Because it is typically diagnosed at an advanced stage, survival is poor (<1 year), the population distribution of those who die of pancreatic cancer is similar to those who are diagnosed with the disease. It is estimated that 57,600 new cases will be diagnosed and 47,050 people will die of pancreatic adenocarcinoma in 2020 (SEER 2020). Radiographic imaging, liver function testing, and levels of circulating tumor biomarkers (CA 19-9) are the primary means used for diagnosis and staging.

Surgical resection is the only potentially curative therapy for managing resectable and borderline resectable pancreatic cancer. However, the disease is often difficult to detect in these early stages, and many patients are not diagnosed until the disease has already progressed to an unresectable state, becoming either locally advanced or with distant metastases. For subjects with previously untreated, locally advanced or metastatic disease and good performance status, combination chemotherapy remains the standard of care. Although randomized clinical trials have shown a survival advantage for both FOLFIRINOX and gemcitabine in combination with nab-paclitaxel as first-line therapy, median overall survival remains <12 months and treatment-related severe toxicity (notably myelosuppression and peripheral neuropathy) is common. These data highlight the need to develop safe and effective second-line therapies beyond current standards of care and especially for patients unwilling to receive or intolerant to chemotherapy including nanoliposomal irinotecan, immune-targeted therapy such as pembrolizumab or molecularly targeted therapies (eg, olaparib) (Conroy 2011, Von Hoff 2013, Tempero 2019).

### 1.2.2 Prostate Cancer

Prostate cancer is the most common, noncutaneous cancer in men in the United States (Litwin 2017). In 2020, an estimated 191,930 men will be diagnosed with prostate cancer, which is the second leading cause of cancer death in men with an estimated annual death rate of 33,330 (SEER 2020). Diagnosis is typically made by ultrasound guided needle biopsy. The histological pattern is scored using the Gleason system.

For men with metastatic prostate cancer, androgen deprivation therapy with or without docetaxel is the first line of treatment (Sweeney 2015, James 2016, Litwin 2017). In patients whose metastatic prostate cancer becomes unresponsive to androgen deprivation therapy (ie, castration-resistant), other agents that block the androgen pathway (abiraterone, enzalutamide) may slow disease progression, improve survival, and improve quality of life (de Bono 2011, Scher 2012, Ryan 2013, Beer 2014). Other novel agents such as sipuleucel-T, an autologous cellular therapy (Kantoff 2010, Schellhammer 2013), and cabazitaxel (de Bono 2011), a taxane, may be incorporated into the treatment. Other agents such as denosumab, zoledronic acid, or radium Ra 223 dichloride may be used for protection or treatment of bone-metastases and skeletal -related events (Beer 2014, Parker 2013). While improvements have been made with the advent of these therapies, survival is limited for patients with recurrent metastatic prostate cancer. Overall survival rates for patients with recurrent disease following chemotherapy ranges from 13 to 18 months (Mehtala 2020).

### 1.2.3 PSCA Expression Testing for Study Subjects

#### ***Pancreatic Ductal Adenocarcinomas***

PSCA is expressed in over 50% of PDACs (Abate-Daga 2014, Shaw 2020). In this study the PSCA expression status of pancreatic cancer subjects will be assessed by central testing of a tissue specimen that is formalin-fixed and paraffin-embedded, either from an archived sample or fresh biopsy (Section 8.3.14.1) before enrollment.

#### ***Prostate Cancer***

PSCA is expressed in over 80% of prostate cancers, with 88-94% in primary tumors and 87-100% in bone metastases. Increased expression of PSCA is also correlated with higher Gleason score, higher tumor stage, grade, and androgen-independent disease (Gu 2000; Lam 2005). These results are supported by data from Ruan (2012) who showed 85% of primary tumor samples stained moderate to strong by immunofluorescence histochemistry and immunohistochemistry with positive results correlated to increased Gleason score. In addition, Zhigang (2004) investigated primary prostate tissue samples by both immunohistochemistry and in situ hybridization techniques. They observed an 84% rate of moderate to high intensity staining that increased with Gleason score, tumor stage and androgen independence. Evaluation of PSCA expression in primary and metastatic prostate cancer reported by Gu (2000) and Lam (2005) was carried out by immunohistochemistry using the murine monoclonal antibody clone 1G8. The single-chain variable fragment incorporated into the BPX-601 T cell product was derived from a humanized 1G8 antibody (Olafsen 2007) and therefore recognizes a similar epitope.

The majority of published data on PSCA protein expression in normal prostate tissue supports the conclusion that expression is at best limited. Ruan (2012) demonstrated by immunohistochemistry that 85% of tissue samples from patients with benign prostatic hyperplasia were negative or stained only weakly for PSCA and Ross (2002) using *in situ* hybridization observed a 76% rate of negative or 1<sup>+</sup> staining samples from benign prostatic hyperplasia samples. In addition, testing of 20 normal prostate tissue samples for which both *In situ* hybridization and immunohistochemistry expression of PSCA RNA and protein was observed, Zhigang (2004) reported weak to negative staining by both methods in 14 of 20 samples. In only 4 samples was staining by both methods at best moderate and, notably, 2 samples demonstrated moderate RNA expression with weak/negative protein expression suggesting some level of disconnect between these 2 processes.

As of the date of this protocol amendment, no severe or uncontrolled antigen-directed toxicities targeting normal prostate tissue have been observed in subjects treated with BPX-601 T cells. A total of 8 adverse events (AEs) in the Renal and Urinary Disorders System Organ Class have been reported. Hematuria and dysuria have each been reported 4 times. One event of hematuria was Grade 3. None of the events were considered serious adverse events (SAEs) (BPX-601 Investigator's Brochure [IB]). The lack of prostate-specific AEs is consistent with the observation that there is limited expression of PSCA protein antigen in normal prostatic tissues as noted above (Ruan 2012, Ross 2002). Based on these data, Bellicum believes enrollment of subjects with prostate cancer without prospective PSCA expression testing is appropriate (Section 1.4.2). Tissue specimens from subjects will

potentially be tested retrospectively for PSCA expression to evaluate the need to prescreen subjects with prostate cancer in the future.

### **1.3 PSCA-targeted CAR-T Cells (BPX-601 T cells) and Rimiducid**

BPX-601 T cells are a PSCA-directed, genetically modified, autologous GoCAR-T<sup>®</sup> cell product candidate that binds to PSCA-expressing cells (see [BPX-601 IB](#) for more information). In addition to the PSCA chimeric antigen receptor (CAR), BPX-601 T cells contain an activation switch (inducible myeloid differentiation primary response 88 [MyD88]/CD40 [iMC]), inducible by the small molecule dimerizer rimiducid (see [Rimiducid IB](#) for more information).

Nonclinical data with this first-in-clinic, controllable GoCAR-T<sup>®</sup> cell product candidate show enhanced T cell proliferation, persistence and in vivo antitumor activity compared to traditional CAR T therapies ([Foster 2017](#), [Mata 2017](#), [Duong 2019](#), [Wang 2020](#)). To date, meaningful clinical activity of traditional CAR T cell immunotherapy has been limited to hematologic malignancies whereas efficacy in solid tumor indications is thought to be limited by generally low CAR T cell persistence and therefore a lack of sustained antitumor activity over time. It is hypothesized that the addition of an inducible “on” switch to BPX-601 T cells provides a controlled activation and proliferation signal, thereby not only improving the persistence of modified T cells but also prolonging the potential for antitumor efficacy.

For the most comprehensive nonclinical and clinical information regarding BPX-601 T cells and rimiducid, refer to the latest version of the IB for each product ([BPX-601 IB](#), [Rimiducid IB](#)).

### **1.3.1 BPX-601 T cells**

BPX-601 T cells are a PSCA-directed, genetically modified, autologous GoCAR-T<sup>®</sup> cell product candidate that binds to PSCA-expressing cells. BPX-601 T cells target PSCA with a first-generation CAR construct containing a traditional cluster of differentiation zeta chain (CD3 $\zeta$ ) cytoplasmic signaling domain together with a single-chain variable fragment of the humanized PSCA A.11 antibody ([Figure 3](#), [Lepin 2010](#), [Foster 2017](#)). In addition to the anti-PSCA CAR, BPX-601 T cells are engineered to express an inducible dual co-stimulatory domain comprised of 2 FK binding proteins (FKBP) in-frame with the signaling domains from MyD88 and CD40 (iMC).

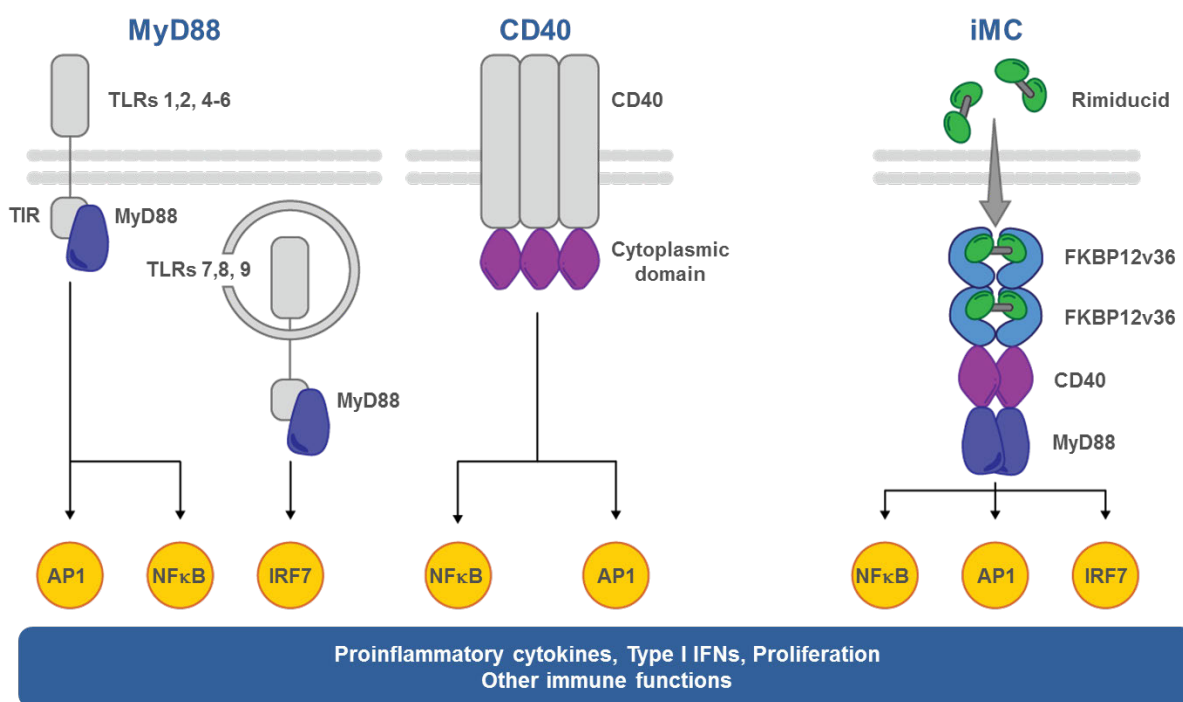
The rationale for the molecular design as well as the in vitro and in vivo characterization of this inducible activation domain are described elsewhere ([Narayanan 2011](#)).

iMC functions as a molecular switch to enhance and control the activation and proliferation of T cells in the presence of the small molecule dimerizer rimiducid (Figure 4). The tandem FKBP domains provide a ligand dimerization scaffold, which induces iMC in a rimiducid -dependent manner (Narayanan 2011) to initiate downstream signaling pathways that upregulate proinflammatory cytokines and type I interferons (IFNs) as well as promote cell proliferation and survival (Foster 2017).

Thus, BPX-601 T cells have been rationally designed to proliferate in response to distinct signals (Figure 5):

- Antigen-specific activation through PSCA recognition and CD3 $\zeta$  signaling domain (Signal 1)
- Rimiducid-dependent co-stimulation through iMC (GoCAR-T® cells) (Signal 2)

**Figure 4 Co-opting MyD88 and CD40 Signaling Pathways to Generate Inducible Costimulation**



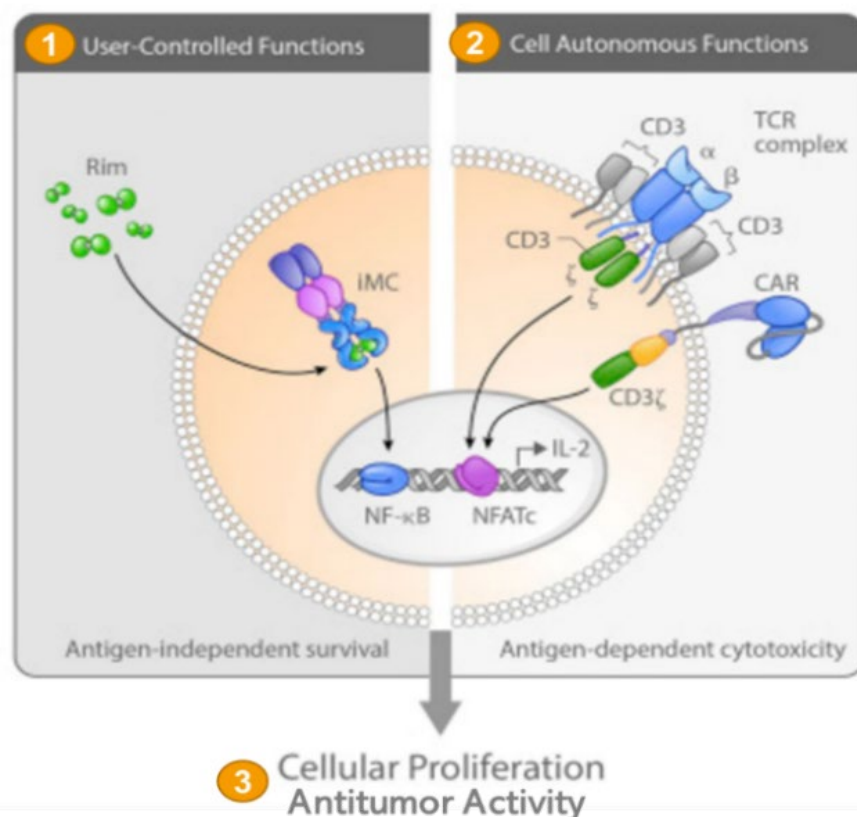
Abbreviations: AP-1 = activator protein-1; FKBP = FK506-binding protein; iMC = Inducible-MyD88/CD40; IRF-7 = interferon regulatory factor 7; NFκB = nuclear factor kappa B

Adapted from Foster 2017.



It is hypothesized that this GoCAR-T<sup>®</sup> cell design optimizes BPX-601 T cells for both antigen-directed as well as antigen-independent T cell activation, proliferation, and persistence and thereby may afford enhanced clinical activity relative to traditional CARs for the treatment of solid tumor malignancies (Signal 3; [Figure 5](#)).

**Figure 5 T Cells Engineered with Inducible Costimulation**



Abbreviations:  $\alpha$  = alpha chain of TCR;  $\beta$  = beta chain of TCR; CAR = chimeric antigen receptor; CD3 = cluster of differentiation 3; CD3 $\zeta$  = CD3 zeta chain (signaling domain of the TCR); IL-2 = interleukin 2; iMC = inducible MyD88/CD40 molecule; MyD88 = myeloid differentiation primary response 88; NFATc = nuclear factor of activated T cells cytoplasmic-1; NF- $\kappa$ B = nuclear factor kappa-light-chain-enhancer of activated B cells; Rim = rimiducid; TCR = T cell receptor.

Adapted from [Foster 2017](#).

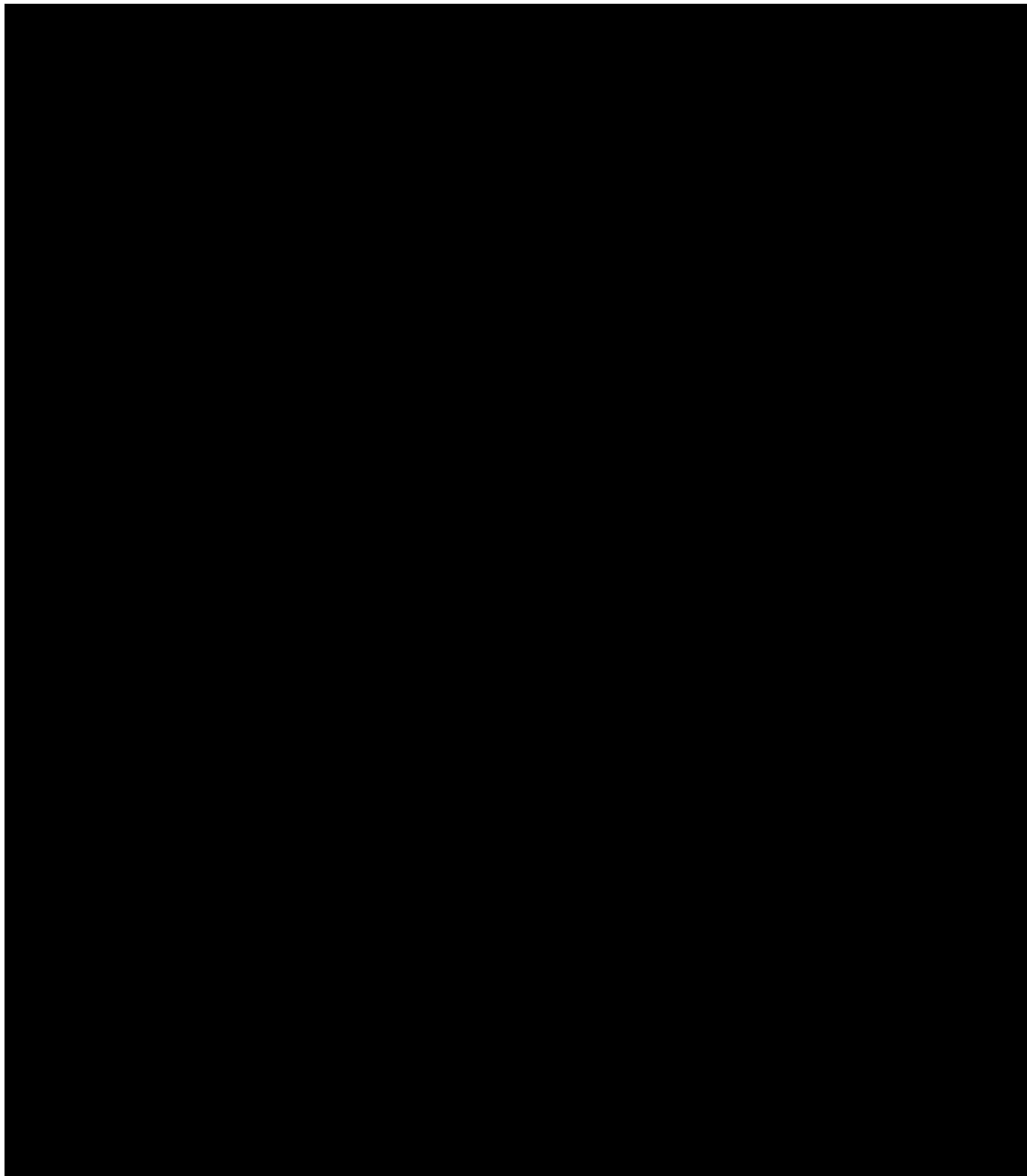
### 1.3.2 Rimiducid: Dimerizer Drug

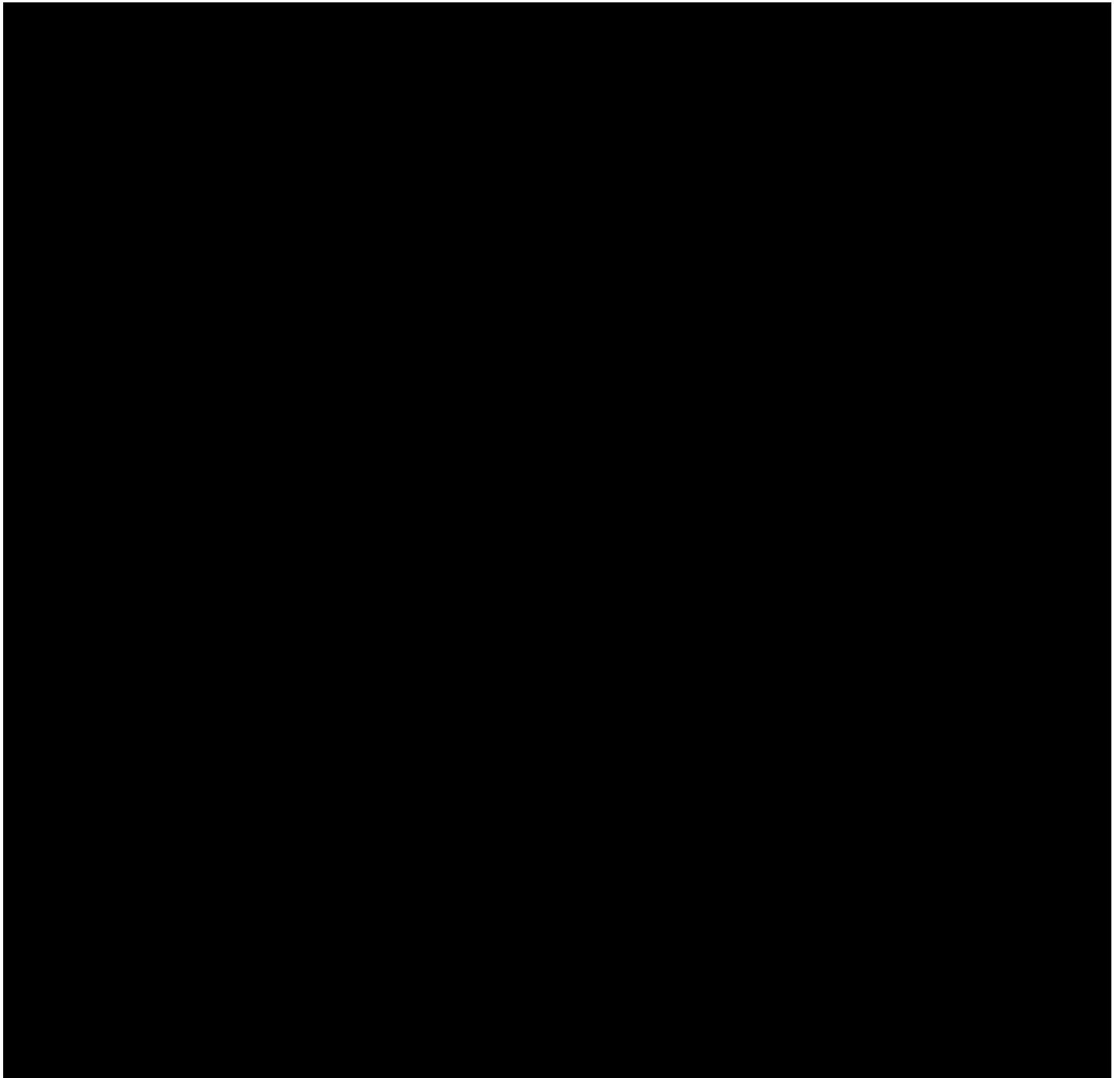
Rimiducid is a member of a class of synthetic lipid-permeable compounds termed chemical inducers of dimerization. Rimiducid is a small molecule, high affinity ligand (~0.1 nM) that functions to promote cross linking and activation of engineered proteins inside cells. By chemical design, rimiducid has no known natural biologic target; ligand binding is restricted to a mutated signaling domain of the human protein FKBP.



#### **1.4 Summary of Nonclinical Experience**

For the most comprehensive nonclinical information regarding BPX-601 T cells and rimiducid, refer to the latest version of the IB for each product ([BPX-601 IB](#), [Rimiducid IB](#)).







### **1.5 Summary of BPX-601 T Cells Plus Rimiducid Clinical Experience**

For the most comprehensive clinical information regarding BPX-601 T cells and rimiducid, refer to the latest version of the IB for each product ([BPX-601 IB](#), [Rimiducid IB](#)).

## 2 STUDY RATIONALE

The purpose of the current trial is to determine the feasibility, safety, and clinical activity of BPX-601 T cells with rimiducid in subjects with previously treated, PSCA-positive advanced pancreatic and prostate tumors.

This protocol amendment (Version 9.0) plans to introduce optimization of BPX-601 T cells and rimiducid dosing and infusion time. Once the safety of the BPX-601 T cell dose in combination with the rimiducid once weekly (QW) regimen at a dose of 0.4 mg/kg infused over 2 hours is established in Cohort 5C ( $5 \times 10^6$  cells/kg, a previously cleared dose of cells and single dose of rimiducid in Cohorts 5A and 5B), Cohorts 6 and 7 may be explored to evaluate rimiducid doses of 0.8 mg/kg infused over 4 hours and 1.6 mg/kg infused over 6 hours, respectively, and Cohorts 8 and 9 to evaluate BPX-601 T cell doses of  $7.5 \times 10^6$  and  $10 \times 10^6$  cells/kg, respectively, in combination with rimiducid at a dose of 1.6 mg/kg infused over 6 hours ([Section 4.2](#)). If Cohorts 5C, 6, or 7 are not cleared, the cell dose will be de-escalated to  $2.5 \times 10^6$  cells/kg in Cohorts 5C1, 6.1, and 7.1.

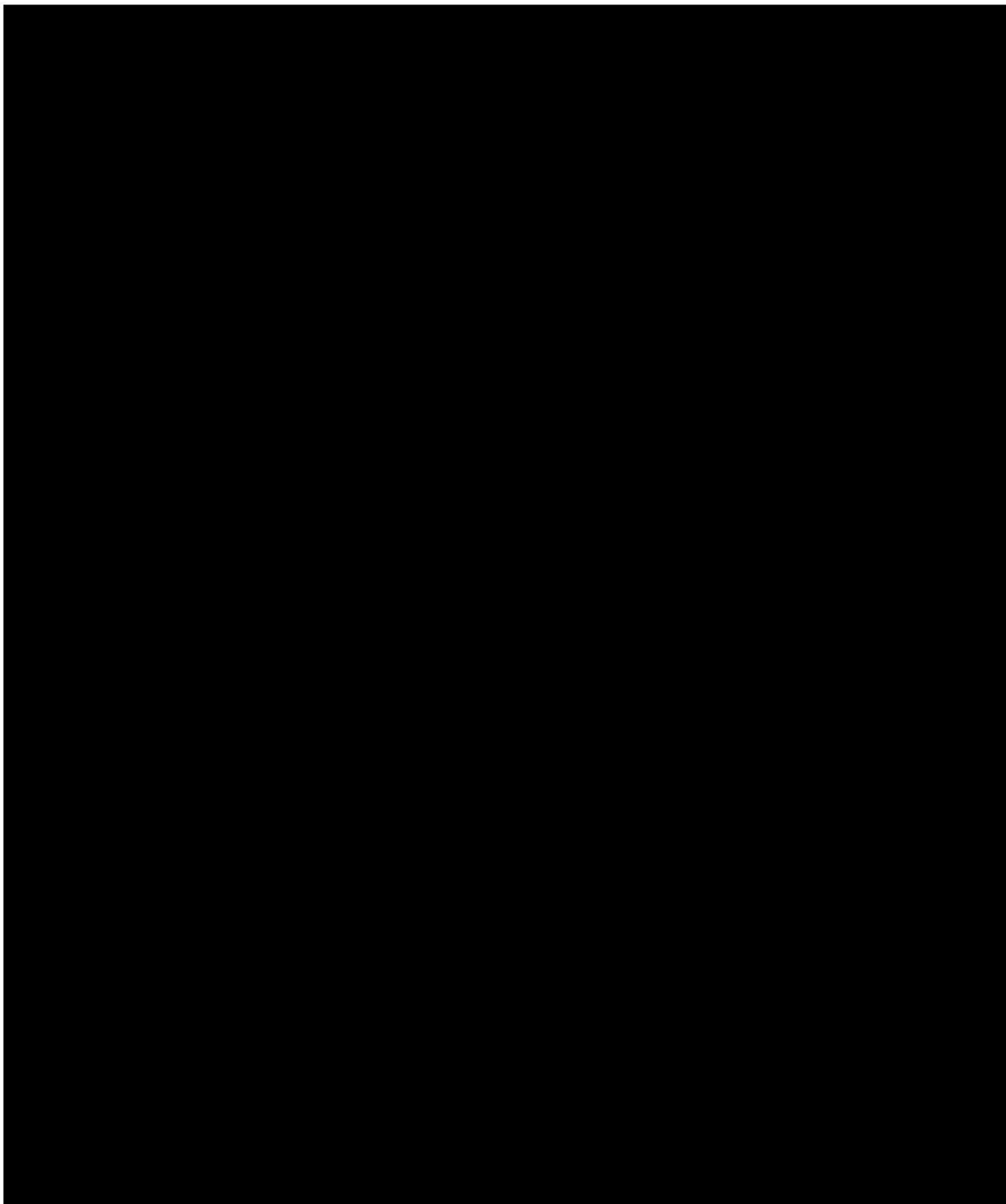
### 2.1 BPX-601 T cell Dose Rationale

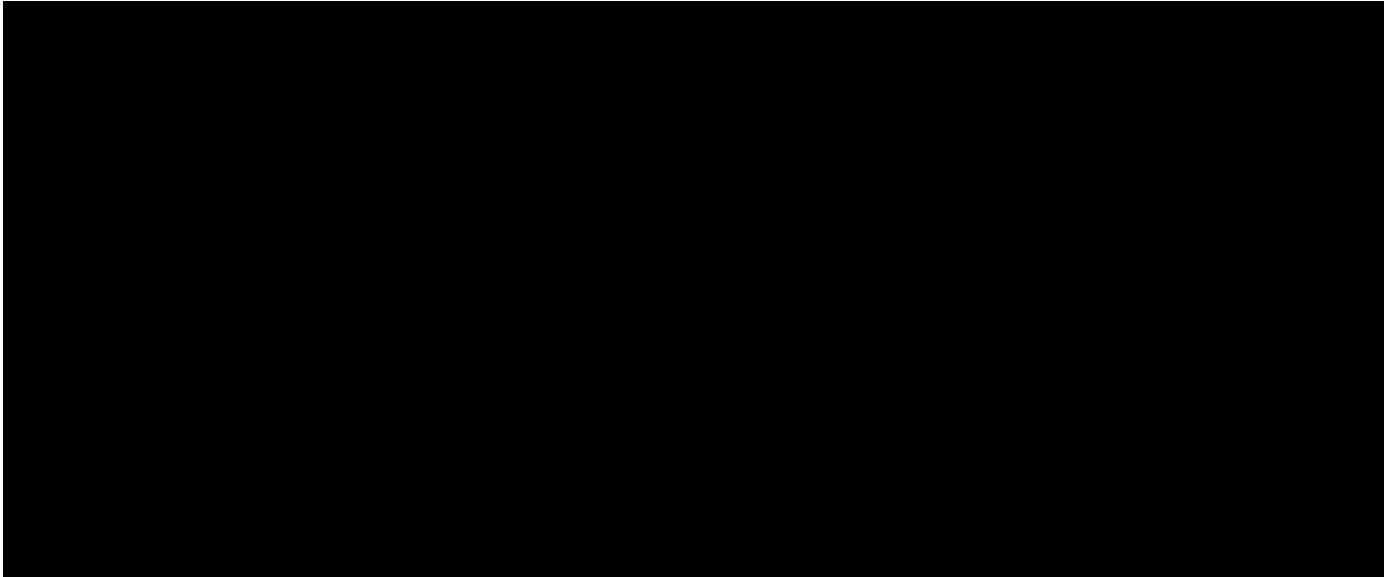
The recommended initial starting dose for BPX-601 is  $1.25 \times 10^6$  cells/kg. This dose is based on nonclinical data that established it as the minimum threshold dose for tumor growth inhibition in the presence of rimiducid ([Figure 6](#)). BPX-601 T cells administered at this initial dose of  $1.25 \times 10^6$  cells/kg as a single IV infusion, either with or without subsequent rimiducid 1 week later, resulted in no dose-limiting toxicity (DLTs) ([Becerra 2018](#)). The optimal cell dose will be explored using a standard 3+3 dose escalation design starting at the initial dose of  $1.25 \times 10^6$  cells/kg. Escalation may proceed until the maximum tolerated dose (MTD) is determined, or in the absence of an MTD, escalation will stop at the maximum administered cell dose (MAD) of  $10 \times 10^6$  cells/kg.

Cells will be administered either with or without rimiducid depending on the dosing cohort ([Table 2](#)). The starting cell dose of  $1.25 \times 10^6$  cells/kg and the MAD of  $10 \times 10^6$  cells/kg are similar to or lower than the cell dose levels previously explored in Phase 1 studies of other experimental CAR-T cells directed against alternate solid tumor antigens ([NCT01218867](#), [NCT01897415](#), [NCT02159716](#), [NCT02414269](#), [NCT02465983](#)).

## 2.2 Rimiducid Regimen Rationale

To date, this study has explored the effect of administering a fixed dose of rimiducid (0.4 mg/kg infused over 2 hours) given as a single dose or given QW in combination with BPX-601 T cells in sequential cohorts. This dose is based on prior clinical experience with rimiducid IV doses up to 1 mg/kg with no evidence of clinical intolerability ([Iulivucci 2001](#)) and provides rationale for this recommended dose in accordance with the IB ([Rimiducid IB](#)).





### 3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
<b>Primary</b>	
<ul style="list-style-type: none"> <li>• <b>Phase 1:</b> To determine the safety, tolerability, and MTD and/or recommended Phase 2 dose/schedule (RP2D) of BPX-601 T cells and rimiducid to subjects with advanced solid tumors</li> </ul>	<ul style="list-style-type: none"> <li>• Incidence of DLTs, frequency and severity of treatment-emergent adverse events and SAEs, and change from baseline in safety parameters</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Phase 2:</b> To evaluate the antitumor activity of BPX-601 T cells administered with rimiducid in select solid tumor types</li> </ul>	<ul style="list-style-type: none"> <li>• Percentage of subjects with objective response determined by the Investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or the Prostate Cancer Working Group 3 (PCWG3) criteria (prostate cancer only)</li> </ul>
<b>Secondary</b>	
<ul style="list-style-type: none"> <li>• To characterize the safety and tolerability of BPX-601 T cells administered with rimiducid at the RP2D</li> </ul>	<ul style="list-style-type: none"> <li>• Frequency and severity of treatment emergent AEs and SAEs, change from baseline in safety parameters</li> </ul>
<ul style="list-style-type: none"> <li>• To characterize the PK of rimiducid</li> </ul>	<ul style="list-style-type: none"> <li>• Serum concentration-time profiles and PK parameters (including <math>C_{max}</math> and area under the time-concentration curve)</li> </ul>
<ul style="list-style-type: none"> <li>• To evaluate the clinical efficacy of BPX-601 T cells administered with rimiducid in select solid tumor types</li> </ul>	<ul style="list-style-type: none"> <li>• Progression free survival, percentage of subjects with disease control, and duration of response determined by the Investigator; and overall survival</li> </ul>
<ul style="list-style-type: none"> <li>• To assess the long-term safety of BPX-601 T cells</li> </ul>	<ul style="list-style-type: none"> <li>• Proportion of subjects with detectable replication competent retrovirus in peripheral blood up to 15 years following BPX-601 T cell infusion</li> </ul>
<b>Exploratory</b>	
<ul style="list-style-type: none"> <li>• To assess the immunogenicity of BPX-601 T cells</li> </ul>	
<ul style="list-style-type: none"> <li>• To characterize the pharmacodynamics of BPX-601 T cells administered with and without rimiducid (eg, expansion and persistence of peripheral BPX-601 T cells over time)</li> </ul>	
<ul style="list-style-type: none"> <li>• To explore the relationship between rimiducid PK and BPX-601 T cell pharmacodynamic biomarkers as applicable (eg, BPX-601 T cell persistence, phenotyping, functional activity, tumor infiltration) and genetic and/or protein profiles in tumor tissue and peripheral blood</li> </ul>	
<ul style="list-style-type: none"> <li>• To explore the relationship between tumor tissue/blood-based immune biomarkers, including serum cytokines, and clinical response or resistance to BPX-601 T cells</li> </ul>	
<ul style="list-style-type: none"> <li>• To describe the PSCA expression level on tumor cells before CAR T cell infusion, and the relationship it may have with disease response and observed toxicities</li> </ul>	



## 4 STUDY DESIGN

### 4.1 Overview

Historical clinical data from the first-generation CAR-T cells demonstrated tumor killing effects in CD19-positive malignancies; yet the adoptive transfer to CAR-T cells to treat solid tumors has had limited clinical success. Reasons for diminished CAR T cell function in the context of solid tumors may include insufficient homing of engineered T cells to tumor sites or reduced functionality within the immunosuppressive solid tumor microenvironment. A strategy to selectively modulate CAR T cell function in vivo could potentially overcome these limitations, thereby enhancing antitumor activity against solid tumor targets.

Nonclinical data demonstrate that the iMC activating effect by the dimerizer (rimiducid) contributes to the proliferation and persistence of the PSCA-directed CAR-T cells in vivo, and thus provide the scientific rationale for the evaluation of the BPX-601 T cells in PSCA-expressing advanced solid tumors. Previous clinical evaluation of single-dose rimiducid in healthy volunteers ([Iuliucci 2001](#)), as well as multiple-dose rimiducid, together with an iMC- and PSCA-expressing dendritic cell vaccine in metastatic prostate cancer subjects ([Bellicum Protocol BP-002](#)) showed rimiducid to be safe and supports its use in combination with BPX-601 T cells.

This is a Phase 1/2, open-label, multicenter, nonrandomized study to investigate the safety, tolerability, and clinical activity of PSCA-specific CAR-T cells (BPX-601 T cells) administered with rimiducid to subjects with PSCA-expressing advanced solid tumors (pancreatic and prostate cancers). The study will be comprised of multiple parts:

- **Phase 1 (Part 1): Dose escalation** to evaluate the safety and tolerability of increasing dose levels of BPX-601 T cells with increasing rimiducid dose and infusion duration in order to identify the MTD and/or the RP2D
- **Phase 2 (Parts 2 and 3): Indication-specific dose expansion** to assess the safety, pharmacodynamics (including BPX-601 T cell persistence), and clinical activity at the recommended dose identified in Part 1 in various PSCA-expressing solid tumors

A study flow diagram is provided in [Figure 7](#).

Study eligibility will be determined based on sequenced Prescreening and Screening assessments. Accrual of eligible subjects will begin in Part 1. Once the RP2D is determined in Part 1, enrollment in Part 2 will be initiated. Part 3 will commence provided sufficient clinical activity in 1 or more disease indications is observed in Part 2. Alternately, if the combination treatment regimen of BPX-601 T cells with rimiducid is not tolerable, there is an unfavorable change to risk/benefit, there is insufficient pharmacodynamic response, or the clinical activity is considered inadequate, Parts 2 and 3 (any or all indication groups) may not be initiated and/or the study may be prematurely terminated before completing the planned enrollment.

Independent of the phase of study, each subject will follow the same study treatment schedule and procedural requirements ([Figure 8](#)). Each subject will proceed through the following study periods:

- Prescreening (pancreatic cancer subjects only)
- Screening
- Enrollment/Apheresis
- Baseline assessment and lymphodepletion (LD)
- Treatment with investigational product(s): BPX-601 T cells and rimiducid (as applicable)
- Post-treatment and long-term follow-up

Study requirements assigned to each study period are described in [Section 8](#) and the Schedule of Assessments ([Appendix 1](#)).

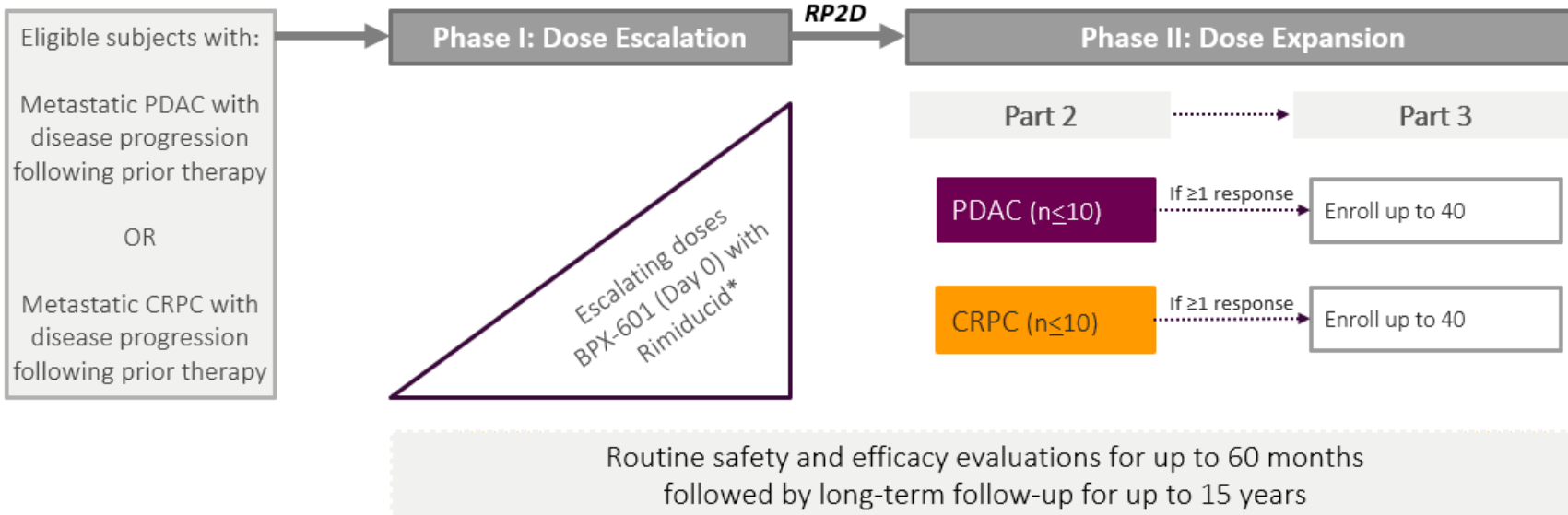
**Figure 7 Study Flow Diagram**

**Prescreening**

Assess PSCA expression by central testing  
(pancreatic cancer subjects only)

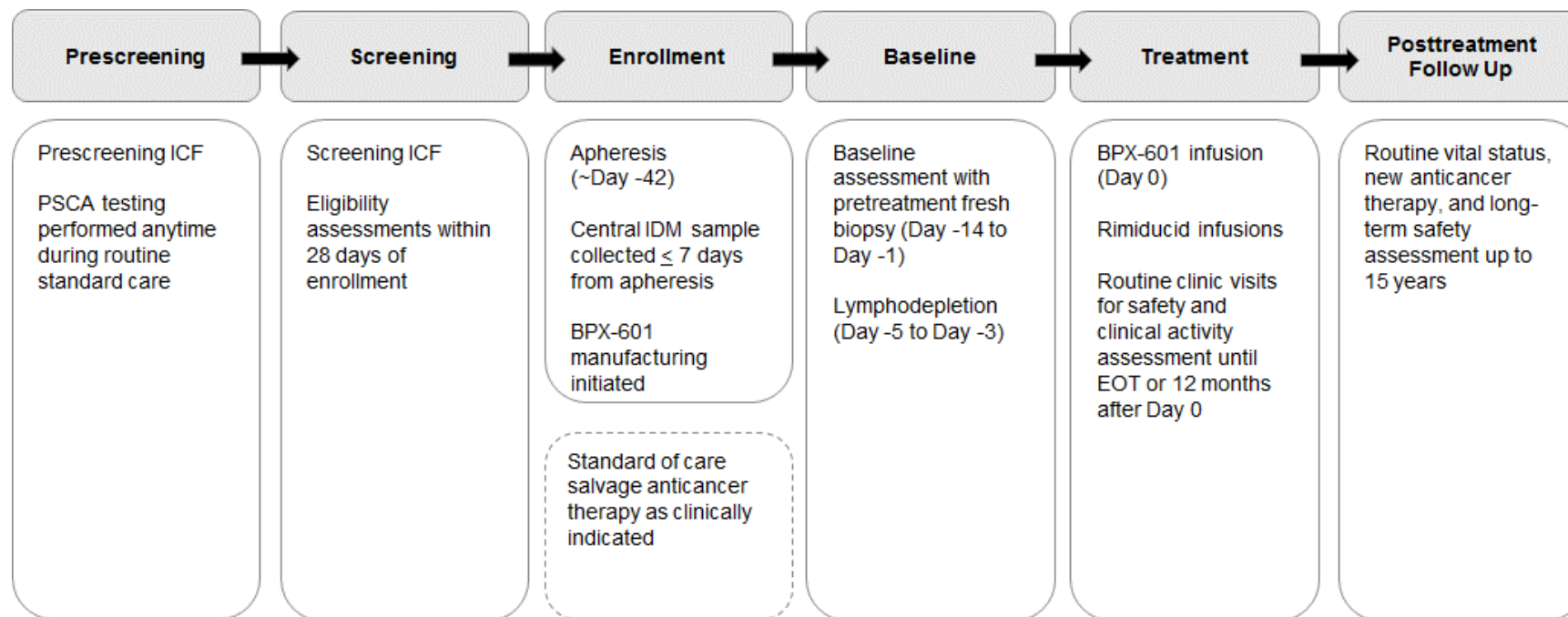


**Screening**



\* Lead-in cohort without rimiducid previously enrolled

**Figure 8 Study Periods and Visit Schema**



## 4.2 Phase 1 (Part 1) Dose Escalation

Phase 1 is a dose escalation study designed to determine the optimal BPX-601 T cell dose and rimiducid dose and regimen. All cohorts will use the 3+3 dose escalation rules, with the exception that additional subjects (up to 10 total subjects/cohort) may be enrolled in previously completed dosing cohorts at the Sponsor's discretion in order to further investigate safety and acquire translational information. Enrollment in dose-escalation cohorts will proceed as described in [Table 2](#).

The lead-in Cohort 0 was previously completed. Three subjects received a single dose of BPX-601 ( $1.25 \times 10^6$  cells/kg) on Day 0 in the absence of subsequent rimiducid. No DLTs were observed and there were no AEs, elevated cytokine levels, or other signs of toxicity associated with BPX-601 T cell infusion. Quantitative polymerase chain reaction (qPCR) analysis of peripheral blood samples revealed BPX-601 T cells increasing approximately between Days 0 to 15, with maximum expansion observed from Days 5 to 15, followed by an eventual decrease below the level of assay detection by Day 21. Based on the favorable safety profile and early clearance of BPX-601 T cells demonstrated in Cohort 0, the FDA supported the addition of a single dose of rimiducid (0.4 mg/kg) on Day 7 to the investigational treatment regimen.

Cohort 3 was the initial starting cohort for cell-dose escalation decisions in Phase 1 with BPX-601 ( $1.25 \times 10^6$  cells/kg) administered with a single dose of rimiducid (0.4 mg/kg).

Cohort 4 increased the BPX-601 T cell dose ( $2.5 \times 10^6$  cells/kg) administered with a single dose of rimiducid (0.4 mg/kg).

Cohort 5A increased the BPX-601 T cell dose ( $5.0 \times 10^6$  cells/kg) administered with a single dose of rimiducid (0.4 mg/kg).

Cohort 5B changed the LD regimen to fludarabine plus cyclophosphamide (Flu/Cy). Before the implementation of Amendment 4, subjects who enrolled in Cohorts 0, 3, 4 and 5A received cyclophosphamide only as the LD regimen; following the implementation of Amendment 4, enrollment in Cohort 5B proceeded with Flu/Cy LD ([Table 2](#)). Dose decisions were made collectively for Cohorts 5A and 5B after evaluation of  $\geq 3$  DLT evaluable subjects. As of March 2021, safety data from Part 1 are limited to subjects with pancreatic cancer ([Section 1.4.2](#)). To permit an initial assessment of risk-benefit in subjects with prostate cancer, the Safety Review Committee (SRC) decided to initiate enrollment of prostate cancer subjects in Cohort 5B at a previously cleared dose level in pancreatic cancer subjects who showed an acceptable safety profile (enrollment in this cohort is currently ongoing). SRC review of Cohort 5B data will determine subsequent cohort enrollment of prostate cancer subjects.

Cohort 5C increased the frequency of rimiducid dosing to QW. Following the cumulative analysis of clinical and biomarker data from Cohorts 0 to 5B, Amendment 5 included repeat rimiducid dosing for Cohort 5C. Following the enrollment of 3 DLT evaluable subjects, the SRC determined that the Grade 4 cytokine release syndrome (CRS) described above ([Section 1.4.2](#)) constituted a DLT. Therefore, 3 additional DLT-evaluable subjects were enrolled in this cohort.

Once the safety of the BPX-601 T cell dose in combination with the rimiducid QW regimen at a dose of 0.4 mg/kg infused over 2 hours is established in Cohort 5C ( $5 \times 10^6$  cells/kg, a previously cleared dose of cells and single dose of rimiducid in Cohorts 5A and 5B), Cohorts 6 and 7 may be explored to evaluate rimiducid doses of 0.8 mg/kg infused over 4 hours and 1.6 mg/kg infused over 6 hours, respectively. Cohorts 8 and 9 will evaluate BPX-601 T cell doses of  $7.5 \times 10^6$  and  $10 \times 10^6$  cells/kg, respectively, with a rimiducid dose of 1.6 mg/kg infused over 6 hours. (Section 4.2). If Cohorts 5C, 6, or 7 are not cleared, the cell dose will be de-escalated to  $2.5 \times 10^6$  cells/kg in Cohorts 5C1, 6.1, and 7.1 (Figure 9).

If the SRC determines that RP2D criteria are met in Cohort 6, the Part 2 portion of the study will be initiated. Based on safety results, the SRC may elect to enroll subjects in subsequent cohorts either sequentially or in parallel.

The LD regimen, BPX-601 T cell dose, and rimiducid treatment regimen are presented in Table 3. Cohorts of  $\geq 3$  and up to 6 evaluable subjects will be treated with escalating doses of BPX-601 T cells on Day 0 followed by rimiducid either as a single (0.4 mg/kg infused over 2 hours) or weekly (0.4 mg/kg infused over 2 hours, 0.8 mg/kg infused over 4 hours, or 1.6 mg/kg infused over 6 hours) dose beginning on Day 7. Dose escalations will proceed until the MTD is determined, or in the absence of an MTD, escalation will stop at the MAD ( $10 \times 10^6$  cells/kg) plus maximal rimiducid dose (1.6 mg/kg).



**Table 2 Dose Escalation/De-Escalation Rules**

Cohort <sup>a</sup>	If 0/3 subjects have DLT <sup>b</sup>	If 1/3 subjects have DLT	≤1/6 subjects have DLT	≥2/6 subjects have DLT
0 <sup>c</sup>	Proceed to Cohort 3			
3 <sup>d</sup> (Starting Dose)	Escalate to Cohort 4	Expand to 6 evaluable subjects	Escalate to Cohort 4	MTD exceeded; de-escalate to Cohort 2
4	Escalate to Cohort 5A		Escalate to Cohort 5A	MTD exceeded; no further enrollment at dose level
5A, B <sup>e</sup>	Escalate to Cohort 5C, or expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Escalate to Cohort 5C	MTD exceeded; de-escalate to a previously completed dose level
5C	Escalate to Cohort 6		Escalate to Cohort 6	MTD exceeded; de-escalate to Cohort 5C1
5C1	Escalate to Cohort 6.1	Expand to 6 evaluable subjects	Escalate to Cohort 6.1	MTD exceeded; de-escalate to a previously completed dose level
6	Escalate to Cohort 7	Expand to 6 evaluable subjects	Escalate to Cohort 7	MTD exceeded; de-escalate to Cohort 6.1
6.1	Escalate to Cohort 7.1		Escalate to Cohort 7.1	MTD exceeded; de-escalate to a previously completed dose level
7	Escalate to Cohort 8	Expand to 6 evaluable subjects	Escalate to Cohort 8	MTD exceeded; de-escalate to Cohort 7.1
7.1	Declare MAD		Declare MAD	MTD exceeded; de-escalate to a previously completed dose level
8	Escalate to Cohort 9	Expand to 6 evaluable subjects	Escalate to Cohort 9	MTD exceeded; de-escalate to a previously completed dose level
9	Declare MAD		Declare MAD	

DLT = dose-limiting toxicity; MTD = maximum tolerated BPX-601 T cell dose; MAD = maximum administered dose

Note: Shading indicates cohorts that have been enrolled. MTD exceeded indicates no further enrollment at that BPX-601 T cell dose level.

- See Table 2 for planned BPX-601 T cell and rimiducid dose regimens assigned to each Cohort.
- DLT evaluation period is Day 0 (BPX-601 T cell infusion) through 4 weeks from first rimiducid infusion.
- Lead-in cohort (previously completed). BPX-601 T cell infusion on Day 0. Rimiducid not administered. 3 subjects enrolled; BPX-601 T cell infusions were staggered by ≥1 month.
- Cohort 3 was the initial cohort for BPX-601 T cell dose escalations. For the first 3 subjects enrolled in Cohort 3, rimiducid infusions were staggered by ≥1 month. Cohorts 1 and 2 were not enrolled, as these were de-escalation cohorts in case toxicities were observed in Cohort 3.
- Dose decisions were made collectively for Cohorts 5A and 5B. Assignment of next cohort for subjects with prostate cancer after Cohort 5B dependent on Safety Review Committee recommendation.

**Table 3**                      **Planned BPX-601 T cell Dose Levels, Lymphodepleting Regimens and Rimiducid Dose and Infusion Duration**

Cohort	Lymphodepletion Regimen <sup>a</sup>	BPX-601 (cells/kg; Day 0)	Rimiducid <sup>b</sup> (starting on Day 7)
0 (Lead-in Cohort) <sup>c,d</sup>	Cy (Day -3)	1.25×10 <sup>6</sup> (±20%)	No rimiducid
3 <sup>c,e</sup> (Starting Dose)		1.25×10 <sup>6</sup> (±20%)	Single dose (0.4 mg/kg) 2-hour infusion
4 <sup>c</sup>		2.5×10 <sup>6</sup> (±20%)	
5A <sup>c</sup>		5×10 <sup>6</sup> (±20%)	
5B <sup>c</sup>	Flu/Cy (Day -5, -4, -3)	5×10 <sup>6</sup> (±20%)	Single dose (0.4 mg/kg) 2-hour infusion
5C		5×10 <sup>6</sup> (±20%)	Multiple doses (0.4 mg/kg) 2-hour infusion, QW <sup>f</sup>
5C1		2.5×10 <sup>6</sup> (±20%)	Multiple doses (0.4 mg/kg) 2-hour infusion, QW <sup>f</sup>
6		5×10 <sup>6</sup> (±20%)	Multiple doses (0.8 mg/kg) 4-hour infusion, QW <sup>f</sup>
6.1		2.5×10 <sup>6</sup> (±20%)	
7		5×10 <sup>6</sup> (±20%)	Multiple doses (1.6 mg/kg) 6-hour infusion, QW <sup>f</sup>
7.1		2.5×10 <sup>6</sup> (±20%)	
8		7.5×10 <sup>6</sup> (±20%)	Multiple doses (1.6 mg/kg) 6-hour infusion, QW <sup>f</sup>
9		10×10 <sup>6</sup> (±20%)	

Abbreviations: Cy = cyclophosphamide; Flu/Cy = fludarabine plus cyclophosphamide; QW = every week; TBD = to be determined.

Note: Shading indicates cohorts that have been enrolled.

a Study Day is relative to the BPX-601 T cell infusion on Day 0.

b Subjects must meet clinical criteria (Section 8.2.5) to receive rimiducid; first infusion of rimiducid may be delayed up to 14 days.

c Previously completed.

d BPX-601 T cell infusion on Day 0. Rimiducid not administered. 3 subjects enrolled; BPX-601 T cell infusions were staggered by ≥1 month.

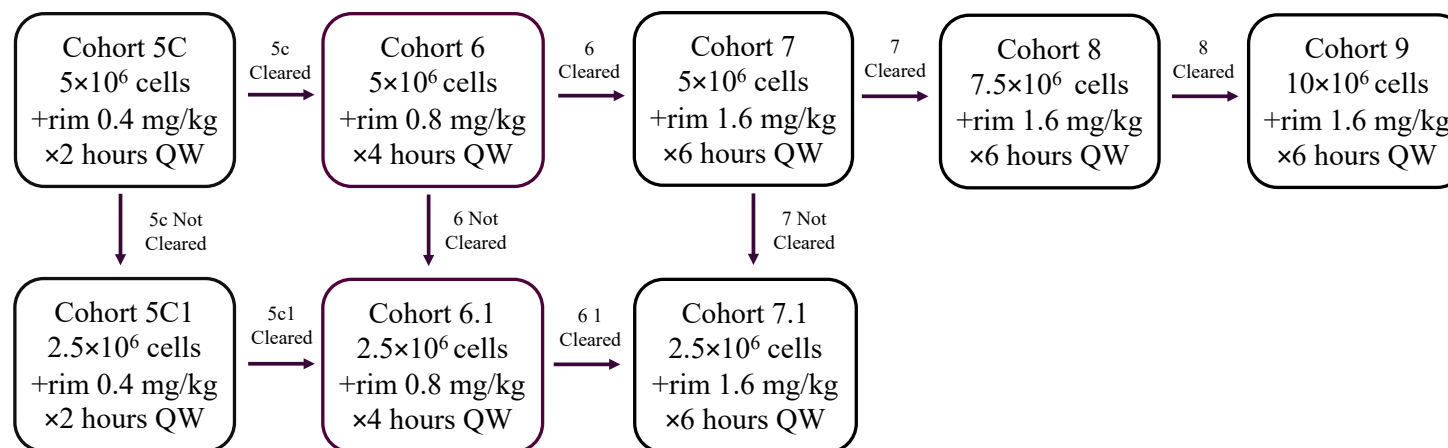
e Cohort 3 was the initial cohort for BPX-601 T cell dose escalations. Cohorts 1 and 2 were not enrolled, as these were de-escalation cohorts in case toxicities were observed in Cohort 3.

f QW dosing starts on Day 7 (±3 days) and continues every 7 (±2 days) days during Month 1 and every 7 (±3 days) days during Months 2-11 until treatment discontinuation criteria are met (Section 5.3.4).

Enrollment in Cohorts 5C through Cohort 9 will proceed as described in Figure 9.



**Figure 9**      **Detail of Phase 1 Dose-escalation Schema for Cohorts 5C through Cohort 9**



Abbreviations: QW = once weekly; rim = rimiducid.

The DLT period is defined in [Section 4.3](#). In order to be considered evaluable for DLT, a subject must satisfy the following:

- Received the scheduled doses of BPX-601 T cells, an initial dose of rimiducid, and  $\geq 50\%$  of any additional scheduled doses of rimiducid during the DLT period
- Received a sufficient number of BPX-601 T cells to satisfy dose level requirements
- The DLT evaluation period (Day 0 through 4 weeks after the first planned rimiducid infusion [ie, Day 35]) was completed

If the subject was infused with an inadequate number of BPX-601 T cells, did not receive the minimum scheduled doses of rimiducid, or could not complete scheduled evaluations (due to reasons other than toxicity) in the DLT evaluation period (eg, disease progression, missed visits, noncompliance, subject withdrawal), the subject will be considered nonevaluable for DLT and will be replaced with a new subject. Evaluation of a cell dose level and/or rimiducid dose/schedule with  $\geq 3$  subjects completing the DLT evaluation period is required before determining the BPX-601 T cell dose and/or rimiducid dose/schedule for the next cohort.

#### **4.3 Definition of Dose-Limiting Toxicity and Other Terms**

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, except for CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) which will be assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Scale ([Lee 2019](#)).

The evaluation period for defining DLT and informing dose escalation decisions begins with BPX-601 T cell infusion (Day 0) and concludes 4 weeks after the first planned rimiducid infusion (ie, Day 35). However, toxicities that occur outside of this window may be considered in decisions regarding the RP2D.

Dose-limiting toxicity is defined as any of the following unless clearly due to disease progression or extraneous causes:

- Any treatment-emergent Grade 4 or 5 CRS
- Any treatment-emergent Grade 3 CRS that does not resolve to Grade  $\leq 2$  within 7 days
- Grade  $\geq 3$  infusion reaction that does not resolve within 7 days
- Grade  $\geq 3$  organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, neurologic or autoimmune) not pre-existing or due to the underlying malignancy that does not resolve to Grade  $\leq 2$  within 7 days

The **Maximum Tolerated Dose (MTD)** is defined as the highest BPX-601 T cell dose level and/or rimiducid dose and infusion duration at which <33% of subjects experience a DLT during the DLT evaluation period. An MTD may not be defined in this study.

The **Maximum Administered Dose (MAD)** is defined as the highest BPX-601 T cell dose level and rimiducid dose and infusion duration in the event an MTD cannot be defined.

The **Recommended Phase 2 Dose (RP2D)** is either identical to the MTD or MAD or a lower BPX-601 T cell dose level and rimiducid dose and infusion duration selected on the basis of cumulative review of all available treatment emergent data observed in Part 1. The RP2D will be represented by both the dose of BPX-601 T cells administered and the rimiducid dose and infusion duration which provides adequate T cell persistence and biological activity while not exceeding the MTD or MAD.

Additional subjects (up to a total of 10 subjects/cohort) may be enrolled to a completed dose level that has previously been declared safe to better characterize safety and pharmacodynamic relationships, including the safety and pharmacodynamics of investigational product following LD with Flu/Cy. Intermediate dose levels between a non-tolerated dose level (or the MAD) and a previous dose level determined to be safe may also be explored.

The total number of subjects enrolled in Part 1 will depend on the frequency of DLTs and when the RP2D is determined; however, it is estimated that up to 75 subjects may be treated. Dose escalation will proceed until the MTD is determined, or in the absence of an MTD, escalation will stop at the MAD.

#### **4.4 Phase 2 Dose Expansion (Parts 2 and 3)**

Part 2 and Part 3 of Phase 2 comprise an indication-specific dose expansion phase designed to further assess safety, pharmacodynamics (including BPX-601 T cell persistence), and clinical activity of BPX-601 T cells and rimiducid administered at the RP2D. Part 2 will begin once the RP2D is determined in Phase 1 (Part 1). Initially, the expansion groups based on tumor type will consist of up to 10 subjects including those enrolled at the RP2D in Phase 1 of the study. The decision to initiate enrollment in each disease indication in Part 2 will be made by the SRC ([Section 4.5](#)). As of March 2021, safety data from Part 1 are limited to subjects with pancreatic cancer ([Section 1.4.2](#)). The opening of Part 3 is dependent upon antitumor activity observed in Part 2.

Within each group, subjects will be monitored for clinical response to enable early stopping for futility if sufficient antitumor activity is not demonstrated. If no responses are observed within the first 10 evaluable subjects for a given indication, including those enrolled at the RP2D in Phase 1, no further subjects with that tumor type will be enrolled. For subjects with pancreatic cancer, response will be defined according to RECIST v1.1. For subjects with prostate cancer, response will be defined according to RECIST v1.1, PCWG3, or a prostate specific antigen (PSA) decline  $\geq 50\%$  from baseline measured twice  $\geq 3$  to 4 weeks apart ([Mohler 2019](#)). If 1 or more responses are observed, the Sponsor may elect to open Part 3 of study to enroll up to an additional 30 subjects with the tumor type of interest. For each

indication, the maximum planned enrollment in dose expansion is 40 subjects (Parts 2 and 3 combined).

#### **4.5 Safety Review Committee**

Subject safety will be monitored throughout all parts of the study by a SRC established by the Sponsor and will include representatives from Clinical Science (including the Sponsor Medical Monitor), Safety Science/Pharmacovigilance and/or Safety Operations (Safety/Back-up Medical Monitor), and Biostatistics, in addition to the study Investigators. The SRC will meet at a regular frequency throughout execution of the clinical study to review all necessary cumulative data. At each SRC review, appropriate recommendations will be made to the study team (eg, continuation of the study as planned, study pause to enrollment pending new safety evaluations, study discontinuation, specific indication or treatment arm/part closure, protocol modification/amendment, alternative dosing or infusion time of BPX-601 T cells and/or rimiducid). Decisions by the SRC will be made based on the totality of the available data including continuation of enrollment based on efficacy results. Ad-hoc SRC meetings may be called in addition to regularly scheduled meetings, as necessary, to provide recommendations on management of new or emerging safety concerns. Specific operational details of the SRC composition, frequency/timing of meetings, and member roles and responsibilities are detailed in the SRC charter.

In addition to routine safety and clinical assessments by the SRC, a review of the incidence, nature, and severity of AEs, SAEs, deaths, and laboratory abnormalities will be performed by the Principal Investigators and the Sponsor Medical Monitor to decide upon events qualifying as DLTs, dose escalation to next cohort, and MTD or dose recommended for expansion/Phase 2.

#### **4.6 Study Duration**

Subjects will undergo routine safety monitoring and disease evaluations according to the schedule of assessments ([Appendix 1](#)) until disease progression is confirmed or other treatment discontinuation criteria are met ([Section 5.3.4](#)). At the time of confirmed progression or 12 months after the BPX-601 T cell infusion, whichever comes first, subjects will complete an end-of-treatment (EOT) safety assessment. Following the EOT visit, disease evaluations will be performed as described in [Section 8.2.6](#). Subjects will continue to be followed for long-term safety and gene therapy monitoring per current FDA guidelines at least once annually for 15 years after the BPX-601 T cell infusion. All subjects who receive BPX-601 T cells will be asked to enroll in a Bellicum-sponsored long-term follow-up (LTFU) study at the time of completion or discontinuation from this study, when LTFU study is available at the site. Until the LTFU study is available at the site, subjects will continue to be followed on this current trial. Subjects who enroll in the LTFU protocol will sign a separate Informed Consent Form (ICF) and may be followed per current FDA guidelines for up to 15 years after BPX-601 T cell administration for long-term safety, progression free survival, and overall survival.

#### **4.6.1 End of Study**

The end of the study is defined as the date when all subjects have completed the final protocol specified safety assessment and/or discontinued study participation (withdrawal of consent or lost to follow-up), whichever occurs first.

The Sponsor may terminate the study at any time for any reason. Should the study be terminated, subjects will be required to complete protocol-defined safety follow-up procedures.

#### **4.7 Study Stopping Rules**

The Sponsor has the right to terminate the study at any time. Reasons for study termination may include but are not limited to incidence or severity of AEs in this or other related studies which may indicate a potential hazard to subjects, business decision, or unsatisfactory subject enrollment. The Sponsor will notify the Investigators if the Sponsor decides to terminate the study. Subjects will be monitored throughout the study for treatment emergent safety, DLTs and unacceptable toxicities ([Section 4.3](#)) by the SRC. Data will be reviewed on a regular basis with study Investigators and before opening a new dose level/cohort, at a minimum. The following safety stopping rules will be applied to mitigate potential risk to subjects:

- Grade 5 toxicity (death) in any subject which is not due to progressive disease (PD) as assessed by the Investigator and occurs within 30 days of BPX-601 T cells/rimiducid administration, unless clearly unrelated to investigational product(s)
- Grade  $\geq 3$  neurotoxicity in  $\geq 20\%$  of subjects unless clearly related to an alternative cause other than the investigational product(s)

#### **4.8 Study Completion**

A subject will be considered to have completed the study if he or she has completed assessments up to and including the last protocol-specified visit or has experienced a clinical endpoint that precludes further continuation in the study (eg, death).

The end of the study is defined as the date of the last scheduled assessment shown in the Schedule of Assessments ([Appendix 1](#)) for the last subject in the trial.

## 5 SUBJECT ELIGIBILITY

Subject eligibility will be evaluated during the Prescreening and Screening periods of the study ([Appendix 1](#)).

No waivers for study participation will be issued by the Sponsor; subjects must meet all eligibility criteria as defined below.

### 5.1 Inclusion Criteria

1. Each subject must sign and date an ICF approved by the Institutional Review Board/Ethics Committee (IRB/EC), as appropriate, indicating that he/she understands the purpose of, and procedures required for, the study and are willing to comply. Consent is to be obtained before the performance of any study-specific procedures or tests that are not part of the standard of care for the subject's disease.
2. Histologically or cytologically confirmed diagnosis of 1 of the following:
  - Metastatic PDAC with disease progression within 6 months of the most recent anti-cancer treatment.
    - Prior treatment with first or second-line therapy including targeted immunotherapy. Subjects eligible for approved targeted therapy based on microsatellite instability high/deficient mismatch repair status and/or gene profiling should have received such therapy as appropriate unless contraindicated. Subjects with mixed histology may be included if the predominant component is adenocarcinoma.
    - Measurable disease ( $\geq 1$  target lesion) per RECIST v1.1 at Baseline ([Eisenhauer 2009](#)).
    - Documented positive tumor expression of PSCA as determined by central testing of an available, representative tissue specimen (formalin-fixed paraffin-embedded tissue, either from an archived sample or fresh biopsy).
  - Metastatic castration-resistant adenocarcinoma of the prostate (CRPC) defined as serum testosterone level  $\leq 50$  ng/dL with prior surgical castration or ongoing androgen deprivation, with PD:
    - Progressive disease is defined by rising PSA or radiographic imaging according to the PCWG3 criteria ([Scher 2016](#)) during or following the direct prior line of therapy in the setting of medical or surgical castration
    - At least 2 prior therapies including a standard  $17\alpha$  lyase inhibitor or second-generation anti-androgen therapy for the treatment of castrate resistant prostate cancer
    - Must have measurable disease by RECIST v1.1 at Baseline or bone only metastases with measurable PSA ( $\geq 1$  ng/mL) at Baseline
3. Age  $\geq 18$  years.
4. Life expectancy  $> 12$  weeks.
5. Agreement to consent to a pretreatment as well as on treatment, fresh tumor biopsy where tissue collection is clinically feasible.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 ([Appendix 2](#)).

7. Subjects must have adequate venous access for apheresis or agree to use of a central line for apheresis collection.
8. Subject has adequate organ function:  
**Cardiac:** Left ventricular ejection fraction at rest must be  $\geq$  lower limit of institutional normal  
**Coagulation:** International normalized ratio  $\leq 1.5$   
**Hematologic:**
  - White blood cell count  $\geq 2 \times 10^3/\mu\text{L}$
  - Absolute neutrophil count  $\geq 1 \times 10^3/\mu\text{L}$  without granulocyte colony-stimulating factor (G-CSF) support
  - Platelets  $\geq 100 \times 10^3/\mu\text{L}$
  - Hemoglobin  $\geq 9$  g/dL**Hepatic:**
  - Direct bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), or  $\leq 3 \times \text{ULN}$  if due to Gilbert's disease
  - Aspartate aminotransferase and alanine aminotransferase  $\leq 2.5 \times \text{ULN}$ , or  $\leq 5 \times \text{ULN}$  if liver metastases are present**Renal:** Creatinine  $\leq 1.5 \times \text{ULN}$  or a calculated glomerular filtration rate  $> 50$  mL/min/1.73m<sup>2</sup>
9. From the time of Screening/Study Treatment ICF signature, a female subject must be either:
  - Not of childbearing potential defined as:
    - (1) Premenarchal
    - (2) Postmenopausal ( $> 45$  years of age with amenorrhea  $\geq 12$  months)
    - (3) Permanently sterilized
    - (4) Otherwise incapable of pregnancy
  - Of childbearing potential and agrees to use 2 highly effective methods of birth control ([Effectiveness of Contraception Methods, CDC 2018](#)) for  $\geq 12$  months after LD
10. From the time of Screening/Study Treatment ICF signature, male subjects with female partners of childbearing potential must agree to use 2 highly effective methods of birth control ([Effectiveness of Contraception Methods, CDC 2018](#)) from the time of Screening/Study Treatment ICF signature until  $\geq 12$  months after LD.



## 5.2 Exclusion Criteria

Subjects who meet any of the following criteria are NOT eligible for the study. Waivers are NOT permitted.

1. Pancreatic cancer subjects with:
  - Islet cell neoplasms
  - Clinical or radiographic evidence of deep vein thrombosis, pulmonary embolism, or other known thromboembolic event that has not been definitely treated. Subjects with prior history of coagulopathy must be asymptomatic within 4 weeks of enrollment.
2. Prostate cancer subjects with:
  - Structurally unstable bone lesions suggesting impending fracture
  - Clinical or radiographic evidence of deep vein thrombosis, pulmonary embolism, or another known thromboembolic event that has not been definitely treated. Subjects with prior history of coagulopathy must be asymptomatic within 4 weeks of enrollment.
  - History of Grade  $\geq 2$  hematuria within the previous 6 months.
3. Symptomatic, untreated, or actively progressing central nervous system metastases. Subjects with prior brain metastases treated  $\geq 2$  weeks before the planned infusion who are clinically stable and do not require chronic corticosteroid treatment are allowed.
4. History or presence of clinically relevant central nervous system pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or leptomeningeal disease.
5. Ongoing toxicities related to prior anticancer therapy that have not resolved to Grade  $\leq 1$ . Current unresolved Grade  $\geq 2$  nonhematologic toxicity may be allowed following discussion with and approval by the Sponsor.
6. Participation in any investigational drug study within 4 weeks before enrollment.
7. Chemotherapy, targeted therapy, or radiotherapy (excluding palliative radiation) within 2 weeks or 5 half-lives, whichever is shorter, or immunotherapy within 4 weeks before enrollment (Note, salvage chemotherapy as clinically indicated may be administered following apheresis and before LD as described in [Section 7.7](#)).
8. Prior CAR-T cell or other genetically modified T cell therapy. Prior treatment with an immune-based therapy for the treatment of prostate cancer, including cancer vaccine therapies (such as Sipuleucel-T, PROSTVAC) are allowable. Immune checkpoint inhibitors, radium-223 and immunoconjugate therapies are also allowable pending discussion with the Sponsor.
9. Any disease requiring chronic immunosuppressive therapy.



10. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
  - Symptomatic congestive heart failure requiring treatment
  - Clinically significant cardiac arrhythmia
  - Uncontrolled hypertension
  - Acute myocardial infarction or unstable angina pectoris within 3 months before enrollment
  - QT interval corrected for heart rate using Fredericia's formula (QTcF) >480 msec
  - Marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort (ie, New York Heart Association Functional Class III-IV; [Appendix 3](#)).
11. Major surgical procedure, other than for diagnosis, within 4 weeks prior enrollment, or anticipation of the need for a major surgical procedure during the study.
12. Received a vaccine containing live virus within 4 weeks before enrollment. Seasonal flu vaccines that do not contain live virus are permitted.
13. Treatment with systemic chronic steroid therapy (prednisone of  $\geq 10$  mg/day or equivalent) within 7 days or 7 half-lives of the prescribed corticosteroid, whichever is shorter, before the planned apheresis date (refer to [Appendix 4](#) on half-lives of common corticosteroids).
14. Uncontrolled intercurrent illness including but not limited to poorly controlled hypertension or diabetes, or any medical condition determined by the Investigator to be a risk for enrolling on the protocol.
15. Untreated or active infection at the time of initial Screening, at the time of leukapheresis, or within 72 hours before LD. Prior oral or IV antibiotics, antifungals, or antiviral medications must be discontinued  $\geq 2$  weeks before BPX-601 T cell infusion except for use of prophylactic antimicrobial agents.
16. Active hepatitis B, active hepatitis C, or any human immunodeficiency virus (HIV) infection at the time of Screening:
  - Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test during Screening. Subjects with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody test at screening are eligible for the study if HBV DNA test is negative. If a subject has a negative HBsAg test and a positive total hepatitis B core antibody test at screening, an HBV DNA test should be performed.
  - Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test during Screening. The HCV RNA test will be performed only for subjects who have a positive HCV test.
17. Subject is a woman of child-bearing potential and is pregnant (positive serum  $\beta$ -human chorionic gonadotropin test at Baseline), planning to become pregnant within 12 months after LD, or is breastfeeding.

18. Subject is a man who plans to donate sperm or father a child within 12 months after LD.
19. Known bovine product allergy.
20. Malignant disease other than that being treated in this study. Exceptions to this exclusion are:
  - Malignancies that were treated curatively and have not recurred within 2 years before Screening
  - Completely resected basal cell or squamous cell skin cancers
  - Any malignancy considered to be indolent and that has never required therapy
21. Any other clinically significant disease or co-morbidity which may adversely affect the safe delivery of treatment within this trial.

### **5.3 Removal of Subjects from Treatment or Study**

At the time of consent, subjects will be advised that they are free to withdraw from the study at any time for any reason; however, all subjects who have received treatment with BPX-601 T cells will be encouraged to continue with all study evaluations through the EOT visit and to participate in the LTFU study. The Sponsor must be notified immediately if a subject is withdrawn from the study, and the reason(s) for withdrawal must be documented.

#### **5.3.1 Screen Failures**

Screen failures are defined as subjects who consent to participate in the clinical study but are determined not to meet all eligibility criteria required to participate in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and, if applicable, any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once. Additional rescreening may be permitted following consultation with the Sponsor.

### **5.3.2 Subject Withdrawal from Study**

A subject may be withdrawn from the study for any of the following reasons:

- Lost to follow-up defined as documented, repeated failure after  $\geq 3$  attempts to contact the subject
- Withdrawal of consent
- Study termination by the Sponsor or regulatory authority

When a subject is withdrawn before completing the study, an EOT visit will be scheduled as soon as possible and all of the assessments listed for the EOT visit will be performed. The Investigator will provide a reason for withdrawal which will be documented in the case report form (CRF).

### **5.3.3 Subject Evaluability and Replacement**

The criteria for subject evaluability and replacement for Phase 1 (Part 1) is described in [Section 4.2](#).

In Phase 2 (Parts 2 and 3), subjects may be replaced when 1 of the following occurs:

- The subject is infused with a sub-optimal or an inadequate number of BPX-601 T cells that does not satisfy the RP2D
- The subject discontinues before the first planned on-study disease evaluation after receiving BPX-601 T cells for reasons other than disease progression
- The subject does not receive  $\geq 1$  full dose of rimiducid (ie, rimiducid is not administered or the infusion is started but not completed)

Any subject that meets the above replacement criteria must still be followed for treatment-emergent safety ([Section 9](#)) as well as long-term gene therapy safety monitoring ([Section 8.3.16](#)).

### **5.3.4 Treatment Discontinuation and Study Withdrawal**

#### **5.3.4.1 BPX-601 T cell Treatment Discontinuation**

A subject may be discontinued from treatment with BPX-601 T cells for any of the following reasons:

- Withdrawal of consent
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to protocol requirements
- Disease progression
- Unacceptable toxicity including but not limited to DLT, SAE or other clinically significant AE or medical condition which indicates to the Investigator that BPX-601 T cell treatment is not in the best interest of the subject
- Pregnancy
- Noncompliance with protocol requirements
- Study termination by the Sponsor or regulatory authority

Subjects who do not receive BPX-601 T cells will not receive rimiducid. The Investigator will provide a reason for treatment discontinuation. Adverse events that are ongoing at the time of discontinuation and considered related to apheresis or LD will continue to be followed for 30 days after the last dose of apheresis or LD, whichever is later.

#### **5.3.4.2 Rimiducid Treatment Discontinuation**

A subject may be discontinued from treatment with rimiducid for any of the following reasons:

- Withdrawal of consent
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to protocol requirements
- Disease progression
- Unacceptable toxicity including but not limited to DLT, SAE, or other clinically significant AE or medical condition which indicates to the Investigator that rimiducid treatment is not in the best interest of the subject
- Pregnancy
- Noncompliance with protocol requirements
- Study termination by the Sponsor or regulatory authority

Failure to receive rimiducid will **not** result in automatic withdrawal of the subject from the study. The Investigator will provide a reason for treatment discontinuation. Subjects who receive BPX-601 T cells but not rimiducid will be followed for safety according to the reporting periods defined in [Section 9.6](#) and will be asked to complete EOT and follow-up assessments.

## **6 STUDY TREATMENTS AND ADDITIONAL MEDICATIONS**

### **6.1 Treatment Terminology**

The following terms will be used to describe and define protocol treatment:

- **Lymphodepleting chemotherapy:** the LD regimen used in this study will consist of Flu/Cy
- **Investigational products:** BPX-601 T cells and rimiducid

### **6.2 Lymphodepleting Chemotherapy**

Fludarabine and cyclophosphamide will be supplied by the investigative site from commercial stock. Refer to the current product labels for fludarabine and cyclophosphamide, respectively, for guidance on packaging, storage, preparation, administration, dose modifications, and toxicity management associated with these chemotherapy agents ([Fludarabine Phosphate Prescribing Information](#), [Cyclophosphamide Prescribing Information](#)).

### **6.3 Investigational Products**

Refer to the Apheresis and Cellular Therapy Manual and Pharmacy Manual for details on the storage, preparation, and administration of BPX-601 T cells and rimiducid, respectively.

#### **6.3.1 BPX-601 T cells**

BPX-601 T cells are a PSCA-directed genetically modified, autologous GoCAR-T<sup>®</sup> cell product candidate that binds to PSCA-expressing cells.

[REDACTED]

[REDACTED]

**Labeling:** The product label and insert for BPX-601 T cells contain the following

[REDACTED]

[REDACTED]

### **6.3.2 Rimiducid**

Rimiducid for Injection is a lipid-permeable analog of tacrolimus that functions as a dimerizing agent to induce clustering of engineered proteins containing the cognate dimerizer-binding domain.

**Packaging and Formulation:** Rimiducid for Injection is packaged in a 3 mL Type 1 clear glass serum vial. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **6.4 Study Treatment Schedule**

### **6.4.1 Apheresis**

After signing the Screening/Study Treatment ICF, subjects will undergo PBMC collection according to local institutional standards.

Using standardized continuous flow centrifugation, collect and process approximately 15 to 19 liters of total blood volume (goal range of  $\geq 7.5 \times 10^9$  total nucleated cells) per institutional standard procedures. Record the volume processed, the duration of apheresis, and the



mononuclear count of the apheresis product. Refer to the Apheresis and Cellular Therapy Manual for further details.

Before, during, and after the apheresis procedure, subjects should undergo infectious disease monitoring per established regulatory guidelines. A protocol-specific infectious disease monitoring sample must be collected and sent to a Bellicum-designated central laboratory within 7 days before the apheresis procedure ([Appendix 1](#)). Refer to the Laboratory and Study Procedures Manual for additional information on collection, shipping and handling.

Evaluation before apheresis, venous access, monitoring, and treatment of apheresis complications will be conducted according to institutional guidelines and must comply with federal, state, and the Foundation for the Accreditation of Cell Therapy guidelines.

#### **6.4.2 Lymphodepletion Before BPX-601 T cell Infusion**

Confirm availability of BPX-601 T cells with the Sponsor before initiating the LD regimen.

Refer to the Schedule of Assessments ([Appendix 1](#)) for safety assessments to be completed and recorded before initiation of LD. Results must demonstrate that the subject meets institutional standards for LD; chemotherapy should be withheld until resolution of clinically significant symptoms. If LD is delayed in order to allow symptom management and recovery, the Sponsor Medical Monitor should be notified as soon as possible.

Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m<sup>2</sup> IV over 60 min followed by fludarabine 30 mg/m<sup>2</sup> IV over 30 min on the fifth, fourth, and third day before infusion of BPX-601 T cells. Lymphodepletion may be administered as an outpatient or inpatient per the Investigator's discretion. Appropriate supportive care for prevention of urinary toxicity (eg, hemorrhagic cystitis) should be implemented per institutional standards with consideration for use of prophylactic hydration (oral or IV) and/or mesna.

If the combination of cyclophosphamide and fludarabine is not tolerated, or if the Investigator determines that combination-based LD presents an unfavorable safety risk to a subject, then LD should proceed with cyclophosphamide alone as per aforementioned, following discussion with the Sponsor.

#### **6.4.3 BPX-601 T cell Infusion**

***BPX-601 T cells are for autologous use only.***

***The Subject Identification number must match the subject identifiers on the BPX-601 T cell infusion bag(s). Do not infuse BPX-601 T cells if the information on the subject-specific label does not match the intended subject.***

Before administering BPX-601 T cells, subjects should receive premedication with acetaminophen and diphenhydramine per institutional standards for cellular therapy products. Institutional guidelines for hydration prophylaxis as described for cyclophosphamide-containing LD should also be followed. For example, fluids (3 L/m<sup>2</sup>/day, oral or IV) are recommended in order to maintain urine specific gravity <1.01 for ≥48 hours after BPX-601 T cell infusion.



BPX-601 T cells should be thawed and diluted as instructed in the Apheresis and Cellular Therapy Manual. Briefly, BPX-601 T cells should be thawed, diluted, and infused immediately using either central or peripheral venous access devices. The start and stop time of the infusion will be recorded. The duration between end of thaw and end of infusion must not exceed 90 min.

BPX-601 T cells may be administered in an outpatient (preferred for asymptomatic subjects) or inpatient basis, as deemed appropriate by the Investigator and/or per discussion with the Sponsor. Regardless of treatment setting, subjects will be observed in the clinic for  $\geq 4$  hours after infusion and released once considered clinically stable.

#### **6.4.4 Rimiducid Infusion and Premedication**

Rimiducid drug product is dissolved in Solutol<sup>®</sup> HS15 (also known as Kolliphor<sup>®</sup> HS15) and therefore has the potential to induce an infusion or hypersensitivity reaction. To minimize or mitigate infusion-related toxicity, subjects should receive premedication with acetaminophen, diphenhydramine, famotidine (or their equivalents), and other supportive care therapy per institutional standards for potential anaphylaxis. Institutional guidelines for hydration prophylaxis as described for cyclophosphamide-containing LD should also be followed. For example, fluids (3 L/m<sup>2</sup>/day, oral or IV) are recommended in order to maintain urine specific gravity  $< 1.01$  for  $\geq 48$  hours after rimiducid infusion.

Before administration, the required rimiducid formulation will be diluted into normal saline as described in the Pharmacy Manual. All subjects (except for Cohort 0) will receive IV rimiducid at a dose of 0.4 mg/kg infused over 2 hours, 0.8 mg/kg infused over 4 hours, or 1.6 mg/kg infused over 6 hours.

Rimiducid may be administered using either central or peripheral venous access devices. The start and stop time for the infusion will be recorded.

Rimiducid will be infused on an outpatient (preferred for asymptomatic subjects) or inpatient basis, as deemed appropriate by the Investigator and/or per discussion with the Sponsor. Regardless of treatment setting, subjects will be observed in the clinic for  $\geq 4$  hours after infusion and released once considered clinically stable.

#### **6.5 Recommended Supportive Care, Additional Treatment, and Monitoring**

Because of the risk of CRS and other CAR T-associated toxicities, subjects treated on this protocol should initially remain within approximately 60 min of the participating institution for no less than the first 14 days after the infusion of BPX-601 T cells and first 2 infusions of rimiducid, or per institutional guidelines/standard operating procedures.

Close monitoring of subjects should continue for approximately 24 hours (at a minimum) after infusion of BPX-601 T cells and the first 2 doses of rimiducid, following institutional standards and based on investigator discretion. Subjects who do not have adequate support outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluation or emergencies should be considered for hospitalization for the first week of treatment.

Recommendations for management of treatment-related toxicities are detailed in [Section 7](#). Before infusion of BPX-601 T cells and rimiducid, staff should ensure that a minimum of 2 doses of tocilizumab are available on-site for each subject and are ready for immediate administration.

Subjects who develop fever (temperature  $>38.5^{\circ}\text{C}$ ) should be evaluated for infection and treated with antibiotics, fluids, and other supportive care as per institutional or standard clinical practice, and as determined by the Investigator or treating physician. Neutropenic fever should be evaluated promptly (eg, blood cultures obtained, imaging as clinically required for identification of potential source of infection) and managed medically per institutional or standard clinical practice. The possibility of CRS should be considered for all subjects with fever following BPX-601 T cell/rimiducid administration, and any onset of fever ( $>38.5^{\circ}\text{C}$ ) within the first 14 days after infusion should be further investigated and subjects admitted for observation. It is also recommended that febrile subjects are monitored closely for hemodynamic instability and changing neurologic status.

## **7 TOXICITY MANAGEMENT AND SUPPORTIVE CARE GUIDELINES**

All the guidelines within this section are general recommendations and Investigators may use local institutional guidelines and clinical judgments in the management of toxicities and dose modifications. Investigators should also refer to the IBs for BPX-601 T cells and rimiducid ([BPX-601 IB](#), [Rimiducid IB](#)).

### **7.1 Lymphodepleting Chemotherapy**

Refer to the product labels for fludarabine and cyclophosphamide, respectively, for detailed information regarding warnings, precautions, contraindications, AEs, and recommendations for supportive care in the event of conditioning chemotherapy-related toxicity ([Fludarabine Phosphate Prescribing Information](#); [Cyclophosphamide Prescribing Information](#)).

Appropriate supportive care for prevention of urinary toxicity (eg, hemorrhagic cystitis) should be implemented per institutional standards with consideration for use of prophylactic hydration (oral or IV) and/or mesna.

### **7.2 Infusion Reactions/Hypersensitivity**

BPX-601 T cells are an autologous, fully humanized CAR T cell therapy and is therefore less likely to be immunogenic and induce a hypersensitivity reaction. However, mild to severe infusion-related reactions have been previously reported with rimiducid ([Rimiducid IB](#)).

To minimize or mitigate infusion-related toxicity associated with BPX-601 T cells and rimiducid, all subjects should receive premedication as described in [Section 6.4.3](#) and [Section 6.4.4](#), respectively. Additionally, the rate of infusion may be decreased and supportive care according to local standards may be used as needed. In case of infusion-related toxicity during the post-infusion observation period for BPX-601 T cells or rimiducid, subjects should receive symptom-directed supportive care (eg, antihistamines, antipyretics, antiemetics as clinically indicated) as per institutional guidelines.

Infusion-related or hypersensitivity events that meet the criteria for an SAE should be reported accordingly ([Section 9.7](#)).

### **7.3 Management of CAR-T Cell-Related Toxicity**

CRS and neurotoxicity are common after treatment with CAR-T cells as well as other immunotherapies that include immune cell- and bi-specific antibody-based approaches that function by activation of immune effector cells (IECs). Although these data are largely derived from clinical trials of investigational products for the potential treatment of hematologic malignancies, similar toxicities have been reported in patients with nonhematologic cancers ([Lee 2014](#), [Maude 2014](#), [Brudno 2016](#), [Hu 2016](#)). Nonclinical data from *in vitro* models has shown that rimiducid-induced BPX-601 T cell expansion results in transient increases in cytokines typically associated with immune activation (eg, IFN $\gamma$ , interleukin [IL]-6, IP-10, tumor necrosis factor [TNF] $\alpha$ ). Therefore, the biological effect of BPX-601 T cells include cytokine modulation and as neurologic toxicity exists as a potential class effect for IEC therapies, AEs of or related to CRS and neurotoxicity, respectively, may be anticipated.

### 7.3.1 Cytokine Release Syndrome

CRS associated with IEC treatment has been defined as a supraphysiologic response following any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other IECs (Lee 2019). Symptoms can be progressive, must include fever at the onset and may include hypotension, capillary leak (hypoxia), and end organ dysfunction. A reasonable temporal relationship to cell therapy must be present. Symptoms may have acute onset within the first few days after CAR T cell administration and may coincide with peak CAR T cell and cytokine levels (Lee 2014, Santomasso 2019). Alternately, symptoms may be delayed by a week or more following T cell infusion (Corrigan-Curay 2014). Subjects should be closely monitored during and after the BPX-601 T cell infusion, and particularly following subsequent rimiducid infusions, for signs and symptoms indicative of CRS. If CRS is suspected, it is recommended that the site follow best practice guidelines for management of CRS and contact the Bellicum Medical Monitor for further discussion.

Grading criteria for CRS are provided in Table 4. Recommendations for the clinical management of CRS are described in Table 5.

**CRS is considered an adverse event of special interest (AESI) for this study.** Refer to Section 9.8 for reporting procedures.

**Table 4 ASTCT Grading Criteria for Cytokine Release Syndrome**

Grade	Toxicity
1	Fever <sup>a</sup> defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause
2	Fever <sup>a</sup> defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause with either: <ul style="list-style-type: none"> <li>Hypotension not requiring vasopressors<sup>b</sup></li> <li>Hypoxia requiring low-flow nasal cannula<sup>c</sup> or blow-by</li> </ul>
3	Fever <sup>a</sup> defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause with either: <ul style="list-style-type: none"> <li>Hypotension requiring 1 vasopressor with or without vasopressin<sup>b</sup></li> <li>Hypoxia requiring high-flow nasal cannula<sup>c</sup>, facemask, non-rebreather mask, or Venturi mask</li> </ul>
4	Fever <sup>a</sup> defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause with either: <ul style="list-style-type: none"> <li>Hypotension requiring multiple vasopressors (excluding vasopressin)<sup>b</sup></li> <li>Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)</li> </ul>
5	Death due to CRS where another cause is not the principal factor leading to this outcome

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; BiPAP = bilevel positive.

- In subjects who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is determined by hypotension and/or hypoxia.
- CRS grade is determined by the more severe event hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature  $39.5^{\circ}\text{C}$ , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
- Low-flow nasal cannula is defined as oxygen delivered at  $\leq 6$  liters/min. Low flow also includes blow-by oxygen directly, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at  $> 6$  liters/min.

Adapted from Lee 2019.



**Table 5 Recommendations for the Management of Cytokine Release Syndrome**

Grade <sup>a</sup>	Sign/Symptom	Management
1	Fever	<ul style="list-style-type: none"> <li>Acetaminophen (or ibuprofen if not contraindicated) and hypothermia blanket for fever</li> <li>Assess for infection using blood/urine cultures, chest radiography</li> <li>Empiric broad-spectrum antibiotics and filgrastim, if neutropenic</li> <li>Maintenance IV fluids for hydration</li> <li>Consider tocilizumab 8 mg/kg<sup>b</sup> IV or siltuximab 11 mg/kg IV for persistent (lasting &gt;3 days) and refractory fever</li> </ul>
	Fever	<ul style="list-style-type: none"> <li>Manage fever as indicated for Grade 1</li> </ul>
2	Hypotension	<ul style="list-style-type: none"> <li>IV fluid bolus of 500-1000 mL normal saline (optional second bolus if SBP remains &lt;90 mmHg)</li> <li>If refractory to fluids, administer tocilizumab 8 mg/kg<sup>b</sup> IV or siltuximab 11 mg/kg IV (optional repeat tocilizumab after 6 hours as needed)</li> <li>If refractory to fluids and anti-IL-6 therapy, administer vasopressors, consider transfer to ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring as per institutional guidelines</li> <li>If subject is high-risk<sup>c</sup> or if hypotension persists after 12 doses of anti-IL-6 therapy, consider dexamethasone 10 mg IV every 6 hours</li> </ul>
	Hypoxia	<ul style="list-style-type: none"> <li>Supplemental oxygen</li> <li>Tocilizumab or siltuximab ± corticosteroids and other BSC as recommended for hypotension management</li> </ul>
3	Fever	<ul style="list-style-type: none"> <li>Manage fever as indicated for Grade 1</li> </ul>
	Hypotension	<ul style="list-style-type: none"> <li>IV fluid boluses as needed, as indicated for Grade 2</li> <li>Tocilizumab and siltuximab as indicated for Grade 2, if not administered previously</li> <li>Initiate vasopressor treatment with or without vasopressin</li> <li>Transfer to ICU, obtain ECHO, perform hemodynamic monitoring as for Grade 2</li> <li>Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours</li> </ul>
4	Hypoxia	<ul style="list-style-type: none"> <li>Supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation</li> <li>Tocilizumab or siltuximab ± corticosteroids and other BSC as described above</li> </ul>
	Fever	<ul style="list-style-type: none"> <li>Manage fever as indicated for Grade 1</li> </ul>
4	Hypotension	<ul style="list-style-type: none"> <li>IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as indicated for Grade 3</li> <li>Methylprednisolone 1 g/day IV</li> </ul>
	Hypoxia	<ul style="list-style-type: none"> <li>Mechanical ventilation</li> <li>Tocilizumab or siltuximab ± corticosteroids and other BSC as described above</li> </ul>

Abbreviations: BSC = best standard care; CRS = Cytokine release syndrome; ECHO = echocardiogram; ICU = intensive care unit; IL = interleukin; IV = intravenous; SBP = systolic blood pressure.

Note: Institutional standards are appropriate as well for CRS and other complications.

a Toxicity grade according to [Table 4](#).

b Maximum amount of tocilizumab per dose is 800mg.

c High-risk subjects include those with bulky disease, comorbidities, and those who develop early onset CRS (≤3 days of BPX-601 T cell infusion).

Adapted from [Lee 2019](#).

### 7.3.2 Neurotoxicity

Neurologic toxicity or ICANS associated with IEC treatment has been defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other IECs ([Lee 2019](#)). The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech especially naming objects, impaired attention, apraxia, and mild lethargy. Symptoms can be progressive resulting in aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. Based on historical evidence with other cellular immunotherapies, neurologic symptoms may exhibit early onset (within days to a week) or may be delayed several weeks following treatment ([Lee 2019](#)). Time to symptom resolution may be relatively short (hours to ~2–4 days) or prolonged for several weeks. Symptom severity may also fluctuate rapidly, necessitating close safety monitoring for signs and symptoms indicative of ICANS.

ICANS may be associated with CRS. Any neurotoxicity occurring concurrent with or subsequent to the CRS event does not inform the grade of CRS ([Table 4](#)); rather, the neurotoxicity grade is instead captured separately according to an ICANS-specific scale ([Table 6](#) and [Table 7](#)).

Recommendations for the clinical management of neurotoxicity are described in [Table 8](#).

**Neurologic toxicity is considered an AESIs for this study.** Refer to [Section 9.8](#) for reporting procedures.

**Table 6**                      **ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Consensus Grading for Adults**

Neurotoxicity Domain	Severity <sup>a</sup>			
	Grade 1	Grade 2	Grade 3	Grade 4
<b>ICE Score<sup>b, c</sup></b>	7–9	3–6	0–2	0 (subject is unarousable and unable to perform ICE)
<b>Depressed level of consciousness<sup>d</sup></b>	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
<b>Seizure</b>	NA	NA	Any clinical seizure focal or generalized that resolves rapidly; or, Nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min) Repetitive clinical or electrical seizures without return to baseline in between
<b>Motor findings<sup>e</sup></b>	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
<b>Raised ICP/Cerebral edema</b>	NA	NA	Focal/local edema on neuroimaging <sup>f</sup>	Diffuse cerebral edema on neuroimaging Decerebrate or decorticate posturing Cranial nerve VI palsy Papilledema Cushing's triad

Adapted from [Lee 2019](#).

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; EEG = electroencephalogram; NA = not applicable.

- a. ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.
- b. Refer to [Table 7](#).
- c. A subject with an ICE score of 0 may be classified as having Grade 3 ICANS if the subject is awake with global aphasia. But a subject with an ICE score of 0 may be classified as having Grade 4 ICANS if the subject is unarousable.
- d. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
- e. Tremors and myoclonus associated with IEC therapies may be graded according to CTCAE but they do not influence ICANS grading.

Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE.



**Table 7 10-Point Immune Effector Cell-Associated Encephalopathy Score**

Category	Assessment	Maximum Points
Orientation	Orientation to year, month, city, hospital	4
Naming	Name 3 objects (eg, point to clock, pen, button)	3
Following commands	eg, Show 2 fingers or close your eyes and stick out your tongue	1
Writing	Ability to write as standard sentence (eg, Our national bird is the bald eagle)	1
Attention	Count backwards from 100 by ten	1
<b>TOTAL:</b>		<b>10 points</b>

**Scoring:**

Score 10: No impairment

Score 7–9: Grade 1 ICANS<sup>a</sup>

Score 3–6: Grade 2 ICANS<sup>a</sup>

Score 0–2: Grade 3 ICANS<sup>a</sup>

Score 0 due to subject unarousable and unable to perform ICE assessment: Grade 4 ICANS<sup>a</sup>

Abbreviations: ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune Effector Cell -Associated Encephalopathy.

<sup>a</sup> Refer to [Table 6](#).

Adapted from [Lee 2019](#).



**Table 8 Recommendations for the Management of Neurotoxicity/ICANS**

Grade <sup>a</sup>	Sign/ Symptom	Management <sup>e</sup>
<b>Grade 1</b>	<b>Any</b>	<ul style="list-style-type: none"> <li>• Symptomatic management as per institutional guidelines</li> </ul>
<b>Grade <math>\geq 2</math></b>	<b>Focal<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• Consider neurology consult and performing EEG</li> <li>• Perform daily neurological and mini-mental status examinations to evaluate for resolution/worsening of symptoms</li> <li>• Perform CNS imaging (MRI and/or contrast enhanced CT if MRI is not feasible or contraindicated) <ul style="list-style-type: none"> <li>◦ For persistent symptoms, consider repeat neuroimaging</li> </ul> </li> <li>• Consider CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria <ul style="list-style-type: none"> <li>◦ If negative for bacteria, consider CSF evaluations for other infectious etiologies (eg, herpes viruses, JC virus, fungal, West Nile virus and toxoplasma)</li> <li>◦ CSF samples should be sent to the Sponsor for research use to evaluate for the presence of BPX-601 T cells</li> </ul> </li> <li>• Administer anti-viral and/or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results)</li> <li>• Consider empiric use of anticonvulsants if seizure is expected</li> <li>• Start management of stroke/ischemia per institutional guidelines if suspected</li> <li>• A brain biopsy, as per the discretion of the site clinical research team, should be considered if other diagnostic tests do not reveal a reasonable etiology</li> <li>• For neurological symptoms without concurrent CRS or evidence of CNS/systemic infection, administer dexamethasone 10 mg IV every 6 hours or the dose equivalent of methylprednisolone <ul style="list-style-type: none"> <li>◦ Continue steroids until improvement to Grade 1 and then taper</li> </ul> </li> <li>• If associated with concurrent CRS, administer tocilizumab 8 mg/kg<sup>d</sup> IV or siltuximab 11 mg/kg IV <ul style="list-style-type: none"> <li>◦ If refractory to anti-IL-6 therapy, administer dexamethasone or methylprednisolone as above<sup>e</sup>.</li> </ul> </li> <li>• Transfer to ICU with consideration of need for mechanical ventilation as clinically indicated</li> </ul>

Grade <sup>a</sup>	Sign/ Symptom	Management <sup>e</sup>
Grade $\geq 2$	General <sup>c</sup>	<ul style="list-style-type: none"> <li>• Perform routine institutional care for subjects with altered mental status/obtundation (eg, continuous vital sign monitoring, oxygen, suction, airway protection measurements and consideration of need for mechanical ventilation, ICU admission)</li> <li>• Neurology consult and EEG evaluation</li> <li>• Complete blood count analysis and peripheral blood smear to evaluate for thrombotic microangiopathy (TTP/HUS)</li> <li>• Evaluate for electrolyte and acid-base etiologies</li> <li>• Evaluate for liver dysfunction and evidence of hyperammonemia/veno-occlusive disease</li> <li>• Perform daily neurological and mini-mental status examinations to evaluate for resolution/worsening of symptoms</li> <li>• Perform CNS imaging (MRI and/or contrast enhanced CT if MRI is not feasible or contraindicated) <ul style="list-style-type: none"> <li>◦ For persistent symptoms, consider repeat neuroimaging</li> </ul> </li> <li>• Perform CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria <ul style="list-style-type: none"> <li>◦ If negative for bacteria, consider CSF evaluations for other infectious etiologies (eg, herpes viruses, JC virus, fungal, West Nile virus and toxoplasma)</li> <li>◦ CSF samples should be sent to the Sponsor for research use to evaluate for the presence of BPX-601 T cells</li> </ul> </li> <li>• Consider empiric anti-viral and/or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results)</li> <li>• A brain biopsy, per the discretion of the site clinical research team, should be considered if other diagnostic tests do not reveal a reasonable etiology</li> <li>• For neurological symptoms without concurrent CRS or evidence of CNS/systemic infection, administer dexamethasone 10 mg IV every 6 hours or the dose equivalent of methylprednisolone <ul style="list-style-type: none"> <li>◦ Continue steroids until improvement to Grade 1 and then taper</li> </ul> </li> <li>• If associated with concurrent CRS, administer tocilizumab 8 mg/kg<sup>d</sup> IV or siltuximab 11 mg/kg IV <ul style="list-style-type: none"> <li>◦ If refractory to anti-IL-6 therapy, administer dexamethasone or methylprednisolone as above<sup>e</sup></li> </ul> </li> </ul>

Abbreviations: CNS = central nervous system; CRS = cytokine release syndrome; CSF = cerebral spinal fluid; CT = computed tomography; EEG = electroencephalogram; HUS = Hemolytic-uremic syndrome; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICU = intensive care unit; IL = interleukin; IV = intravenous; MRI = magnetic resonance imaging; TTP = Thrombotic thrombocytopenic purpura.

- Toxicity grade according to [Table 6](#).
- Includes but is not limited to cranial nerve abnormalities, brachial plexopathy, ischemia, nystagmus, pyramidal tract syndrome, radiculitis, focal seizure, stroke, transient ischemic attack.
- Includes but not limited to aphonia, ataxia, cognitive disturbance, depressed level of consciousness, dysarthria, dysphasia, encephalopathy, headache, hypersomnia, lethargy, memory impairment, meningismus, seizures, somnolence, tremor, visual disturbances.
- Maximum amount of tocilizumab per dose is 800 mg.
- If symptom management includes administration of corticosteroids or anti-IL-6 therapy, refer to [Section 7.6](#) for required safety blood samples for biomarker monitoring

## 7.4 General Toxicity Related to BPX-601 T cells

Toxicity related to BPX-601 T cells may result from antigen-specific attack on host tissues when the targeted tumor antigen is expressed on nonmalignant tissues (ie, “on-target, off-tumor” toxicity). The degree of on-target, off-tumor toxicity is likely related to the affinity of the CAR for its cognate antigen, the level of antigen expression on healthy tissue, the potency of the CAR, and the relative functional importance of the antigen as nontumor target. PSCA is highly overexpressed in a variety of malignancies, including those under investigation in this study, but also has a low level of expression in normal epithelial cells of prostate, urinary bladder, kidney, skin, esophagus, stomach, and placenta ([Abate-Daga 2014](#)). Consistent with its limited expression profile in healthy tissues, autoimmune toxicity has not been observed following treatment with anti-PSCA antibodies ([Antonarakis 2012](#); [Morris 2012](#)). However, the risk of autoimmune toxicity in response to BPX-601 T cell therapy is unknown.

Emerging data from the ongoing study suggest the potential for on-target/off-tumor toxicity following treatment with investigational products. Specifically, 4 of 5 subjects with pancreatic cancer who underwent Flu/Cy LD on Days -5, -4, and -3 followed by BPX-601 ( $5 \times 10^6$  cells/kg) on Day 0 and a single infusion of rimiducid (0.4 mg/kg) on Day 7 (dose regimen for Cohort 5B; [Table 3](#)) reported urological toxicity. Adverse events included mostly mild to moderate dysuria, cystitis, or hematuria (all nonserious and not dose limiting) considered by the Investigator to be related to BPX-601 T cells alone or BPX-601 T cells plus rimiducid.

If clinical signs or symptoms of urological toxicity are observed, subjects should receive symptom-directed supportive therapy. Recommendations for the clinical management of cystitis are described in [Table 9](#).

For clinical signs or symptoms of other suspected anti-PSCA-directed toxicity, subjects should receive symptom-directed supportive care as per institutional standards. If corticosteroid therapy is indicated, consider:

- Dexamethasone 10 mg IV every 6 hours or the dose equivalent of methylprednisolone
- If symptoms do not improve, consider an increased corticosteroid dose (eg, dexamethasone 20 mg IV every 6 hours)
- Continue the corticosteroid regimen until symptoms improve to Grade 1 and then taper.

For persistent symptoms that do not respond to corticosteroid intervention, other treatments may be considered such as anti-T cell antibodies (eg, anti-T cell globulin) or other cytotoxic anti-lymphocyte agents.



**Table 9 Recommendations for the Management of Cystitis**

Grade <sup>a</sup>	Management
<b>Grade 1</b>	<ul style="list-style-type: none"> <li>Assess for infectious etiology (urinalysis with cytology, culture, PCR analysis for BTK, adenovirus, or other infectious etiology)</li> <li>Initiate empiric, broad-spectrum antibiotics with adjustments, as necessary, based on cytology/culture results</li> <li>Initiate or increase hydration support (normal saline, furosemide) <ul style="list-style-type: none"> <li>Administer fluids (3 L/m<sup>2</sup>/day, oral or IV) in order to maintain urine specific gravity &lt;1.01</li> </ul> </li> <li>Ensure adequate pain control (analgesics, anticholinergics/antispasmodics [tolterodine, oxybutynin], phenazopyridine, Uro-BLUE™, hyoscyamine)</li> <li>Perform weekly urinalysis with cytology, culture, PCR analysis as clinically indicated until symptom resolution</li> </ul>
<b>Grade 2 or Grade 3</b>	<ul style="list-style-type: none"> <li>Manage as indicated for Grade 1</li> <li>Consider urology consult</li> <li>Assess and treat accordingly hemodynamic issues/coagulopathies until symptom resolution: <ul style="list-style-type: none"> <li>Measure platelets daily; maintain counts &gt;50,000/μL</li> <li>Measure serum creatinine daily</li> <li>Measure PT/PTT twice weekly</li> <li>As necessary, adjust doses for concomitant medications associated with increased risk for bleeding</li> </ul> </li> <li>Initiate procedures to ensure adequate bladder drainage as clinically indicated (bladder irrigation, continuous bladder irrigation, Foley catheter)</li> <li>Consider cystoscopy, upper urinary tract imaging as clinically indicated</li> </ul>
<b>Grade 4 or Grade 3 symptoms that persist</b>	<ul style="list-style-type: none"> <li>Manage as indicated for Grade 1</li> <li>Assess and treat accordingly hemodynamic/coagulopathies until symptom resolution as above</li> <li>Consider urology consult</li> <li>Consider initiating or supplement bladder irrigation as above with intravesicular instillations (alum, formalin) with or without hyperbaric oxygen therapy</li> </ul>

Abbreviations: BTK = Bruton's tyrosine kinase; IV = intravenous; L = liter; m = meter; PCR = polymerase chain reaction; PT = prothrombin time; PTT = partial thromboplastin time.

Grading criteria as per NCI CTCAE v4.03.

## **7.5 Safety Biomarker Monitoring in Response to BPX-601 T cell Related Toxicity**

For subjects with signs or symptoms of CRS, neurotoxicity, or other toxicity considered related to BPX-601 T cells, the following biomarker samples should be collected for safety monitoring at the time of the event or as soon as possible following diagnosis:

- Blood sample (serum) for peripheral cytokine assessment
- Whole blood sample for BPX-601 T cell tracking and functional activity
- Urine sample for BPX-601 T cell tracking and functional activity (in the event of BPX-601 T cell related urological toxicity only).

## **7.6 Pharmacokinetics and Biomarker Samples following Infusions of Corticosteroids or anti-IL-6 Therapies (tocilizumab, siltuximab)**

In the event of corticosteroid (eg, dexamethasone) or anti-IL-6 (tocilizumab, siltuximab) therapy for symptomatic AE management in response to treatment with investigational products ([Section 7.3](#)), blood (serum) samples for peripheral cytokine assessment, and whole blood samples for BPX-601 T cell tracking and functional activity must be drawn at the following time points: before the infusion (-5 min) and at 4 and 24 hours ( $\pm 30$  min) after the start of the infusion, and every 24 hours ( $\pm 1$  hour) thereafter until symptom resolution. Samples may be collected more frequently as clinically indicated.

If event onset coincides with a planned time point ([Appendix 1](#) and [Appendix 5](#)), proceed with the scheduled collection. Additional samples may be collected as clinically indicated for further safety monitoring. Refer to the Laboratory Manual for collection instructions.

## **7.7 Concomitant Therapies**

Subjects may receive concomitant medications and procedures as required or deemed necessary for supportive care, unless specifically restricted or prohibited in this study ([Section 7.8](#)).

During the study, subjects should continue the use of prescribed medications identified at Screening, consistent with study inclusion and exclusion criteria.

If clinically indicated to control disease, bridging therapy may be administered after apheresis and should be discontinued 2 weeks before lymphodepleting chemotherapy, upon discussion with and approval by the Sponsor.

Ongoing bisphosphonate therapy or denosumab are allowed for supportive/palliative care.

Palliative radiotherapy (eg, focused radiotherapy for bone metastases) may be permitted upon discussion with and approval by the Sponsor.

Continued androgen deprivation therapy is allowed for subjects with prostate cancer.

Anticoagulant prophylaxis for venous thromboembolism per institutional standards is allowed.

## **7.8 Prohibited Therapies**

The following medications are not permitted from the Screening visit through completion of the EOT Visit unless otherwise indicated:

- Approved or investigational nonstudy chemotherapy, small molecule, immunotherapy, monoclonal antibody, radiotherapy (nonpalliative), medical device or other cellular therapy intended to treat the disease under study unless there is clinical or radiographic evidence of confirmed disease progression
- Systemic corticosteroids >10 mg/day of prednisone or equivalent (unless used for management of treatment-related toxicity)
- Live vaccines
  - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed
  - Intranasal influenza vaccines (eg, Flu-Mist<sup>®</sup>) are live attenuated vaccines and are not permitted.

There are no prohibited therapies or procedures once the subject has completed the EOT visit.

## **8 STUDY PERIODS, PROCEDURES, AND ASSESSMENTS**

### **8.1 Subject Enrollment, Registration, and Assignment to Treatment**

Informed consent will be obtained from each subject after the nature of the study is explained and prior to the performance of any study-specific procedures. This study will utilize >1 ICF:

- Prescreening ICF for pancreatic cancer patients: applies only to study assessments during the Prescreening period ([Appendix 1](#)). Consent for Prescreening assessments should be obtained from all potential pancreatic cancer subjects.
- Screening/Study Treatment ICF (if applicable): applies to study assessments during the Screening, Enrollment, Baseline, Treatment, and Post-treatment Follow-up periods ([Appendix 1](#)).

After signing the Screening/Study Treatment ICF, an eligibility determination based on the study inclusion/exclusion criteria ([Section 5](#)) will be conducted for each subject at a Screening Visit ([Appendix 1](#)). The Investigator or designee shall complete a Subject Eligibility Form for eligible subjects and submit to the Sponsor. The Sponsor will provide the site with the planned treatment assignment (ie, study Part and cohort) for the subject. Subjects with assigned treatment will undergo apheresis according to the Schedule of Assessments ([Appendix 1](#)) and subsequently return to the site for a baseline evaluation and LD within 1 week of the planned BPX-601 T cell infusion.

For the purpose of this study, subject enrollment is synonymous with apheresis.

### **8.2 Description of Study Periods**

#### **8.2.1 Prescreening (any time during routine standard of care)**

All pancreatic cancer subjects must sign the Prescreening ICF prior to the conduct of any study-related prescreening procedures. The Prescreening period will begin after applicable ICF signature when the first prescreening assessment is conducted. The includes determination of tumor expression of PSCA, a preliminary review of the study eligibility criteria (ie, in anticipation of subsequent screening and study enrollment) and clinical evaluation as specified in the Schedule of Assessments ([Appendix 1](#)):

##### **Pancreatic Cancer Subjects:**

- PSCA expression testing using tumor tissue sample ([Section 8.3.14.1](#))

Pancreatic cancer subjects with documented positive PSCA tumor expression may proceed to the Screening phase. Subjects with PSCA-negative disease are not eligible for the study.

##### **Prostate Cancer Subjects:**

- Prostate cancer subjects considered suitable candidates for the study may proceed to the Screening phase without PSCA expression testing ([Section 1.2.3](#))

### **8.2.2 Screening (within 28 days of Enrollment/Apheresis)**

All subjects must sign the Screening/Study Treatment ICF prior to conduct of any further study--related procedures. The Screening period will begin after applicable ICF signature when the first screening assessment is conducted and continues through confirmation of enrollment. The Screening period includes a review of the eligibility criteria and clinical evaluation as specified in the Schedule of Assessments ([Appendix 1](#)).

Subjects who fail to meet eligibility criteria will be allowed to rescreen only once. The assessment(s) that initially resulted in the screen failure, including any other procedure including any other procedure that now falls out of designated screening window, must be repeated with the result(s) satisfying relevant eligibility criteria.

### **8.2.3 Enrollment/Apheresis**

In this study, subject enrollment is synonymous with apheresis.

To help mitigate the risk of insufficient sample collection due to treatment-related myelosuppression, the scheduled apheresis date should be  $\geq 14$  days or 5 half-lives, whichever is shorter, after the last dose of any prior or ongoing anticancer therapy. Additionally, systemic corticosteroids ( $\geq 10$ mg /day prednisone or equivalent) and other immunosuppressive therapies must be avoided for 7 days or 7 half-lives, whichever is shorter, before apheresis.

Refer to [Appendix 1](#) for required procedures and assessments to be performed before blood collection on apheresis day. Results must demonstrate that the subject has no evidence of clinically significant infection and adequate bone marrow function:

- Hemoglobin  $\geq 8$  g/dL
- Hematocrit  $\geq 24\%$
- Platelets  $\geq 20/\mu\text{L}$
- Absolute lymphocyte count  $\geq 200/\mu\text{L}$

Use of transfusion and growth factor support is permitted to meet these criteria. Subjects with a clinically significant infection should have cell collection delayed until the event resolves. If the scheduled apheresis is delayed  $>7$  days, hematology assessment must be repeated to confirm the above criteria are still met.



#### **8.2.4 Baseline (Day -14 to Day -1) including Lymphodepletion (Day -5, -4, and -3)**

Refer to [Appendix 1](#) for required baseline clinical assessments, including pretreatment biopsy and administration of lymphodepleting chemotherapy. If any baseline assessments or procedures are outside the eligibility criteria, please contact the Bellicum Medical Monitor before proceeding with LD.

Before initiation of LD, subjects must have:

- No evidence of clinically significant infection
- No clinically significant evidence of cardiac dysfunction
- No acute neurological toxicity Grade >1 (except peripheral sensory neuropathy)
- No temperature reading >38°C within 24 hours of the cyclophosphamide infusion on Day -5.

Should a subject not meet these criteria, please contact the Sponsor Medical Monitor before proceeding with LD.

#### **8.2.5 Treatment with Investigational Products: BPX-601 T cells and Rimiducid**

##### **8.2.5.1 BPX-601 T cells**

The Treatment period begins on Day 0 with BPX-601 T cell infusion ([Section 6.4.3](#)). Before infusion, subjects must have:

- No evidence of clinically significant infection
- No clinically significant evidence of cardiac dysfunction
- No clinically significant evidence of renal dysfunction
- No acute neurological toxicity Grade >1 (except peripheral sensory neuropathy)
- No temperature reading >38°C within 24 hours of the infusion

Additionally, systemic corticosteroids ( $\geq 10$  mg/day prednisone or equivalent) and other immunosuppressive therapies must be avoided for 7 days before cell infusion. Prophylactic use of antimicrobials is allowed, but subjects must not be receiving systemic treatment for an active infection within 2 weeks before BPX-601 T cell administration.

Should a subject not meet these criteria or if the infusion is considered a risk based on the Investigator's clinical judgment, please contact the Sponsor Medical Monitor. The BPX-601 T cell infusion must be delayed until the event resolves. If the BPX-601 T cell infusion is delayed >2 weeks, LD should be repeated unless otherwise agreed between the Investigator and Sponsor Medical Monitor.

#### 8.2.5.2 Rimiducid

Before each rimiducid infusion ([Section 6.4.4](#)), subjects must be assessed by a clinician and must have:

- No evidence of clinically significant infection, cardiac, or renal dysfunction
- No evidence of febrile neutropenia
- No acute neurological toxicity Grade >1 (except peripheral sensory neuropathy)
- No clinically significant ongoing toxicity related to BPX-601 T cells
- No temperature reading >38°C within 24 hours of the infusion

Should a subject not meet these criteria, or if the infusion is considered a risk based on the Investigator's clinical judgment, please contact the Sponsor Medical Monitor. The first rimiducid infusion may be delayed up to 14 days (until Day 21) to allow recovery from LD-related febrile neutropenia or other clinically significant event(s). For applicable subjects who receive subsequent rimiducid infusions, a  $\pm 1$ -day window from the scheduled infusion day may be applied to accommodate scheduling or other logistical issues provided there is  $\geq 48$  hours between consecutive doses. If rimiducid is not administered on the scheduled day, all post-infusion assessments should be shifted accordingly. If a dose is not administered within the protocol-specified window, it will be missed. Missed doses will not be made up.

Up to a 14-day period is allowed between rimiducid infusions to allow for symptom recovery. If the requisite clinical criteria for infusion are not met within this window, rimiducid treatment should be discontinued. Re-initiation of rimiducid dosing beyond the 14-day window may be considered following a discussion between the Investigator and Sponsor Medical Monitor.

During the Treatment phase, subjects will be closely monitored for AEs, laboratory abnormalities, and antitumor response. The frequency of study site visits and required study procedures and assessments to be conducted during the Treatment phase are outlined in [Appendix 1](#). Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

An EOT visit will be scheduled 12 months after BPX-601 T cell infusion or at the time disease progression is confirmed or rimiducid treatment is discontinued unless the subject has died, is lost to follow-up, or has withdrawn consent for study participation. Assessments to be performed at the EOT visit are outlined in [Appendix 1](#). The EOT visit should be completed before starting any subsequent anticancer treatment. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect information on any unresolved AEs.

### **8.2.6 Post-treatment Follow Up**

After the EOT visit, subjects will enter the Post-treatment Follow-up period and will complete routine follow-up visits for long-term safety evaluation and survival assessment (vital status and subsequent anticancer therapy monitoring) at Months 3, 6, and 12 (if not completed as part of the Treatment Period) after BPX-601 T cell infusion and thereafter at least twice annually for 4 years and once annually from years 6 to 15. The frequency of study visits and required procedures to be conducted during the Post-treatment Follow-up phase are specified in [Appendix 1](#).

If the subject discontinues before disease progression, the results of disease assessments performed according to standard of care will be collected, if available. Efficacy evaluations should be performed until disease progression, the start of new anticancer therapy, death, withdrawal of consent, or the subject is lost to follow-up.

### **8.3 General Study Assessments**

The following general assessments will be collected at Screening.

#### **8.3.1 Demography**

- Date of birth, age, gender, ethnicity, and race as allowed by local regulation

#### **8.3.2 Medical History**

- All active conditions, including the disease under study
  - Date of initial diagnosis
  - Primary histology
  - Disease stage and histology at Screening
- Any past medical condition considered to be clinically significant by the Investigator
- Height (without shoes)

#### **8.3.3 Prior Anticancer Therapy**

- All prior therapies, including surgery(ies), radiation, and interventional treatment regimens for management of the disease under study.

### **8.3.4 Safety Assessments**

Subject safety will be evaluated by collection of data on incidence, severity, and type of AEs, routine clinical laboratory assessments, physical examination including neurological evaluation, cardiac function tests, vital signs including weight, and ECOG performance status. Clinically significant changes from pretreatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to [Appendix 1](#). In addition to the weekly clinic visits scheduled during the first 2 months after the BPX-601 T cell infusion, mid-week phone calls may be made to the subject to help determine whether there is an emerging, acute condition that would require immediate safety evaluation by the Investigator on an inpatient or outpatient basis.

### **8.3.5 ECOG Performance Status**

The ECOG performance status scale ([Appendix 2](#)) will be used to grade changes in the subject's daily living activities.

### **8.3.6 Vital Signs**

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature will be obtained at each indicated visit. On infusion days for BPX-601 T cells and 0.4 mg/kg rimiducid infused over 2 hours, collect before dosing (-60 to -5 min) and at 0.25, 0.5, 1, 2, and 4 hours ( $\pm 5$  min) after the start of the infusion. For 0.8 mg/kg rimiducid infused over 4 hours, vital signs should be collected before dosing (-60 to -5 min) and at 0.25, 0.5, 1, 2, 4, and 6 hours ( $\pm 5$  min) after the start of the infusion. For 1.6 mg/kg rimiducid infused over 6 hours, vital signs should be collected before dosing (-60 to -5 min) and at 0.25, 0.5, 1, 2, 4, 6, and 8 hours ( $\pm 5$  min) after the start of the infusion. Vital signs should be obtained thereafter as clinically indicated until completion of the postinfusion safety monitoring period.

### **8.3.7 Physical Examination and Weight**

#### **8.3.7.1 Comprehensive Physical Examination**

Complete physical examinations will be conducted at Screening and EOT. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; and lymph nodes.

#### **8.3.7.2 Symptom-directed Physical Examination**

Symptom-directed physical examinations may be conducted at all other visits as indicated. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

#### **8.3.7.3 Weight**

Weight (kilograms) will be obtained at each indicated visit (before infusion, if applicable). The measurement obtained during Screening will be used in BPX-601 T cell manufacturing. The measurement obtained at Baseline will be used to calculate the appropriate doses of LD therapy.

Rimiducid doses may be calculated on a monthly basis based on weight obtained at the first visit of each month or weight obtained at each visit before rimiducid infusion per institutional standard operating procedures.

### **8.3.8 Neurological Evaluation and ICE Score**

Subjects will undergo neurologic examination according to institutional standards at the frequency specified in [Appendix 1](#). An encephalopathy assessment should be performed in conjunction with all neurologic evaluations using the immune effector cell-associated encephalopathy (ICE) scale ([Table 6, Lee 2019](#)).

### **8.3.9 Cardiac Function Tests**

#### **8.3.9.1 Electrocardiogram**

Electrocardiograms (ECGs) should be conducted at the frequency specified in [Appendix 1](#) and [Appendix 5](#) and as clinically indicated.

Routine 12-lead ECG should be performed according to local standard practice after the subject has rested in a recumbent or semi-recumbent position for  $\geq 5$  min. ECG parameters (eg, heart rate, partial response (PR) interval, QT interval, QRS duration, and QTcF) should be interpreted by the Investigator for clinical significance and eligibility assessment.

#### **8.3.9.2 Echocardiogram/Multi-gated Acquisition Scan**

Routine echocardiogram (ECHO)/multi-gated acquisition (MUGA) should be performed according to local standard practice at the frequency specified in [Appendix 1](#). Cardiac function including left ventricular ejection fraction quantification should be assessed by the Investigator for clinical significance and eligibility assessment.

### **8.3.10 Adverse Events**

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the Investigator as specified in [Section 9](#).

### **8.3.11 Concomitant Medications**

Medications taken within 30 days before Screening/Study Treatment consent will be recorded as prior medications.

All concomitant medication administered from the time of Screening/Study Treatment ICF signature to the EOT visit will be recorded (including infusion premedications, blood products, and all over the counter medications, herbal remedies and dietary supplements). The generic name, dosage, duration, and reason for the concomitant medication should be included.

Following the EOT visit, concomitant medications will only be collected if associated with the management of an ongoing AE.

### 8.3.12 Clinical Laboratory Tests

Blood samples for serum hematology, coagulation, and chemistry will be collected according to the frequency specified in [Appendix 1](#). More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the subject or by abnormalities that warrant more frequent monitoring. The Investigator must review the laboratory reports, document this review, and ensure that any clinically relevant changes occurring during the study are recorded in the AE section of the electronic case report form (eCRF). The laboratory reports must be filed with the source documents.

The following tests will be performed either by the institution's local laboratory or a Bellicum--designated central laboratory:

<b>Hematology (eligibility and routine safety assessment – local laboratory)</b>	
<ul style="list-style-type: none"> <li>• White blood cell counts with differential</li> <li>• Red blood cells</li> <li>• Hemoglobin</li> </ul>	<ul style="list-style-type: none"> <li>• Hematocrit</li> <li>• Platelets</li> <li>• Absolute neutrophil count</li> </ul>
<b>Chemistry (eligibility and routine safety assessment – local laboratory)</b>	
<ul style="list-style-type: none"> <li>• Sodium</li> <li>• Potassium</li> <li>• Chloride</li> <li>• Bicarbonate</li> <li>• Creatinine</li> <li>• Blood urea nitrogen</li> <li>• Glucose, nonfasting</li> <li>• Calcium</li> <li>• Magnesium</li> </ul>	<ul style="list-style-type: none"> <li>• Phosphate</li> <li>• Albumin</li> <li>• ALT</li> <li>• AST</li> <li>• Bilirubin</li> <li>• Direct bilirubin</li> <li>• Alkaline phosphatase</li> <li>• LDH</li> </ul>
<b>Coagulation (eligibility and routine safety assessment – local laboratory)</b>	
<ul style="list-style-type: none"> <li>• PT</li> <li>• PTT</li> <li>• INR</li> </ul>	<ul style="list-style-type: none"> <li>• Fibrinogen</li> <li>• D-Dimer</li> </ul>
<b>Urinalysis (screening only, as clinically indicated thereafter – local laboratory)</b>	
Dipstick: <ul style="list-style-type: none"> <li>• Specific gravity</li> <li>• pH</li> <li>• Protein</li> <li>• Glucose</li> <li>• Ketones</li> <li>• Blood</li> </ul>	If dipstick is abnormal, microscopy will be used to measure sediment: <ul style="list-style-type: none"> <li>• Red blood cells</li> <li>• White blood cells</li> <li>• Epithelial cells</li> <li>• Crystals</li> <li>• Casts</li> <li>• Bacteria</li> </ul>

<b>Infectious Disease Panel (Screening - eligibility assessments to be conducted at local laboratory);</b> <b>(Apheresis/Enrollment - a second sample to be collected ≤7 days of apheresis/enrollment and shipped to a central laboratory)</b>	
<ul style="list-style-type: none"> <li>• Anti-HIV-1 antibody</li> <li>• Anti-HIV-2 antibody</li> <li>• HIV viral load (if indicated)</li> <li>• Hepatitis B surface antigen</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatitis B core antibody</li> <li>• Hepatitis B viral load (if indicated)</li> <li>• Hepatitis C antibody</li> <li>• Hepatitis C viral load (if indicated)</li> </ul>
<b>Pregnancy (eligibility and routine safety assessment – local lab)</b>	
<ul style="list-style-type: none"> <li>• Serum (β-human chorionic gonadotropin [β-hCG] or urine pregnancy testing for women of childbearing potential)</li> </ul>	
<b>Cytokines and CRS markers (routine safety assessment – local and Bellicum designated central lab)</b>	
<ul style="list-style-type: none"> <li>• IFN<sub>γ</sub></li> <li>• TNF<sub>α</sub></li> <li>• CRP</li> </ul>	<ul style="list-style-type: none"> <li>• IL-2</li> <li>• IL-6</li> <li>• Ferritin</li> </ul>
<b>Tumor Biomarkers (routine efficacy assessment – local lab)</b>	
<ul style="list-style-type: none"> <li>• CA19-9 (pancreas subjects only)</li> <li>• CEA</li> <li>• CRP*</li> </ul>	
<ul style="list-style-type: none"> <li>• PSA (routine efficacy assessment for prostate cancer subjects only – local lab); not done with Tumor Biomarkers above</li> </ul>	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen; CRP = C-reactive protein; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; IFN = interferon; IL = interleukin; INR = international normalized ratio; LDH = lactate dehydrogenase; PSA = prostate specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; TNF = tumor necrosis factor.

\* CRP to be collected only once on the days the Tumor and Cytokine/CRS biomarker schedules overlap.

### **8.3.13 Rimiducid Concentration Measurements (Pharmacokinetics)**

Blood samples (plasma) for analysis of rimiducid concentrations will be obtained to characterize the PK profile of rimiducid. Samples will be collected at the visits and time points indicated in [Appendix 1](#) and further detailed in [Appendix 5](#). For all planned PK time points up to 8 hours from start of infusion, blood must be collected from a peripheral vein contralateral to the arm/location into which rimiducid is administered. The time and date of each sample must be recorded; samples will be collected and processed by sites as outlined in the Laboratory Manual. All analyses will be conducted by the Sponsor or designee.

### **8.3.14 Research Laboratory Assessments**

Research laboratory assessments will be conducted to characterize the pharmacodynamics and mechanism of action of BPX-601 T cells administered with and without rimiducid. The results may help to inform dose selection and characterize on-treatment immune responses and cancer progression as well as monitor long-term safety. Research assessments planned for this study include:

- PSCA expression in a tumor biopsy (historical sample) by qPCR
- T cell phenotyping (transduced and nontransduced) using standard markers via flow cytometry analysis of whole blood and PBMCs and evaluation of functional activity
- Persistence of peripheral BPX-601 T cells by flow cytometry (cell counts) and qPCR (vector copy analysis)
- Serum cytokine analysis using a multiplex analysis technique
- Gene expression changes in the tumor microenvironment
- Tumor microenvironment assessment of markers associated with immune infiltrate including BPX-601 T cells
- Gene therapy monitoring for vector and replication competent retrovirus (RCR)

Peripheral blood and tumor tissue (biopsy) samples will be collected at the visits and time points indicated in [Appendix 1](#) and further detailed in [Appendix 5](#). Detailed information regarding sample collection, processing, and shipment is outlined in the Laboratory Manual.

All analyses will be conducted by the Sponsor or designee. Blood samples, tumor biopsies, and available archival tissue may also be used for exploratory evaluation of DNA, RNA, and/or proteins as potential tumor and immune-associated biomarkers.

Based on emerging data, site-specific collection feasibility, or for other operational reasons, the timing for sample collection may be adjusted, or certain samples may not be collected. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy,



completion of biomarker assessments is based on justification and intended utility of the data and/or analyses. No pharmacogenomic analyses will be conducted on biomarker samples.

#### 8.3.14.1 PSCA Evaluation

Study eligibility for pancreatic cancer subjects includes documented PSCA expression in a tumor tissue sample as assessed by a research use-only qPCR detection assay. Formal in-fixed, paraffin embedded tumor tissue is required for PSCA testing. During the Prescreening phase, all potential pancreatic cancer subjects will be required to provide archived tumor tissue or to undergo tumor biopsy if an archived sample is not available.

Due to the high prevalence of PSCA expression in primary and metastatic prostate cancer tissues, particularly in patients with advanced disease, subjects with prostate cancer deemed suitable for the trial may be screened without undergoing PSCA expression testing ([Section 1.2.3](#)). However, prostate cancer subjects are requested to provide archived tumor tissue before the start of LD in order to support exploratory analyses of baseline PSCA expression and safety/efficacy outcomes.

#### 8.3.14.2 BPX-601 T cell Tracking and Functional Activity

Persistence of genetically modified BPX-601 T cells in peripheral blood will be assessed by flow cytometry (eg, absolute count and percentage within the total lymphocyte population) and qPCR at a Bellicum designated central laboratory. Flow cytometry using standard activation markers may also be used for immunophenotyping of both BPX-601-engineered and endogenous T cells. In addition, T cell functional activity may be analyzed in PBMC samples using appropriate techniques.

#### 8.3.14.3 Cytokines

In addition to local serum testing for time-sensitive routine safety monitoring, blood (serum) will also be collected for centralized pharmacodynamic assessment using a multiplexed cytokine assay.

#### 8.3.14.4 Immunogenicity Assessment

Based on emerging data, residual blood (serum) samples collected for centralized cytokine assessment ([Section 8.3.14.3](#)) may be explored for the presence of anti-BPX-601 T cell antibodies. Anti-BPX-601 T cell antibodies will be assessed using a qualified method.

### **8.3.15 Pretreatment and On-Treatment Tumor Biopsy**

All subjects with accessible tumor are required to provide a pretreatment (tissue collected at Baseline) as well as on-treatment, fresh tumor biopsy following BPX-601 T cell therapy (tissue sample collected between Days 14 and 21), provided tissue collection is clinically feasible.

The Investigator should select a representative nontarget lesion amenable to pretreatment and post-treatment fresh biopsy. Both pretreatment and on-treatment biopsies should be obtained from the same tumor site(s) using standard techniques to yield adequate tissue for analysis. Fine needle aspirations will not be acceptable. The on-treatment biopsy may be deferred until the resolution of any ongoing toxicity if the biopsy is deemed by the Investigator to be not feasible during this time. A post-treatment biopsy may also be collected from all subjects at the time of disease progression, provided the same lesion for biopsy is accessible and tissue collection is clinically feasible. Tissue collected from additional clinically indicated biopsies during the study may also be sent to the Sponsor (or Bellicum-designated central laboratory) for analysis, when feasible. Detailed information regarding sample collection, processing, and shipment is outlined in the Laboratory Manual.

### **8.3.16 Gene Therapy Monitoring**

Per FDA guidelines, subjects will undergo blood testing for vector and RCR prior and 3 months after BPX-601 T cell infusion and then every 6 months from the date of infusion (ie, Day 0) for 5 years ([Table 10](#)). Beginning with year 6, blood samples will be drawn annually for another 10 years (total of 15-year follow-up). All samples collected at pre-infusion and during the initial 12 months after BPX-601 T cell therapy will be analyzed for RCR. If a result is positive during this time, all remaining samples for that subject collected during the 15-year follow-up period will also be analyzed. If all results are negative during the initial 12 months of RCR testing, sample collection can stop once 2 consecutive samples collected at least 6 months apart test negative for the presence of vector. Subjects are required to undergo RCR testing per the schedule below regardless of when the End of Treatment visit is completed.

**Table 10 Gene Therapy Monitoring Schedule**

Time Point of Collection	Clinical Evaluation	Blood
Before lymphodepletion	X <sup>a</sup>	X
Month 3 <sup>b</sup>	X <sup>a</sup>	X
Month 6 <sup>b</sup>	X <sup>a</sup>	X
Month 12 <sup>b</sup>	X <sup>a</sup>	X
Every 6 Months up to Year 5 <sup>b</sup>	X <sup>c</sup>	X <sup>d</sup>
Every 12 Months up to Year 15 <sup>b</sup>	X <sup>c</sup>	X <sup>d</sup>

- Includes Eastern Cooperative Oncology Group performance status, vital signs, symptom-directed physical exam, and adverse event monitoring. Refer to [Appendix 1](#).
- Time points of collection are calendar-based from the time of BPX-601 T cell infusion. Samples must be collected according to the specified frequency; the scope and timing of sample collection is independent of an End-of-therapy visit that occurs before Month 12.
- Includes adverse event monitoring.
- If blood samples collected during the initial 12 months after BPX-601 T cell infusion are negative, remaining blood samples collected will be archived, and sample collection can stop following 2 consecutive negative results in testing for vector persistence in samples collected at least 6 months apart.

### 8.3.17 Efficacy Assessments: Tumor Imaging, Laboratory, and Radiological Evaluations

Radiologic evidence of disease is required at Screening to confirm subject eligibility. Standard of care assessments if performed within 6 weeks of Screening may be used to assess disease status. Screening scans will be used for determination of eligibility only, and not for assessment of radiographic response.

#### 8.3.17.1 Subjects with Measurable Disease

Radiographic response will be determined in comparison to tumor measurements obtained at Baseline. The baseline scan must be conducted within 14 days of BPX-601 T cell infusion and after the last dose of any salvage chemotherapy administered after apheresis. Tumor imaging will be performed using the same assessment technique throughout the study. Refer to [Appendix 1](#) for detailed information regarding the schedule and frequency for tumor imaging. Radiographic assessments will be performed at Screening, at Baseline and approximately every 8 weeks thereafter ( $\pm 7$  days) for the first year following BPX-601 T cell infusion, then every 12 weeks ( $\pm 14$  days) for the second year, then annually until confirmed disease progression, the start of new anti-cancer therapy, withdrawal, or study end. If a subject discontinues the Treatment period for reasons other than PD, continue imaging per standard of care frequency until documented disease progression, withdrawal, or study end. Tumor images may be sent to a Bellicum-designated vendor for centralized storage and subsequent analysis.

Radiographic tumor evaluation will include clinical examination and appropriate imaging techniques, preferably computed tomography (CT) scans with contrast of the chest, abdomen, and pelvis with  $\leq 5$  mm slice thickness. Magnetic resonance imaging (MRI) is required at Screening to document central nervous system metastases. Subjects without brain lesions do not require brain imaging on study unless clinically indicated. A bone scan should be

conducted for known or suspected bone metastases. If CT scan is contraindicated (eg, allergy to contrast dye), MRI should be performed. Tumor imaging will be performed using the same assessment technique throughout the study.

Disease imaging will be evaluated locally by the Investigator for response assessment using RECIST v1.1 (pancreas [Appendix 6](#)) or PCWG3 (prostate cancer; [Appendix 7](#)), in addition to serum tumor response (eg, CA19-9 and PSA, respectively).

If an initial complete response (CR) or PR is noted, confirmatory scans must be performed  $\geq 4$  weeks later. In the case of stable disease (SD), follow-up imaging must have met the SD criteria at least once after study entry and no less than 4 weeks.

If radiographic disease progression is observed, another scan should be performed no less than 4 weeks later (or 6 weeks for subjects with prostate cancer) to confirm disease progression before treatment discontinuation. If progression is not confirmed, imaging reassessment and clinic evaluations should continue according to the scheduled frequency provided the subject does not have significant clinical decline. Subjects discontinued after confirmation of progression should complete the EOT Visit and enter the Post-treatment Follow-Up Period.

Prostate cancer subjects with lymph node/soft tissue/visceral metastases will be evaluated by RECIST criteria regardless of bone involvement.

#### 8.3.17.2 Prostate Cancer Subjects with Bone-only Disease

Bone scans will be evaluated per PCWG3 criteria ([Scher 2016](#)) to determine disease progression. Scans will be scheduled at Baseline and then every 8 weeks during study participation. The absence of confirmed new lesions will be considered SD.

Disease progression will be established under the following scenario. In brief, if  $\geq 2$  new lesions are observed on a post-treatment scan, relative to Baseline, and then  $\geq 2$  additional lesions on the next confirmatory scan (2+2 rule) are observed, progression can be declared. If  $\geq 2$  additional new lesions are seen on the confirmatory scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented.

PSA will be measured at Screen, at Baseline and then every 4 weeks. Additional PSA evaluations should be conducted at the investigator's discretion or when clinically indicated. Progression will be determined by PCWG3 criteria. Response to treatment will be defined as a decline  $\geq 50\%$  from baseline when measured twice  $\geq 3$  to 4 weeks apart.



## **9 ADVERSE EVENT REPORTING**

### **9.1 Safety Parameters and Definitions**

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry variables vital signs and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to the FDA, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

### **9.2 Adverse Events**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

1. AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present before the AE reporting period
2. Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
3. Abnormal laboratory values or test results that induce clinical signs or symptoms and are considered clinically significant

### **9.3 Serious Adverse Events**

An SAE is any AE that is any of the following:

1. Fatal (ie, the AE actually causes or leads to death)
2. Life threatening (ie, the AE, in the view of the Investigator, places the subject at immediate risk of death)
3. Requires or prolongs in subject hospitalization
4. Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
5. A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
6. Considered a significant medical event by the Investigator (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **nonserious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the CRF and reported to the Sponsor in accordance with protocol instructions.

#### **9.4 Assessment of Adverse Events by the Investigator**

The Investigator will assess the severity (intensity) of each AE and the potential relationship (causality) between the AE and the study treatment.

##### **9.4.1 Assessment of Severity**

The severity of all AEs except CRS and Immune Effector Cell Associated Neurotoxicity (ICANS) will be graded according to the NCI CTCAE v. 4.03; <http://ctep.cancer.gov/reporting/ctc.html>). Grading criteria for CRS and ICANS are provided in [Table 4](#) and [Table 6](#) respectively. For AEs not listed in the CTCAE, the following grading system will be used:

- Mild (CTCAE Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (CTCAE Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental activities of daily living
- Severe (CTCAE Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life-threatening (CTCAE Grade 4): Life-threatening consequences; urgent intervention indicated
- Death (CTCAE Grade 5): Death related to AE

#### **9.4.2 Assessment of Causality**

The Investigator will estimate the relationship between the applicable study treatment (apheresis, conditioning chemotherapy, investigational products BPX-601 T cells or rimiducid, or any combinations thereof) and the occurrence of each AE or SAE. The relationship (synonym: causality) is based on the Investigator's clinical judgment regarding the likelihood that the event is assessed as "related" or "not related" to the study treatment. An Investigator assessment of "related" means there is a reasonable possibility the event is attributed to the study treatment. An assessment of "not related" means there is no reasonable possibility of the event being attributed to the study treatment.

#### **9.5 Disease-Related Events Not Qualifying as AEs**

An event which is part of the natural course of the disease under study (ie, disease progression, death due to disease progression) should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the definition of an AE or SAE ([Section 9.2](#) and [Section 9.3](#)).

For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE or SAE as applicable.

## 9.6 Adverse Event Reporting Period

Safety reporting periods for this study are defined in [Table 11](#).

**Table 11 Safety Reporting Periods**

Event Type	Reporting Period	Additional Requirements
SAEs (screening)	Date of informed consent and before apheresis	<ul style="list-style-type: none"> <li>Report new SAE only if caused by a protocol-mandated intervention during Prescreening and Screening</li> </ul>
AEs (treatment-emergent)	From the date of apheresis until 30 days following infusion of BPX-601 T cells or rimiducid, whichever occurs later	<ul style="list-style-type: none"> <li>Report new AEs for up to 15 years if assessed as related to the investigational products BPX-601 T cells or rimiducid or other study treatment as defined in <a href="#">Section 6.1</a></li> </ul>
SAEs (treatment-emergent)	From the date of apheresis until 180 days following infusion of BPX-601 T cells or rimiducid, whichever occurs later	<ul style="list-style-type: none"> <li>Report new SAEs for up to 15 years if assessed as related to the investigational products BPX-601 T cells or rimiducid or other study treatment as defined in <a href="#">Section 6.1</a></li> <li>Report diagnosis of any new secondary malignancy regardless of relationship to study treatment for up to 15 years</li> </ul>
Adverse events of special interest (treatment-emergent)	From the date of apheresis until 180 days following infusion of BPX-601 T cells or rimiducid, whichever occurs later	<ul style="list-style-type: none"> <li>Report new AESI for up to 15 years if assessed as related to the investigational products BPX-601 T cells or rimiducid or other study treatment as defined in <a href="#">Section 6.1</a></li> </ul>
Pregnancy of subjects or partner	No less than 12 months following the last dose of cyclophosphamide in the lymphodepletion regimen	<ul style="list-style-type: none"> <li>As per <a href="#">Section 9.10</a></li> <li>Report diagnosis of any congenital abnormality in offspring from a study participant for up to 15 years</li> </ul>

## 9.7 Reporting Requirements for SAEs

### 9.7.1 Initial Reports

An SAE report will be completed for each observed SAE. The Investigator will submit SAE information to the Sponsor or designee within 24 hours of learning about the initial event. The initial report will contain all available details about the event. If the Investigator does not have all information about an SAE within the submission window, the Investigator will not wait to receive additional details before notifying the Sponsor of the event. Relevant follow-up information should be submitted to the Sponsor or designee within 24 hours of awareness of the new information and/or upon request.

### 9.7.2 Expedited Reporting Requirements

Upon receipt of a suspected unexpected serious adverse reaction (SUSAR) report from the Sponsor, the Investigator must comply with all applicable requirements related to the reporting of SUSARs per institutional guidelines.



## **9.8 Adverse Events of Special Interest**

The following events are considered AESI and should be reported following SAE reporting procedures ([Section 9.7](#)). These events have been identified as serious risks associated with approved CAR T cell therapies and can result in severe and fatal reactions. The following AEs (irrespective of severity, attribution, or seriousness) will therefore be monitored as AESI in this study:

- Cytokine release syndrome
- Neurologic toxicity/ICANS
- Any event that satisfies the definition of DLT ([Section 4.3](#))

## **9.9 Adverse Event Follow-Up Reporting**

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized (in the case of persistent impairment), the subject dies or is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the CRF and in the subject's medical record to facilitate source data verification.

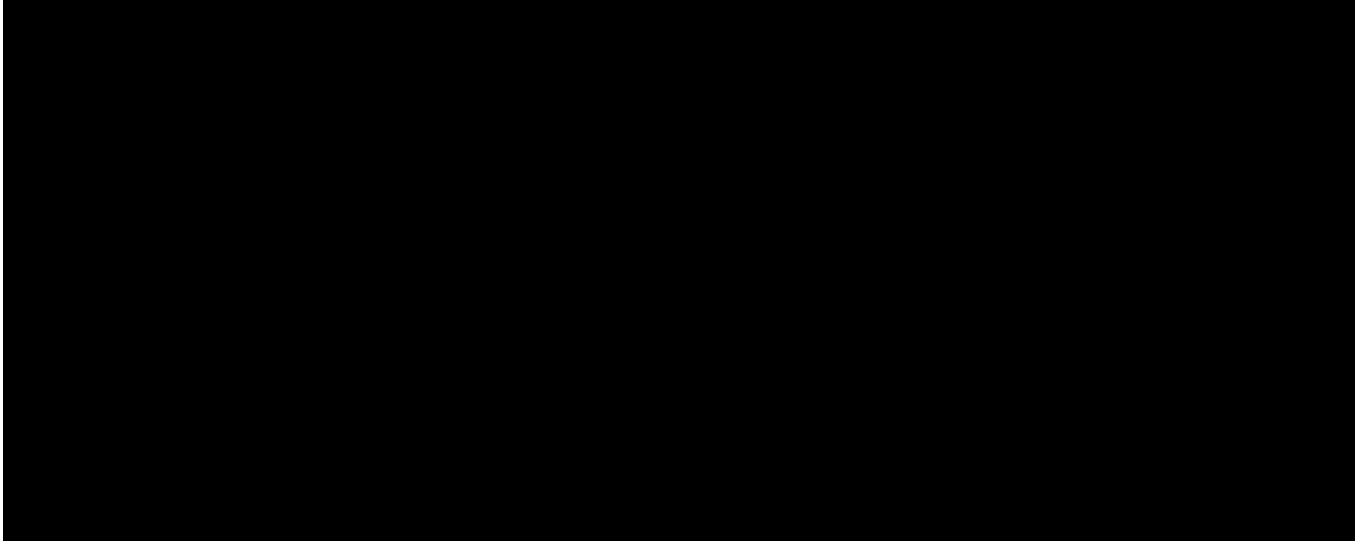
For SAEs, the Sponsor or designee may utilize telephone, fax, or electronic mail communications as well as monitoring visits to obtain additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report). Within 24 hours of receipt of new follow-up information, the Investigator must update the SAE report and submit any supporting documentation to the Sponsor or designee.

## **9.10 Pregnancy Reporting**

The Investigator should report to the Sponsor or designee all instances of pregnancy in female subjects or partners of male subjects within 24 hours of their knowledge of the pregnancy using the Pregnancy Form. In addition, abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

### **9.11 Safety Reporting Contact Information**

SAE and pregnancy reporting contact information are provided below. All reports (initial and follow-up) for screening and treatment-emergent SAEs, AESI, and pregnancy should be directed to the electronic SAE reporting mailbox (primary route of submission) or facsimile (back-up):



## **10 STATISTICAL METHODS**

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics by dose level/Part and tumor type. Continuous variables will be summarized using the number of observations, mean, standard deviation, median, and range as appropriate. The geometric mean and coefficient of variation will be presented for select PK parameters, as appropriate. Categorical values will be summarized using the number and percentage of subjects in each category of interest. Within-group percentages may be accompanied by 2-sided exact 95% CIs, where appropriate. Descriptive summaries of time to event data from Kaplan Meier estimates will include the number of events, number of subjects censored, medians, quartiles and 95% CIs. Graphical summaries of the data may be presented.

The Sponsor will establish a clinical data cutoff date for clinical study report analysis reporting 12 months after the last subject has received BPX-601 T cells or after all subjects have discontinued the study, whichever comes first. Data displayed from Parts 2 and Parts 3 of the Phase 2 portion of the study may be combined, as appropriate.

### **10.1 Sample Size Determination**

#### **Phase 1 (Part 1): Dose Escalation**

One or more dose cohorts of  $\geq 3$  subjects will be enrolled at a cell dose level including up to 6 subjects at the RP2D. Additional subjects (up to 10) may be enrolled to a completed dose level that has previously been assessed as safe to better characterize safety and pharmacodynamic relationships, including the safety and pharmacodynamics of the investigational products following LD with Flu/Cy, before defining the RP2D.

The total number of subjects enrolled in Part 1 will depend on the frequency of DLT and when RP2D is determined.

## **Phase 2 (Parts 2 and 3): Indication-Specific Dose Expansion**

The dose expansion phase of this study is not designed with explicit power and Type I error considerations in mind. Instead, the Phase 2 portion of the study is designed to obtain preliminary efficacy and additional safety and PK/pharmacodynamic data on the activation-inducible CAR T cell therapy, BPX-601, targeting PSCA tumor antigen administered at the RP2D to subjects with disease indications of high unmet clinical need and that express high levels of PSCA. Preliminary efficacy will be assessed by objective response rate (ORR), defined for those subjects with measurable disease at baseline as the proportion of subjects with an objective response (CR or PR) per RECIST v1.1 during Part 2 (and those subjects treated at the RP2D in Phase 1) as well as Part 3 (for those indications that achieve a minimum of 10% ORR in Part 2 and that the Sponsor deems as having a promising risk/benefit profile). For prostate cancer subjects, efficacy will also be assessed per PCWG3 criteria, and for those with bone-only disease, the proportion of subjects who have not progressed at fixed time intervals (eg, 6 and 12 months) will be reported. Response to treatment will be summarized separately for prostate cancer subject with bone-only disease, defined as a decline  $\geq 50\%$  from baseline when measured twice  $\geq 3$  to 4 weeks apart.

In each cohort of the Phase 2 study, an interim analysis will be performed after approximately 10 subjects have been enrolled and completed  $\geq 1$  postbaseline disease evaluation (Part 2). A recommendation regarding further enrollment will be based on observed clinical activity in each disease indication compared to historical controls (eg,  $< 10\%$  ORR). If the interim analysis suggests the clinical activity in an experimental arm is higher than that observed in relevant historical controls, up to 30 additional subjects may be enrolled into Part 3 of the study. Interim analyses will be performed and interpreted by the Sponsor.

### **10.2 Analysis Populations**

The following analysis populations will be used for this study:

- **Intent-to-treat:** all subjects who underwent apheresis
- **Safety-evaluable:** all subjects infused with any quantity of BPX-601 T cells
- **Efficacy-evaluable:** all subjects treated with BPX-601 T cells who had evaluable disease at baseline and  $\geq 1$  post-baseline assessment of tumor response
- **Rimiducid PK:** all subjects treated with the planned dose of BPX-601 T cells and  $\geq 1$  dose of rimiducid with  $\geq 1$  evaluable concentration measurement of rimiducid

### **10.3 Subject Disposition**

Subject disposition summaries will include the number of enrolled subjects, number of subjects receiving conditioning chemotherapy, the number of subjects receiving BPX-601 T cells with and without rimiducid, the number of subjects withdrawing prematurely, and the reasons for treatment and study discontinuation.

Demographics, baseline disease characteristics, prior disease related therapies, and concomitant medications will be summarized using descriptive statistics.

#### 10.4 Safety Analyses

All safety analyses will be performed according to study phase, treatment cohort, and tumor type, as appropriate. The baseline value for safety assessment is defined as the value collected at the time closest to, but before, BPX-601 T cell infusion. The safety parameters to be evaluated are the incidence, severity, and type of AEs, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study treatment and reasons for discontinuation will be tabulated.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA); severity assessment by the Investigator will be performed as described in [Section 9.4.1](#). AEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency. Incidences of AEs and SAEs will be summarized overall and with respect to severity and relationship to study drug. AEs leading to treatment discontinuation, infusion interruption, and with an outcome of death will also be summarized. Incidences of SAEs and AESIs will be summarized overall and with respect to relationship to study treatment.

Clinically significant changes from baseline in ECOG and changes from baseline in CTCAE grading for vital signs, ECG interpretation, and safety laboratory parameters will be examined and presented in shift tables. All abnormal laboratory parameters will be listed.

#### 10.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be described separately outside the context of this protocol.

#### 10.6 Efficacy Variables and Analyses

Clinical response to the investigational product will be determined by the Investigator's assessment. All efficacy endpoints will be defined and analyzed according to RECIST v1.1 (pancreatic cancer; [Eisenhauer 2009](#)) or PCWG3 (prostate cancer; [Scher 2016](#)).

The following efficacy endpoints will be derived and summarized descriptively according to study phase, treatment cohort, and tumor type.

**Objective Response Rate (ORR)** is defined as the proportion of subjects with a best overall response of PR or CR according to RECIST v1.1 or PCWG3 criteria, as applicable, or as a PSA decline  $\geq 50\%$  from baseline when measured twice  $\geq 3$  to 4 weeks apart for prostate cancer subjects.

**Duration of response** is defined as the time from the first tumor assessment that supports the subject's objective disease response to the time of disease progression or death due to any cause.

**Disease control rate** is defined as subjects with CR, PR, or SD per RECIST v1.1 or PCWG3 criteria, as applicable.

**Progression-free survival** is defined as the time from BPX-601 T cell infusion to first documentation of disease progression or death due to any cause. Subjects who do not experience PD and are alive will be censored at the time of last evaluable tumor assessment.

**Overall Survival** defined as the time from BPX-601 T cell infusion until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive.

### **10.7 Research Laboratory Analyses**

Analyses of research laboratory samples, tumor markers, samples for gene therapy monitoring, tumor biopsies, and immune response data will be described separately outside the context of this protocol and in the Statistical Analysis Plan.

### **10.8 Interim Analysis**

For each disease indication in dose expansion, 1 interim analysis is planned to evaluate the antitumor activity of BPX-601 T cells administered with rimiducid. The analysis will be performed after 10 subjects with a given tumor type have been enrolled in Part 2 of the study, including those receiving the RP2D in Part 1, and have  $\geq 1$  postbaseline disease assessment; data will be analyzed separately for each disease indication. The interim analysis will follow the rules outlined in [Section 4.4](#). Review and communication of results will be addressed by the SRC as described in [Section 4.5](#).

### **10.9 Data Monitoring Committee**

There will be no formal Data Monitoring Committee for this study. Treatment emergent safety and efficacy data will be reviewed by the SRC comprised of participating Investigators in the study, the Safety Monitor, and Sponsor representatives ([Section 4.5](#)).

## **11 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS**

### **11.1 Institutional and Ethical Review**

The study will be conducted according to the ethical principles of the declaration of Helsinki, the ICH-Good Clinical Practices (GCP) Guidelines, FDA and other applicable regulatory agencies.

### **11.2 Investigator Responsibilities**

By signing this document, the Investigator agrees to carry out this research in accordance with the protocol approved by the IRB, ICH GCP and all applicable regulatory requirements. The Investigator is responsible for ensuring that site personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

### **11.3 Subject Informed Consent and Human Subject Protection**

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to initiation of any study-related procedures.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by all applicable local regulatory authorities and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. As part of this discussion, the Investigator should clarify alternate therapy options and the associated risks/benefits.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing that the quality of medical care will not be adversely affected if they decline to participate in this study.



#### **11.4 Confidentiality and Privacy**

Participant confidentiality and privacy is held in trust by the participating Investigators, their staff, and the Sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB or EC, or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Subject research data, which is for purposes of statistical analysis and scientific reporting, will be entered into an electronic clinical study database maintained by the Sponsor or designee. This will not include the subject's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived according to the Sponsor's standard policies.

#### **11.5 Clinical Monitoring**

Clinical site monitoring will be conducted by the Sponsor or designee to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

The investigational site will provide direct access to all trial-related information, source data/documents, and reports for the purpose of monitoring by the Sponsor, and inspection by local and national regulatory authorities.

## **11.6 Data Handling and Record Keeping**

### **11.6.1 Data Collection and Management Responsibilities**

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Investigator will review all the CRF of each subject and confirm the completeness, medical correctness, and plausibility of the documented data by his/her electronic signature.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Study data will be entered by the site staff into a 21 Code of Federal Regulations Part 11-compliant electronic data capture system maintained by the Sponsor or designee. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into the electronic CRF from the source documents and should be consistent with the latter.

### **11.6.2 Study Records Retention**

Study documents should be retained by the site for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until  $\geq 2$  years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

## **11.7 Protocol Deviations**

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the reviewing IRB per local regulations.

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Clinical Trials.Gov Identifier NCT02414269: A Phase I Clinical Trial of Malignant Pleural Disease Treated With Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin (accessed 12 June 2018)

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### 13 APPENDICES

#### 13.1 Appendix 1 Schedule of Assessments

##### Appendix 1a Schedule of Assessments for Subjects Receiving a SINGLE Rimiducid Infusion

Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment														EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1							2			3, 4, 5, 6, 9			12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>
Day				-14 to -1	0	1, 2, 4	7	8	10	14	17	21	28	35	42	56						
Window, days					(±1) Day 4		±3		±1	±2							±7			±7	±14	±14
Informed consent	X	X																				
PSCA expression <sup>g</sup>	X																					
Infectious disease monitoring <sup>h</sup>		X	X																			
Inclusion/exclusion criteria		X																				
Demography <sup>i</sup>		X																				
Medical history <sup>i</sup>		X																				
Prior medications, including prior anticancer therapy <sup>i</sup>		X																				
Physical exam (complete) <sup>j</sup>		X																X				
Weight <sup>j</sup>		X		X <sup>k</sup>																		
Apheresis <sup>l</sup>			X																			
Lymphodepletion <sup>m</sup>				D -5 D -4 D -3																		
<b>STUDY TREATMENT</b>																						
BPX-601 T cell infusion <sup>a</sup>					X																	
Rimiducid infusion (Day 7) <sup>o</sup>							X															

Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment														EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1							2			3, 4, 5, 6, 9			12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>
Day				-14 to -1	0	1, 2, 4	7	8	10	14	17	21	28	35	42	56						
Window, days						(±1) Day 4	±3		±1	±2							±7			±7	±14	±14
SAFETY ASSESSMENTS																						
ECOG performance status		X		X <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs <sup>p</sup>				X <sup>k</sup>	X <sup>p</sup>	X	X <sup>p</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam (symptom-directed) <sup>j</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological exam, ICE Score <sup>q</sup>					X <sup>q</sup>	X	X <sup>q</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac function tests <sup>r</sup>		X																				
ECG <sup>s</sup>		X					X	X														
Adverse events <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone contact <sup>u</sup>					Once weekly on nonsite visit days as clinically indicated																	

Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment														EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1								2			3, 4, 5, 6, 9	12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>	
Day				-14 to -1	0	1, 2, 4	7	8	10	14	17	21	28	35	42	56						
Window, days						(±1) Day 4	±3		±1	±2							±7			±7	±14	±14
LAB ASSESSMENTS																						
Hematology		X	X	X <sup>k</sup>	X		X	X		X		X	X	X	X		X		X			
Chemistry		X		X <sup>k</sup>	X		X	X		X		X	X	X	X		X		X			
Coagulation		X		X <sup>k</sup>	X		X	X		X		X	X	X	X		X		X			
Urinalysis		X		X <sup>k</sup>																		
Rimiducid PK <sup>v</sup>							X	X														
Pregnancy test		X		X <sup>k</sup>									X				X		X			
Cytokines <sup>w</sup>				X <sup>k</sup>	X <sup>w</sup>	X	X <sup>w</sup>	X	X	X	X	X	X	X	X							
BPX-601 T cell tracking and functional activity <sup>x</sup>				X <sup>k</sup>	X <sup>x</sup>	X	X <sup>x</sup>	X	X	X	X	X	X	X	X		X		X			
Tumor biomarkers <sup>y</sup>		X		X <sup>k</sup>									X				X	X	X			
Tumor biopsy <sup>z</sup>				X <sup>k</sup>					Days 14-21									X				
Gene therapy monitoring <sup>aa</sup>				X <sup>k</sup>													M3 M6	X		X	X	X
PSA (prostate cancer subjects) <sup>ee</sup>		X		X									X			X	X	X				
EFFICACY ASSESSMENTS																						
Tumor imaging and response assessment		X <sup>bb</sup>		X <sup>cc</sup>											X <sup>dd</sup>		X <sup>dd</sup>			X <sup>dd</sup>	X <sup>dd</sup>	X <sup>dd</sup>
Vital status																				X	X	X
Subsequent anticancer therapy																		X	X	X	X	X

**Appendix 1b Schedule of Assessments for Subjects Receiving WEEKLY Rimiducid Infusions**

Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment																	EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1										2 thru 11				12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>		
Day				-14 to -1	0	1, 2, 4	7	8	10	14	15	17	21	22	28	7	14	21	28	28					
Window, days						±1 Day 4	±3		±1	±2					±3				±7		±7	±14	±14		
Informed consent (Prescreen)	X																								
PSCA expression <sup>g</sup>	X																								
Infectious disease monitoring <sup>h</sup>		X	X																						
Informed consent (Screening/Study Treatment)		X																							
Inclusion/exclusion criteria		X																							
Demography <sup>i</sup>		X																							
Medical history <sup>i</sup>		X																							
Prior medications, including prior anticancer therapy <sup>i</sup>		X																							
Physical exam (complete) <sup>j</sup>		X																		X					
Weight <sup>j</sup>		X		X <sup>k</sup>												X <sup>j</sup>									
Apheresis <sup>l</sup>			X																						
Lymphodepletion <sup>m</sup>				D -5 D -4 D -3																					
STUDY TREATMENT																									
BPX-601 T cell infusion <sup>n</sup>					X																				
Rimiducid infusion <sup>o</sup>							X			X			X		X	X	X	X	X						
SAFETY ASSESSMENTS																									
ECOG performance status		X		X <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X				X			X		
Vital signs <sup>p</sup>				X <sup>k</sup>	X <sup>p</sup>	X	X <sup>p</sup>	X	X	X <sup>p</sup>	X	X	X <sup>p</sup>	X	X <sup>p</sup>	X <sup>p</sup>	X <sup>p</sup>	X <sup>p</sup>	X <sup>p</sup>	X			X		
Physical exam (symptom-directed) <sup>j</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X							X		



Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment																EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1										2 thru 11				12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>	
Day				-14 to -1	0	1, 2, 4	7	8	10	14	15	17	21	22	28	7	14	21	28	28				
Window, days						±1 Day 4	±3		±1	±2					±3				±7		±7	±14	±14	
Neurological exam, ICE Score <sup>g</sup>					X <sup>q</sup>	X	X <sup>q</sup>	X	X	X <sup>q</sup>	X	X	X <sup>q</sup>	X	X <sup>q</sup>	X <sup>q</sup>	X <sup>q</sup>	X <sup>q</sup>	X <sup>q</sup>					
Cardiac function tests <sup>f</sup>		X																						
ECG <sup>s</sup>		X					X	X								X								
Adverse events <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Phone contact <sup>u</sup>					Once weekly on non-site visit days as clinically indicated																			
LAB ASSESSMENTS																								
Hematology		X	X	X <sup>k</sup>	X		X	X		X	X	X	X	X	X	X	X	X	X		X			
Chemistry		X		X <sup>k</sup>	X		X	X		X	X	X	X	X	X	X	X	X	X		X			
Coagulation		X		X <sup>k</sup>	X		X	X		X	X	X	X	X	X	X					X			
Urinalysis		X		X <sup>k</sup>																				
Rimiducid PK <sup>v</sup>							X	X								X M3								
Pregnancy test		X		X <sup>k</sup>											X			X			X			
Cytokines <sup>w</sup>				X <sup>k</sup>	X <sup>w</sup>	X	X <sup>w</sup>	X	X	X <sup>w</sup>	X	X	X <sup>w</sup>	X	X <sup>w</sup>	X <sup>w</sup>	X <sup>w</sup>	X <sup>w</sup>	X <sup>w</sup>					
BPX-601 T cell tracking and functional activity <sup>x</sup>				X <sup>k</sup>	X <sup>x</sup>	X	X <sup>x</sup>	X	X	X <sup>x</sup>	X	X	X <sup>x</sup>	X	X <sup>x</sup>	X <sup>x</sup>	X <sup>x</sup>	X <sup>x</sup>	X <sup>x</sup>		X			
Tumor biomarkers <sup>y</sup>		X		X <sup>k</sup>											X				X		X			
Tumor biopsy <sup>z</sup>				X <sup>k</sup>						Days 14-21											X			
Gene therapy monitoring <sup>aa</sup>				X <sup>k</sup>														M3 M6	X		X	X	X	
PSA <sup>ee</sup> (prostate cancer subjects)		X		X										X				X	X	X				

Study Period	Prescreening <sup>a</sup>	Screening <sup>b</sup>	Enrollment	Baseline	Treatment																EOT <sup>c</sup>	Post Treatment Follow Up		
Month					1										2 thru 11				12		3, 6, 12 <sup>d</sup>	q6m ×8 <sup>e</sup>	q12m ×10 <sup>f</sup>	
Day				−14 to −1	0	1, 2, 4	7	8	10	14	15	17	21	22	28	7	14	21	28	28				
Window, days						±1 Day 4	±3		±1	±2				±3				±7		±7	±14	±14		
EFFICACY ASSESSMENTS																								
Tumor imaging and response assessment		X <sub>bb</sub>		X <sub>cc</sub>												X <sup>dd</sup>					X <sup>dd</sup>	X <sup>dd</sup>	X <sup>dd</sup>	
Vital status																					X	X	X	
Subsequent anticancer therapy																				X	X	X	X	

Abbreviations: CNS = central nervous system; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-Therapy; ICE = informed consent form; M = month; MRI = magnetic resonance imaging; PK = pharmacokinetic; PSA = prostate specific antigen; PSCA = prostate stem cell antigen; q6m = every 6 months; q12m = every 12 months

- May occur at any time during routine standard of care.
- Screening assessments must be conducted within 28 days of Enrollment.
- Twelve months after the BPX-601 T cell infusion, or at the time disease progression is confirmed or rimiducid treatment is discontinued unless the subject has died, is lost to follow-up, or has withdrawn consent for study participation. Visit should be completed before starting any subsequent anticancer treatment. If a subject is unable to return for EOT, the subject should be contacted to collect information on any unresolved AEs. Serum pregnancy test required if not performed within the past 28 days.
- Post-treatment visits at Months 3, 6, and/or 12 after the BPX-601 T cell infusion apply only for subjects who did not complete corresponding Month 3, 6, and/or 12 visits, respectively, during the Treatment period.
- Months 18, 24, 30, 36, 42, 48, 54, and 60 from the BPX-601 T cell infusion. Refer to [Section 8.3.16](#).
- Years 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 from the BPX-601 T cell infusion. Refer to [Section 8.3.16](#).
- Centralized testing for tumor expression of PSCA for pancreatic cancer subjects only (not required for mCRPC). All potential pancreatic subjects are required to provide archived tumor tissue or to undergo a fresh tumor biopsy if an archived sample is not available. mCRPC subjects are requested to provide archived tumor tissue if available. Refer to [Section 8.3.14.1](#).
- Screening sample: local assessment to determine eligibility; refer to [Section 8.2.2](#) for panel scope. Enrollment sample: Collect within 7 days of apheresis and send to a Bellicum designated central laboratory for analysis.
- As described in [Section 8.3](#).
- As described in [Section 8.3.7](#). Obtain standing height at Screening only. Weight at screening will be used to determine BPX-601 T cell dose; weight at baseline will be used to calculate doses of lymphodepleting chemotherapy and rimiducid infusion(s) in Month 1. Beginning with the Month 2/Day 7 visit, for

applicable subjects, additional rimiducid doses will be calculated on a monthly basis based on weight obtained at the first visit of each month, or weight obtained at each visit before rimiducid infusion per institutional standard operating procedures. Symptom-directed physical exam should occur before each rimiducid infusion, if needed.

- k. Must be performed before initiation of lymphodepletion.
- l. Provided subjects meet criteria in [Section 8.2.3](#). Perform as described in [Section 6.4.1](#) or as approved by the Sponsor.
- m. Provided subject meets criteria in [Section 8.2.4](#). Administer as described in [Section 6.4.2](#).
- n. Administer by IV infusion as described in [Section 6.4.3](#) and the Apheresis and Cellular Therapy Manual provided subject meets criteria in [Section 8.2.5.1](#). Subjects should be monitored for safety  $\geq 4$  hours after the end of the infusion and released once clinically stable.
- o. Provided subject meets criteria in [Section 8.2.5](#) administer rimiducid by weekly (0.4 mg/kg infused over 2 hours, 0.8 mg/kg infused over 4 hours, or 1.6 mg/kg infused over 6 hours based on assigned cohort) dosing starting on Day 7 as described in [Section 6.4.4](#) and the Rimiducid Pharmacy Manual. Subjects should be monitored for safety  $\geq 4$  hours after the end of the infusion and released once clinically stable. Refer to [Table 3](#) and [Section 8.2.5.2](#) for additional information on dose frequency and dose interruptions. All planned post-infusion time points for blood sample collection will be performed relative to rimiducid administration. If rimiducid is not given on the planned visit day, post-infusion assessments should be shifted accordingly. Rimiducid dosing for Cohort 5B is a single dose on Day 7. Rimiducid dosing for Cohorts 5C, 6, 7, 8, and 9 is weekly on Days 7, 14, 21, and 28 of each month.
- p. As described in [Section 8.3.6](#). On infusion days for BPX-601 T cells and 0.4 mg/kg rimiducid infused over 2 hours, collect vital signs before infusion (-60 to -5 min) and at 0.25, 0.5, 1, 2, and 4 hours ( $\pm 5$  min) after the start of the infusion. For 0.8 mg/kg rimiducid infused over 4 hours, vital signs should be collected before dosing (-60 to -5 min) and at 0.25, 0.5, 1, 2, 4, and 6 hours ( $\pm 5$  min) after the start of the infusion. For 1.6 mg/kg rimiducid infused over 6 hours, vital signs should be collected before dosing (-60 to -5 min) and at 0.25, 0.5, 1, 2, 4, 6, and 8 hours ( $\pm 5$  min) after the start of the infusion, and thereafter as clinically indicated until completion of the post-infusion safety monitoring period.
- q. As described in [Section 8.3.8](#). On infusion days for BPX-601 T cells and 0.4 mg/kg rimiducid infused over 2 hours, perform neurological exam at 4 hours ( $\pm 5$  min) after the start of the infusion. For 0.8 mg/kg rimiducid infused over 4 hours, neurological exam should be performed at 6 hours ( $\pm 5$  min) after the start of the infusion. For 1.6 mg/kg rimiducid infused over 6 hours, neurological exam should be performed at 8 hours ( $\pm 5$  min) after the start of the infusion. Additional assessments may be performed on infusion days as clinically indicated; all neurological exams should be accompanied by an ICE assessment ([Table 7](#)).
- r. Includes left ventricular ejection fraction determination by echocardiogram or multi-gated acquisition as described in [Section 8.3.9.2](#).
- s. Before each PK blood sample collection, obtain a time-matched ECG; triplicate assessments no more than 5 min apart are required if the initial tracing is abnormal, clinically significant.
- t. Collect from date of informed consent (Prescreening) according to safety reporting periods defined in [Section 9.6](#) and reporting procedures described in [Section 9](#).
- u. Once weekly telephone contact on nonclinic days following the BPX-601 T cell infusion on Day 0 through EOT for extended safety monitoring. Calls should assess overall subject well-being and symptom review to determine whether an acute safety risk requiring Investigator evaluation before the next scheduled clinic visit is indicated.
- v. Blood sample (plasma) before applicable rimiducid infusion(s) according to [Appendix 5](#). Rimiducid PK sampling for Cohort 5B is on Days 7/8 only.
- w. Refer to [Section 8.3.14.3](#) for panel scope. On infusion days for BPX-601 T cells and rimiducid (as applicable), collect blood samples (serum) according to [Appendix 5](#). For each time point, duplicate samples should be collected for local and central assessment, respectively.
- x. Refer to [Section 8.3.14.2](#) for panel scope. On infusion days for BPX-601 T cells and rimiducid (as applicable), collect whole blood samples according to [Appendix 5](#). On noninfusion days, collect samples anytime during the clinic visit.
- y. Refer to [Section 8.3.12](#) for scope.



- z. As described in [Section 8.3.15](#). Required pretreatment and on-treatment tumor biopsy. Collect pretreatment sample following last dose of any salvage chemotherapy and before initiation of lymphodepletion. Collect on-treatment sample between Days 14 and 21. An additional biopsy at disease progression (EOT visit) is requested, if feasible. Refer to the Laboratory Manual for sample collection procedures.
- aa. As described in [Section 8.3.16](#). Time points of collection are calendar-based from the time of BPX-601 T cell infusion. Samples must be collected according to the specified frequency; the scope and timing of sample collection is independent of an EOT visit that occurs before Month 12.
- bb. Radiologic evidence of measurable disease required at Screening to confirm eligibility for all subjects, excluding those with bone-only prostate cancer. Standard of care assessments if performed within 6 weeks of Screening may be used to assess disease status.
- cc. CT scan with contrast of the chest, abdomen, and pelvis (all subjects) within 14 days of BPX-601 T cell infusion and after the last dose of any salvage chemotherapy administered after apheresis. Subjects with pancreatic cancers: MRI and bone scan also required to document known or suspected CNS and bone metastases, respectively, if applicable. Subjects with prostate cancer: bone scan required; perform MRI as clinically indicated to document known or suspected CNS metastases. Refer to [Section 8.3.17](#).
- dd. Use the same assessment technique for tumor imaging throughout the study. The first response evaluation after BPX-601 should be between weeks 6–9, followed by every 8 weeks ( $\pm 7$  days) for the first year following BPX-601 infusion, then every 12 weeks ( $\pm 14$  days) for the second year, then annually until confirmed disease progression, the start of new anti-cancer therapy, withdrawal, or study end. If a subject discontinues the Treatment period for reasons other than progressive disease, continue imaging and response assessments per standard of care frequency until documented disease progression, withdrawal, or study end. Response assessment by the Investigator using RECIST v1.1 (pancreas cancer; [Appendix 6](#)) or PCWC3 (prostate cancer; [Appendix 7](#)). Confirmation of response or disease progression is required as described in [Section 8.3.17](#).
- ee. PSA will be measured at Screening, at Baseline and then every 4 weeks. Additional PSA evaluations may be conducted at the investigator's discretion.

### 13.2 Appendix 2 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Adapted from [Oken 1982](#).

### 13.3 Appendix 3 New York Heart Association Criteria

The following table presents the New York Heart Association Classification of Functional Capacity and Objective Assessment:

Class	Functional Capacity	Objective Assessment
<b>I</b>	<ul style="list-style-type: none"> <li>Patients with cardiac disease but without resulting limitations of physical activity.</li> <li>Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</li> </ul>	No objective evidence of cardiovascular disease.
<b>II</b>	<ul style="list-style-type: none"> <li>Patients with cardiac disease resulting in slight limitation of physical activity.</li> <li>They are comfortable at rest.</li> <li>Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</li> </ul>	Objective evidence of minimal cardiovascular disease.
<b>III</b>	<ul style="list-style-type: none"> <li>Patients with cardiac disease resulting in marked limitation of physical activity.</li> <li>They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.</li> </ul>	Objective evidence of moderately severe cardiovascular disease.
<b>IV</b>	<ul style="list-style-type: none"> <li>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort.</li> <li>Symptoms of heart failure or the anginal syndrome may be present even at rest.</li> <li>If any physical activity is undertaken, discomfort is increased.</li> </ul>	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at [http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment\\_UCM\\_423811\\_Article.jsp](http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp). Accessed 18 June 2018.

### 13.4 Appendix 4 Common Corticosteroids and Conversion Half-Lives

Glucocorticoid	Approximate equivalent dose (mg)	Half-life (hour)	Clearance/ 7 half-lives (days)
<b>Short-Acting</b>			
Cortisone	25	8–12	3.5
Hydrocortisone	20	8–12	3.5
<b>Intermediate-Acting</b>			
Methylprednisolone	4	18–36	10.5
Prednisolone	5	18–36	10.5
Prednisone	5	18–36	10.5
Triamcinolone	4	18–36	10.5
<b>Long-Acting</b>			
Betamethasone	0.6–0.75	36–54	15.75
Dexamethasone	0.75	36–54	15.75

Source: [Hunter \(1992\)](#), [Meikle \(1977\)](#), [Singer \(2009\)](#).

### 13.5 Appendix 5 Pharmacokinetics and Biomarker Sampling Schedule on Infusion Days (Day 0 through Month 11) for All Subjects

Type of Sample/ Assessment	Rimiducid Dose Regimen Cohort	Planned Visits	Collection Time points <sup>a</sup> (Sample Collection Window)
<b>Rimiducid Pharmacokinetics</b>			
Blood Sample (Plasma) <sup>b</sup>	Day 7 only (Cohort 5B)	<b>Month 1:</b> Day 7	Time points relative to start of <b>rimiducid</b> infusion:
Electro- cardiogram	Weekly (Cohort 5C)	<b>Month 1:</b> Day 7 <b>Month 3:</b> Day 7	<b>2-hour infusion:</b> <ul style="list-style-type: none"><li>• preinfusion (-60 to -5 min)<sup>b</sup></li><li>• 1<sup>c</sup> hour (±15 min)</li><li>• 2<sup>c</sup> hours immediately before end of infusion (-15 min)</li><li>• 4<sup>c</sup> hours (±15 min)</li><li>• 8<sup>c</sup> hours (±15 min)</li><li>• 24 hours (±60 min)</li></ul> <b>4-hour infusion:</b> <ul style="list-style-type: none"><li>• preinfusion (-60 to -5 min)<sup>b</sup></li><li>• 2<sup>c</sup> (±15 min)</li><li>• 4<sup>c</sup> hours immediately before end of infusion (-15 min)</li><li>• 6<sup>c</sup> hours (±15 min)</li><li>• 26 hours (±60 min)</li></ul> <b>6-hour infusion:</b> <ul style="list-style-type: none"><li>• preinfusion (-60 to -5 min)<sup>b</sup></li><li>• 2<sup>c</sup> (±15 min)</li><li>• 6<sup>c</sup> hours immediately before end of infusion (-15 min)</li><li>• 8<sup>c</sup> hours (±15 min)</li><li>• 28 hours (±60 min)</li></ul>
<b>Pharmacodynamic Biomarkers</b>			
Blood (serum) for cytokines <sup>b,e</sup>	Day 7 only (Cohort 5B)	<b>Month 1:</b> Days 0, 7	Time points relative to start of <b>BPX-601 T cell infusion</b> :
	Weekly (Cohort 5C)	<b>Month 1:</b> Days 0, 7, 14, 21, 28 <b>Month 2:</b> Days 7, 14, 21, 28 <b>Month 3:</b> Days 7, 10 <b>Months 4-11:</b> Day 7	<b>2-hour infusion:</b> <ul style="list-style-type: none"><li>• Preinfusion (-60 to -5 min)</li><li>• 1 hour (±15 min)</li><li>• 4 hours (±15 min)</li><li>• 8 hours (±15 min) optional for subjects receiving rimiducid in outpatient setting, required if subject admitted</li><li>• 24 hours (±60 min)<sup>d</sup></li></ul> Time points relative to start of <b>rimiducid</b> infusion: <b>2-hour infusion:</b> <ul style="list-style-type: none"><li>• Preinfusion (-60 to -5 min)</li><li>• 1 hour (±15 min)</li><li>• 4 hours (±15 min)</li><li>• 8 hours (±15 min) optional for subjects receiving rimiducid in outpatient setting, required if subject admitted</li><li>• 24 hours (±60 min)<sup>d</sup></li></ul>



Type of Sample/ Assessment	Rimiducid Dose Regimen Cohort	Planned Visits	Collection Time points <sup>a</sup> (Sample Collection Window)
			<b>4-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5 min)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 8 hours (<math>\pm 15</math> min) optional for subjects receiving rimiducid in outpatient setting, required if subject admitted</li> <li>• 26 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul> <b>6-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5 min)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 8 hours (<math>\pm 15</math> min) optional for subjects receiving rimiducid in outpatient setting, required if subject admitted</li> <li>• 28 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul>
Whole blood sample for BPX-601 T cell tracking and functional activity <sup>a,f</sup>	Day 7 only (Cohort 5B)	<b>Month 1:</b> Days 0, 7	Time points relative to start of <b><u>BPX-601 T cell infusion</u></b> :
	Weekly (Cohort 5C)	<b>Month 1:</b> Days 0, 7, 14, 21, 28 <b>Months 2-11<sup>d</sup>:</b> Days 7, 14, 21, 28	<b>2-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 24 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul> Time points relative to start of <b><u>rimiducid</u></b> infusion: <b>2-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5 min)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 24 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul> <b>4-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 26 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul> <b>6-hour infusion:</b> <ul style="list-style-type: none"> <li>• Preinfusion (-60 to -5)</li> <li>• 1 hour (<math>\pm 15</math> min)</li> <li>• 4 hours (<math>\pm 15</math> min)</li> <li>• 28 hours (<math>\pm 60</math> min)<sup>d</sup></li> </ul>

Abbreviations: min = minutes

- Record date and time
- Refer to Laboratory Manual for detailed sample collection, processing, and shipment instructions.
- Blood samples for all planned PK time points up to 8 hours from start of infusion must be collected from a peripheral vein contralateral to the arm/location into which rimiducid is administered.
- 24-hour samples will be collected following BPX-601 T cells and the first 4 planned rimiducid infusions in Month 1 (ie, on Days 8, 11, 15, 18, 22, 25, 29 as applicable) and following the first planned rimiducid

- infusion in Month 3 (ie, on Day 8) as applicable. Starting with the second rimiducid infusion in Month 3 (ie, Day 10) only pre-infusion samples will be collected.
- e. Cytokine sample should be drawn at the indicated timepoints. The 1-hour sample may be omitted if there are concerns about blood volume. Starting from Month 3, Day 10, only the pre-infusion sample should be drawn. If rimiducid is discontinued, cytokine samples should be collected on a monthly basis, ie, the first scheduled visit that month.
  - f. If rimiducid is discontinued, a sample for T cell tracking and functional activity should be collected on a monthly basis, ie, the first scheduled visit that month.

### 13.6 Appendix 6 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Quick Reference

Eligibility
<p>Only patients with measurable disease at baseline or bone-only prostate disease should be included in this protocol.</p> <p><b>Measurable disease</b> - the presence of <math>\geq 1</math> measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.</p> <p><b>Measurable lesions:</b></p> <p><b>Tumor lesions</b> must be accurately measured in <math>\geq 1</math> dimension with longest diameter <math>\geq 10</math>mm by CT scan (slice thickness <math>\leq 5</math> mm), <math>\geq 10</math>mm caliper measurement by clinical exam, <math>\geq 20</math>mm by chest x-ray.</p> <p><b>Malignant lymph nodes</b> must be considered pathologically enlarged and measurable with a diameter <math>\geq 15</math>mm in the short axis when assessed by CT scan (slice thickness <math>\leq 5</math> mm)</p> <p><b>Nonmeasurable lesions</b> - all other lesions, including small lesions (longest diameter <math>&lt; 10</math>mm or pathological lymph nodes with <math>\geq 10</math> to <math>&lt; 15</math>mm short axis) as well as truly nonmeasurable lesions, ie, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are neither confirmed nor followed by reproducible imaging techniques.</p> <p>All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never <math>&gt; 4</math> weeks before the beginning of the treatment.</p> <p>The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.</p> <p>Clinical lesions will only be considered measurable when they are superficial and <math>\geq 10</math>mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging is preferred.</p>
Methods of Measurement
<ul style="list-style-type: none"> <li>CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with cuts of 5mm or less in slice thickness contiguously. MRI is also acceptable in certain situations (eg, for body scans).</li> <li>Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, chest CT is preferable.</li> <li>Ultrasound is not a useful assessment of lesion size and should not be used as a method of measurement as they are not reproducible and operator dependent. If new lesions are identified by ultrasound, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.</li> <li>The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.</li> <li>Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR.</li> <li>Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).</li> </ul>



Baseline documentation of Target and Nontarget Lesions			
<ul style="list-style-type: none"><li>• All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as <b>target lesions</b> and recorded and measured at baseline.</li><li>• Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).</li><li>• A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for <b>all target lesions</b> will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize any objective tumor regression in the measurable dimension of the disease.</li><li>• All other lesions (or sites of disease) including pathological lymph nodes should be identified as <b>nontarget lesions</b> and should also be recorded at baseline. Measurements of these lesions are not required, but these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’.</li></ul>			
Response Criteria			
Evaluation of Target Lesions			
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10mm.		
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.		
Progressive Disease (PD):	At least a 20% increase in the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5mm. The appearance of 1 or more new lesions is also considered progression.		
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters since treatment started.		
Evaluation of Nontarget Lesions			
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10mm short axis).		
Non-CR/Non-PD:	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.		
Progressive Disease (PD):	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.		
Evaluation of Best Overall Response			
The best overall response is the best response recorded from the start of the treatment until the end-of-treatment taking into account any requirement for confirmation. In general, the subject's best response assignment will depend on findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.			
Target lesions	Nontarget lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Unevaluable
PD	Any	Yes or No	PD

Any	PD	Yes or No	PD
Any	Any	Yes	PD
<ul style="list-style-type: none"> <li>Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.</li> <li>In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.</li> </ul>			
<b>Confirmation</b>			
<ul style="list-style-type: none"> <li>The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.</li> <li>To be assigned a status of confirmed PR or confirmed CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.</li> <li>In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.</li> </ul>			

Adapted from [Eisenhauer 2009](#).



### 13.7 Appendix 7 Prostate Cancer Working Group 3 Response Criteria Quick Reference

Criteria for Disease Progression at Trial Eligibility by Disease Manifestation	
Variable	Criteria
<b>Blood-based</b>	
PSA	<ul style="list-style-type: none"> <li>Obtain sequence of rising values at <math>\geq 1</math>-week intervals</li> <li>1.0 ng/mL is the minimum starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma</li> <li>Estimate pretherapy PSA-doubling time if <math>\geq 3</math> values available <math>\geq 4</math> weeks apart</li> </ul>
<b>Radiographic Imaging</b>	
Nodes	<ul style="list-style-type: none"> <li>Use RECIST v1.1 (<a href="#">Eisenhauer 2009</a>) to record nodal lesions as target or nontarget with modification: <ul style="list-style-type: none"> <li>Separate pelvic, extrapelvic disease</li> <li>Record up to 5 total nodal lesions</li> </ul> </li> <li>Nodal progression sufficient for trial entry independent of PSA</li> <li>Previously normal (<math>&lt; 1.0</math> cm) nodes must have grown by <math>\geq 5</math>mm in the short axis from baseline or nadir and be <math>\geq 1.0</math> cm in the short axis to be considered to have progressed</li> <li>If the node progresses to <math>\geq 1.5</math> cm in the short axis, it is measurable; nodes that have progressed to 1.0 to <math>&lt; 1.5</math>cm are pathologic, subject to clinical discretion, and are nonmeasurable</li> </ul>
Viscera	<ul style="list-style-type: none"> <li>Use RECIST v1.1 (<a href="#">Eisenhauer 2009</a>) visceral lesions as target or nontarget with modification: <ul style="list-style-type: none"> <li>Visceral sites: lung, liver, adrenal, central nervous system</li> <li>Record up to 5 lesions per site</li> </ul> </li> </ul>
Prostate/ prostate bed (primary site)	<ul style="list-style-type: none"> <li>Record prior treatment of primary tumor</li> <li>Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease</li> </ul>
Bone	<ul style="list-style-type: none"> <li>2 new lesions</li> <li>Confirm ambiguous results by other imaging modalities (eg, CT or MRI), but only positivity on the bone scan defines metastatic disease to bone</li> </ul>
Other sites of disease	<ul style="list-style-type: none"> <li>Patients with treated epidural lesions and other epidural progression are eligible</li> </ul>
Outcome Measures by Disease Manifestation	
Variable	Outcome
<b>Blood-based</b>	
PSA	<ul style="list-style-type: none"> <li>Progression <ul style="list-style-type: none"> <li>After decline from baseline: time from start of therapy to first PSA increase that is <math>\geq 25\%</math> and <math>\geq 2.0</math> ng/mL above the nadir, and which is confirmed by a second value <math>\geq 3</math> weeks later</li> <li>No decline from baseline: PSA progression <math>\geq 25\%</math> and <math>\geq 2.0</math> ng/mL after 12 weeks</li> </ul> </li> </ul>

Criteria for Disease Progression at Trial Eligibility by Disease Manifestation	
Variable	Criteria
<b>Radiographic Imaging</b>	
Nodes	<ul style="list-style-type: none"> <li>• Response assessment according to RECIST v1.1 (<a href="#">Eisenhauer 2009</a>) with modification: <ul style="list-style-type: none"> <li>– Only report changes in nodes that were <math>\geq 1.5</math>cm in the short axis</li> <li>– Record changes in pelvic versus extrapelvic nodes separately</li> <li>– Confirm favorable changes with second scan</li> <li>– Confirm progression by a second scan no less than 4 weeks later</li> <li>– Record complete elimination of disease at any site separately</li> </ul> </li> <li>• Previously normal (<math>&lt; 1.0</math>cm) nodes must have grown by <math>\geq 5</math>mm in the short axis from baseline or nadir and be <math>\geq 1.0</math>cm in the short axis to be considered to have progressed</li> <li>• Nodes that have progressed to 1.0 to <math>&lt; 1.5</math>cm are pathologic, subject to clinical discretion, and are nonmeasurable</li> <li>• For existing pathologic adenopathy (<math>\geq 1.5</math>cm), progression is defined per RECIST v1.1 (<a href="#">Eisenhauer 2009</a>)</li> </ul>
Viscera	<ul style="list-style-type: none"> <li>• Response assessment according to RECIST v1.1 (<a href="#">Eisenhauer 2009</a>) with modification: <ul style="list-style-type: none"> <li>– Only report changes in lesions that were <math>\geq 1.0</math>cm in the longest dimension</li> <li>– Record changes in lung, liver, adrenal, and central nervous system separately</li> <li>– Confirm favorable changes with second scan</li> <li>– Confirm progression by a second scan no less than 6 weeks later</li> <li>– Record complete elimination of disease at any site separately</li> </ul> </li> </ul>
Bone	<ul style="list-style-type: none"> <li>• Record changes as improved or stable (no new lesions) or worse (new lesions); changes in intensity of uptake alone do not constitute progression or regression <ul style="list-style-type: none"> <li>– No new lesions: continue current therapy</li> <li>– New lesions: perform a confirmatory scan no less than 6 weeks later</li> </ul> </li> <li>• Progression: <ul style="list-style-type: none"> <li>– At least 2 new lesions on the first post-treatment scan with <math>\geq 2</math> additional lesions on the next scan</li> <li>– If <math>\geq 2</math> additional new lesions are observed on the confirmatory scan, the date of progression is the date of the first post-treatment scan</li> <li>– For scans after the first post-treatment scan, <math>\geq 2</math> new lesions relative to the first post-treatment scan confirmed on a subsequent scan</li> <li>– Date of progression is the date of the scan that first documents the second lesion</li> </ul> </li> </ul>

Adapted from [Scher 2016](#).