Ligand-Inducible, Prostate Stem Cell Antigen (PSCA)-Directed GoCAR-T® Cells in Advanced Solid Tumors: Preliminary Results With Cyclophosphamide (Cy) ± Fludarabine (Flu) Lymphodepletion (LD)

Abstract #2536

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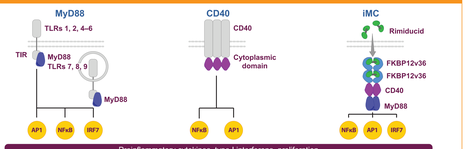
BACKGROUND

- Inducible MyD88/CD40 (iMC) is a novel co-activation switch comprised of two synergistic signaling domains regulated by the synthetic small-molecule ligand, rimiducid[1] (**Figure 1**)
- iMC contains a rimiducid-binding domain (two FK506-binding proteins) coupled with the signaling components from MyD88 and CD40, which play critical roles in initiation and maintenance of an innate and adaptive immune response[1]
- Transcription factor activation via the MyD88 and CD40 signaling domains leads to upregulation of proinflammatory cytokines and type I interferons, which promote proliferation, activation, and survival of immune cells, including T cells[1]

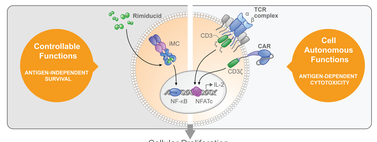
Figure 1. Inducible MyD88/CD40 (iMC)



CD40, cluster of differentiation 40; FKBP, FK506-binding protein; MyD88, myeloid differentiation primary response 88; TIR, toll/interleukin-1 receptor; TLR, toll-like receptor.

- GoCAR-T technology combines antigen-specific CAR-T cells with iMC in order to allow control of T cell survival even in the absence of antigen[1] (**Figure 2**)
- BPX-601 is an autologous GoCAR-T product candidate engineered to contain a prostate stem cell antigen (PSCA)-directed CAR (PSCA-CD3ζ) plus iMC

Figure 2. GoCAR-T: BPX-601 Overview



CAR, chimeric antigen receptor; iMC, inducible MyD88/CD40; PSCA, prostate stem cell antigen; TCR, T cell receptor.

- PSCA is a target of particular interest for therapeutic intervention as it is upregulated in many solid tumors, including cancers of the pancreas[2]
- Additionally, expression of PSCA has been observed in normal prostate epithelium, urinary bladder, kidney, esophagus, stomach, and placenta[3]
- By combining the properties of PSCA-specificity and control of T cell survival, BPX-601 is optimized for antigen-dependent and -independent T cell activation, proliferation and persistence, which potentially may enhance its efficacy in solid tumors compared with traditional CAR-T cells
- Standard treatment in the second- and third-line settings for metastatic pancreatic cancer is associated with a median progression free survival of 2-3 months[4]

OBJECTIVE

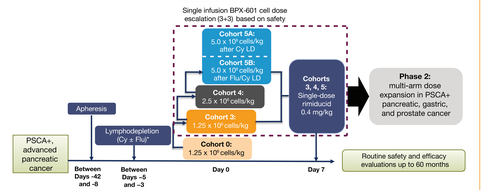
- To determine safety and tolerability, recommended dose for expansion, pharmacodynamics, and anti-tumor activity of BPX-601 with or without rimiducid in patients with previously treated advanced solid tumors with high PSCA expression

METHODS

Study Design

- BP-012 is a 2-phase, first-in-human study to assess the safety, biologic, and clinical activity of BPX-601 plus rimiducid in select PSCA-positive solid tumors (**Figure 3**)
- Phase 1 is an ongoing 3+3 cell dose escalation designed to identify the recommended BPX-601 dose given in combination with rimiducid for use in Phase 2 dose expansion
- After apheresis and LD with cyclophosphamide (Cy; 1 g/m²) alone on Day −3 (cohorts 0, 3, 4, and 5A) or fludarabine + Cy (Flu/Cy; 30 mg/m² and 500 mg/m², respectively) on Days −5 to −3 (cohort 5B), patients were treated with escalating doses of BPX-601 (single intravenous [IV] infusion) on Day 0 followed by a fixed dose of rimiducid (0.4 mg/kg, single IV infusion) on Day 7
- To evaluate the safety of T cell therapy alone, an initial cohort received BPX-601 on Day 0 and did not receive subsequent rimiducid (cohort 0)
- Patients treated with BPX-601 with or without rimiducid were followed for routine safety, blood biomarkers, and efficacy evaluations as specified by the study protocol

Figure 3. BP-012 (NCT02744287) Study Design



*Cohorts 0, 3, 4, and 5A received Cy alone on Day −3 for LD; cohort 5B received Flu/Cy on Day −5 to −3 for LD.
Cy, cyclophosphamide; Flu, fludarabine; LD, lymphodepletion; PSCA, prostate stem cell antigen.

Main Inclusion Criteria

- Histologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma with disease progression after standard or investigational therapy for non-resectable disease
- Positive tumor expression of PSCA as determined by qPCR performed by a central laboratory
- Age ≥18 years
- Performance status 0 or 1 with adequate organ function

Main Exclusion Criteria

- Islet cell neoplasms
- Investigational therapy within 4 weeks or chemotherapy or immunotherapy within 2 weeks prior to BPX-601 infusion
- Active autoimmune disease requiring systemic immunosuppressive therapy
- Uncontrolled systemic infection

Statistical Analysis

- All patients who were infused with BPX-601 were included in this data set
- Adverse events (AEs) were summarized by system organ class and preferred term
- Incidence of AEs and serious AEs (SAEs) were summarized overall and with respect to CTCAE grade and relationship to study treatment
- Anti-tumor activity was analyzed according to RECIST v1.1

RESULTS

- As of April 23, 2019, 18 patients have been treated across 4 BPX-601 dose levels, including one cohort that received cells without subsequent rimiducid (**Table 1**)
- Per FDA request, conditioning chemotherapy was originally limited to a single IV infusion of Cy only on Day −3 for 13 patients (cohorts 0-5A); following a protocol amendment, 5 patients were treated with Flu/Cy on Days −5 to −3 prior to receiving 5.0 x 10⁶ cells/kg on Day 0 (cohort 5B)
- All patients had advanced pancreatic cancer and had been treated with 1 or more prior systemic therapies
- PSCA copy number was measured at screening and ranged from 5,000 to over 969,000

Table 1. Patient Demographics and Clinical Characteristics

Cohort	LD Regimen*	BPX-601 Dose (x10⁶ cells/kg)	Rim (Y/N)	Patient	Age/Sex	# Prior Systemic Therapies	PSCA (copies)†
0	Cy only	1.25	N	1	50/F	1	5,000
			N	2	58/F	3	377,000
			N	3	65/F	5	15,000
3	Cy only	1.25	Y	1	59/F	2	34,000
			Y	2	70/M	1	7,000
			Y	3	58/F	1	31,000
4	Cy only	2.5	Y	1	71/F	2	7,686
			Y	2	60/F	3	354,730
			Y	3	65/M	2	8,243
5A	Cy only	5.0	Y	1	61/M	2	14,238
			Y	2	64/M	1	19,533
			N	3	59/M	5	969,094
			Y	4	55/M	2	52,979
5B	Flu/Cy	5.0	Y	1	56/M	4	201,277
			Y	2	77/M	2	18,980
			Y	3	72/M	1	21,099
			Y	4	58/M	1	149,110
			Y	5	68/F	1	54,877

*Cy (1 g/m²) by IV infusion on Day −3, Flu/Cy (30 mg/m² and 500 mg/m², respectively) by IV infusion on Days −5 to −3; †PSCA (copies per 10⁶ copies hACTB) was measured at screening; ‡Patient was scheduled to receive Rim, but infusion was delayed then withdrawn due to an AE associated with worsening disease. Patient subsequently died due to disease progression.
AE, adverse event; Cy, cyclophosphamide; Flu, fludarabine; hACTB, human beta-actin; LD, lymphodepletion; PSCA, prostate stem cell antigen; Rim, rimiducid.

- All BPX-601-treated patients reported at least 1 adverse event (AE); the most common AEs (in >20% of all patients) regardless of causality, LD regimen, or BPX-601 dose were febrile neutropenia (33%), fatigue (28%), neutropenia (28%), pyrexia (28%), dysuria (22%), hematuria (22%), and nausea (22%) (**Table 2**)
- As of the data cut off, no BPX-601 dose limiting toxicities were observed
- Nine patients (50%) reported treatment-related AEs (TRAEs); dysuria (n = 4), hematuria (n = 4), pyrexia (n = 3), and hypotension (n = 2) were reported by ≥2 patients
- All TRAEs were mild/moderate except for Grade 3 hematuria and Grade 3 groin pain reported by 1 patient; no Grade 4 TRAEs were reported
- Ten patients (56%) reported SAEs; febrile neutropenia was the only SAE reported by >1 patient (n = 5)
- In patients who received Flu/Cy LD (cohort 5B):
  - All events of febrile neutropenia and neutropenia were Grade ≥3 and were not related to BPX-601/rimiducid; frequency and severity of the observed hematologic toxicity is generally consistent with Flu/Cy LD[5,6]
  - The events of dysuria and hematuria were mostly Grade 1-2 (1 event of Grade 3 hematuria) and were related to BPX-601/rimiducid
  - Patient 4 experienced an SAE of Grade 2 cytokine release syndrome (CRS) 1 day after rimiducid infusion; the patient was treated with IV tocilizumab (single infusion) and the event resolved the same day
  - Patient 2 experienced an SAE of Grade 2 encephalopathy on the same day of rimiducid infusion; no concurrent CRS was observed, the patient was treated with IV dexamethasone, and the event resolved within 1 week

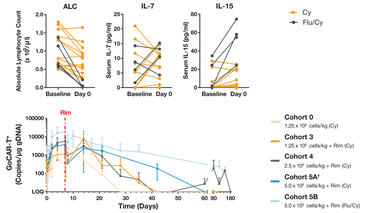
Table 2. Safety Summary

Patients, n (%)	Cohort 0 n = 3	Cohort 3 n = 3	Cohort 4 n = 3	Cohort 5A n = 4	Cohort 5B n = 5	All Patients N = 18
Any AE	3 (100)	3 (100)	3 (100)	4 (100)	5 (100)	18 (100)
Any SAE	2 (67)	1 (33)	0	3 (75)	4 (80)	10 (56)
Grade 3 & 4 TRAEs	0	0	0	0	1 (20)	1 (<1)
AEs in >15% of all patients, n (%)						
Febrile neutropenia	0	0	0	2 (50)	4 (80)	6 (33)
Fatigue	2 (67)	1 (33)	0	2 (50)	0	5 (28)
Neutropenia	0	0	0	1 (25)	4 (80)	5 (28)
Pyrexia	0	0	1 (33)	2 (50)	2 (40)	5 (28)
Dysuria	0	0	0	0	4 (80)	4 (22)
Hematuria	0	0	0	0	4 (80)	4 (22)
Nausea	2 (67)	0	0	0	2 (40)	4 (22)
Abdominal pain	1 (33)	1 (33)	0	0	1 (20)	3 (17)
Abdominal pain upper	0	1 (33)	1 (33)	1 (25)	0	3 (17)
Anemia	0	0	0	1 (25)	2 (40)	3 (17)
Back pain	1 (33)	1 (33)	0	1 (25)	0	3 (17)
Blood bilirubin increased	0	0	0	1 (25)	2 (40)	3 (17)
Hypotension	0	0	2 (67)	1 (25)	0	3 (17)

AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.

- Flu/Cy LD resulted in a mean reduction in absolute lymphocyte count of 93.8% (SD 5.9%; n = 5) compared with 25.3% (SD 23.5%; n = 13) with Cy LD alone (**Figure 4**)
  - Increased peripheral IL-7 and IL-15 was observed in patients who received Flu/Cy, but not Cy alone for LD
- Rapid T cell expansion by Day 4 was observed in the majority of patients; limited peripheral expansion occurred when BPX-601 was infused without rimiducid
- Nine of 17 patients (53%) with a minimum of 28 days of follow-up samples had BPX-601 persistence for >21 days, including all 5 patients in cohort 5B
- Analysis of the relationship between PSCA copy number and maximum CAR vector copy number showed a weak correlation (R^2 = 0.1294; P=.1426)

Figure 4. BPX-601 Expansion and Persistence



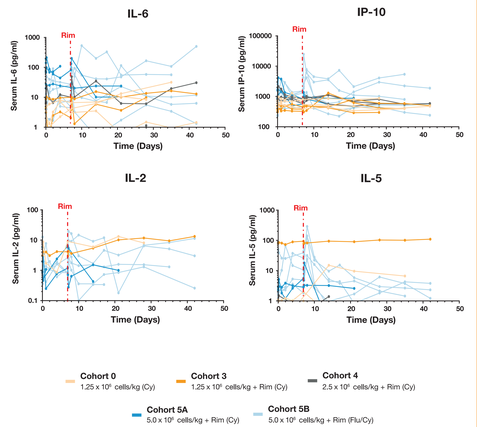
*Data points represent the mean log VCN for each cohort and the dotted red line represents rimiducid administration at Day 7; †Patient 3 in cohort 5A did not have data for time points beyond Day 4 and thus is not included in the summary of cell persistence.
ALC, absolute lymphocyte count; Cy, cyclophosphamide; Flu, fludarabine; LOQ, limit of quantitation; pts, patients; Rim, rimiducid; VCN, vector copy number.

Peak VCN Comparisons

Patient Subsets	Difference in Peak VCN	*P* value
All Flu/Cy pts (n = 5) vs all Cy alone pts (n = 13)	All Flu/Cy pts had 4.9-fold higher peak VCN	P=.0028
Flu/Cy + Rim pts (n = 5) vs Cy alone + Rim pts (n = 10)	Flu/Cy + Rim pts had 4-fold higher peak VCN	P=.0080
5.0 x 10⁶ cells/kg and Flu/Cy LD pts (n = 5) vs 5.0 x 10⁶ cells/kg and Cy alone LD pts (n = 4)	5.0 x 10⁶ cells/kg and Flu/Cy LD pts had 6.8-fold higher peak VCN	P=.0159

- As shown in **Figure 5**, following single-dose rimiducid on Day 7:
  - Rimiducid-dependent elevations in IL-2, IL-5, IL-6, and IP-10 were observed in most patients, particularly those in cohort 5B, and correlated with cell expansion
  - Similar rimiducid-dependent increases in IL-8, G-CSF, MCP-1, MIP-1α, and MIP-1β were also observed (data not shown)
  - Increased serum IP-10 was indicative of prior IFN-γ production and, together with increased serum TNF-α, supports T cell activation in response to activation of iMC by rimiducid
  - Increased BPX-601 dose was associated with overall increased serum cytokine and chemokine levels
- Limited peripheral cytokine changes were observed when BPX-601 was infused alone

Figure 5. Peripheral Cytokine Profiles Over Time*



*Each line represents data for an individual patient in the indicated cohort.
Rim, rimiducid.

- Of 13 efficacy-evaluable patients treated with BPX-601 and a single dose of rimiducid, 8 patients (62%) had stable disease including 3 patients with tumor shrinkage of 10% to 24% (**Figure 6**)
- Since the previous data cutoff, tumor shrinkage (–13%) has been seen in 1 patient in cohort 5B (patient 5)

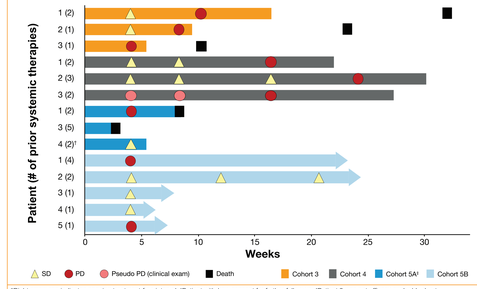
Figure 6. Evidence of Anti-Tumor Activity in BPX-601-Treated Patients

Best Response (RECIST v1.1)	Cohort 0 n = 3	Cohort 3 n = 3	Cohort 4 n = 3	Cohort 5A n = 2*	Cohort 5B n = 5	All Patients N = 16
Progressive Disease (PD), n	2	1	1	1	2	7
Stable Disease (SD), n	1	2	2	1	3	9
Partial Response (PR), n	0	0	0	0	0	0
Complete Response (CR), n	0	0	0	0	0	0
Overall Response Rate (CR + PR), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Disease Control Rate (CR + PR + SD), n (%)	1 (33)	2 (67)	2 (67)	1 (50)	3 (60)	9 (56)

*2 patients in cohort 5A (2 and 3) were not efficacy evaluable due to non-measurable disease at baseline and death due to disease under study prior to first post-baseline efficacy measurement, respectively.

- With 9.1 weeks median duration of follow-up (range: 2.9–30.3 weeks), the median time to follow-on cancer therapy in patients who received subsequent therapy was 16.6 weeks (range: 5.6–30.3 weeks; **Figure 7**)
- At the highest cell dose (5.0 x 10⁶ cells/kg) after Flu/Cy LD followed by a single rimiducid dose at Day 7:
  - 2 patients with at least 9.1 weeks of follow-up had a time to next treatment of >22 weeks which was ongoing at the time of the data cutoff
  - 1 patient who had previously received 2 lines of systemic therapy (patient 2) had stable disease that was ongoing at 6 months

Figure 7. Swim Plot after BPX-601 Administration*



*Right arrow cap indicates ongoing treatment-free interval; †Patient withdrew consent for further follow-up; ‡Patient 2 was not efficacy evaluable due to non-measurable disease at baseline.
PD, progressive disease; pseudo, pseudoprogression; SD, stable disease.

CONCLUSIONS

- Administration of BPX-601 followed by single-dose rimiducid was well tolerated with no dose-limiting toxicities
  - Frequent AEs were generally consistent with those experienced by advanced cancer patients undergoing cytotoxic chemotherapy or other cancer immunotherapies
  - The majority of AEs related to BPX-601/rimiducid were mild to moderate in intensity and resolved with or without supportive care
- Compared with a single dose of Cy alone, more intense lymphodepletion with Flu/Cy is associated with elevations of IL-7 and IL-15 and significantly increased BPX-601 expansion and prolonged persistence in patients treated with single-dose rimiducid
- Evidence of biological activity/stable disease has been observed in heavily pre-treated pancreatic cancer patients
- Evaluation of safety and efficacy of BPX-601 followed by repeat-dose rimiducid is planned
- Collection of pre- and on-treatment biopsies were added to the study in a recent protocol amendment; tissue analysis results will be presented at a later date

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DISCLOSURES

- CR Becerra has received honoraria from Taiho Pharmaceutical; has consulted for SOBI, Ipsen, Takeda, Bayer, Heron Therapeutics, and Agenus; has participated in speakers' bureaus for Taiho Pharmaceutical, Bristol-Myers Squibb, Merck Serono, and Celgene
- GA Manji has received research funding from Plexxikon and ASCO; has been a consultant/advisory board member for Ardelyx
- DW Kim has no disclosures to report
- O Gardner, A Malankar, J Shaw, D Blass, X Yi, A Foster, and P Woodard are employees of Bellicum Pharmaceuticals and may own company stock/options

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