Phase 1/2 study of BT7480, a CD137/Nectin-4 Bicycle tumor-targeted immune cell agonist, with nivolumab in Nectin-4–associated advanced solid tumors

Poster # 1979P

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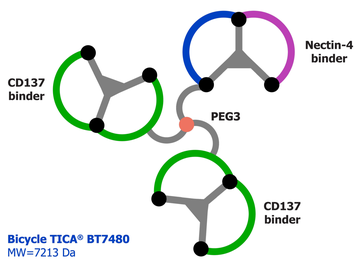
INTRODUCTION

- Bicycle® molecules are an innovative therapeutic class in development that offer the manufacturing and pharmacokinetic (PK) properties of a small molecule with the high binding specificity of a biologic,[1-3] making them ideally suited for the targeted delivery of a range of payloads (eg, cytotoxins) to solid tumors
- The Bicycle® molecule BT7480 is a novel, synthetic Bicycle tumor-targeted immune cell agonist® (Bicycle TICA®) comprising three bicyclic peptides, one targeting Nectin-4 and two targeting CD137, conjugated by a three-arm branched PEG3 linker (**Figure 1**)[4,5]
  - Nectin-4 is a cell surface adhesion molecule that is highly expressed in many cancers, including lung, breast, esophageal, head and neck, and urothelial cancers, and is implicated in tumor growth, survival signaling, and immune evasion[6-9]
  - CD137, a member of the TNF receptor superfamily, is expressed on activated immune cells and in tumor cells; on ligation, CD137 provides costimulatory signals for immune cells, such as T-cell proliferation, anti-apoptosis, cytokine secretion, chromatin remodeling, and mitochondrial fitness[10-13]
- Co-ligation of Nectin-4 and CD137 by BT7480 is hypothesized to cause tumor-localized CD137 agonism based on preclinical findings[4]
- As monotherapy, BT7480 was well tolerated and showed preliminary antitumor activity in patients with Nectin-4–expressing advanced solid tumors[14]

FIGURE 1. BT7480 STRUCTURE



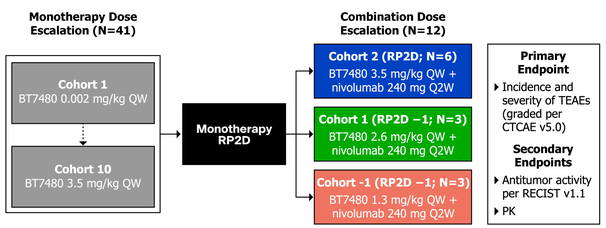
OBJECTIVE

- Here we report the results of the Phase 1 dose escalation part of a multicenter, open-label Phase 1/2 study (NCT05163041) evaluating BT7480 + nivolumab in patients with advanced malignancies associated with Nectin-4 expression

METHODS

- Adults with advanced solid tumors associated with Nectin-4 expression and with disease refractory to or ineligible for standard therapy were included in this study (**Figure 2**)
- Key eligibility criteria included the following:
  - Aged ≥18 years
  - Histologically or cytologically confirmed malignant solid tumor, including urothelial (transitional cell) carcinoma (UC); head and neck squamous cell carcinoma (HNSCC); non-small cell lung cancer (NSCLC); and ovarian, breast, gastric, or esophageal carcinoma
  - ECOG PS 0 or 1
  - No prior CD137 targeted therapy
- BT7480 was administered as an IV infusion, starting at 2.6 mg/kg once weekly (Cohort 1; one dose level lower than the monotherapy RP2D); patients were enrolled sequentially in a 3+3 design up to 3.5 mg/kg once weekly (monotherapy RP2D)
- Nivolumab was administered as an IV infusion at 240 mg once every 2 weeks
- The primary endpoint was incidence and severity of TEAEs (per CTCAE v5.0); secondary endpoints included antitumor activity (per RECIST v1.1) and PK

FIGURE 2. STUDY DESIGN



RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- As of July 29, 2025, 12 patients (median age, 62.5 years) had received BT7480 across 3 doses ranging from 1.3 to 3.5 mg/kg once weekly IV in combination with nivolumab (240 mg Q2W IV) (**Table 1**)
- NSCLC was the most common primary tumor (n=6; 50%) followed by UC and breast cancer (n=2; 17% each)
- Median number of prior lines of therapy was 3.5 (range, 2–14)

TABLE 1. BASELINE PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Patient Characteristic	Patients (N=12)
Median age, years (range)	62.5 (33–76)
Sex, n (%)	
Male	8 (66.7)
Female	4 (33.3)
Race, n (%)	
White	8 (66.7)
Black or African American	1 (8.3)
Other	3 (25.0)
ECOG PS, n (%)	
0	3 (25.0)
1	9 (75.0)
Primary tumor type, n (%)	
NSCLC	6 (50.0)
UC	2 (16.7)
Breast (ER+, HER2–)	2 (16.7)
HNSCC	1 (8.3)
Esophageal	1 (8.3)
Prior lines of therapy, median (range)	3.5 (2–14)
Prior ICI	10 (83.3)[a]

[a]The 2 patients who did not receive prior ICI were the 2 patients with ER+, HER2– BC.

SAFETY

- BT7480-related adverse events (AEs) of any grade occurred in 5 (42%) patients, with nausea (25%) the most common (**Table 2**)
- Low rates of Grade ≥3 BT7480-related AEs (8%) and BT7480-related SAEs (8%) were reported (Grade 3 neutropenia in a single patient)
- No DLTs or BT7480-related deaths were reported
- Importantly, no liver toxicity or cytokine release syndrome (CRS), AEs often associated with T-cell–engaging therapies and CD137 agonists, were observed

TABLE 2. SAFETY SUMMARY FOR BT7480 + NIVOLUMAB

AEs, n (%)	Patients (N=12)
TEAEs	11 (91.7)
Grade ≥3	8 (66.7)
SAEs	8 (66.7)
Grade ≥3	8 (66.7)

	BT7480-related	Nivo-related
TRAEs	5 (41.7)	5 (41.7)
Grade ≥3	1 (8.3)	0
TRSAEs	1 (8.3)	0
Grade ≥3	1 (8.3)	0
TRAEs leading to dose reduction	0	NA
TRAEs leading to dose interruptions	1 (8.3)	1 (8.3)
TRAEs leading to dose discontinuation	0	0
BT7480-related AEs (any grade) reported in ≥10% of patients, n (%)		
Nausea	3 (25.0)	
Decreased appetite	2 (16.7)	
Dysgeusia	2 (16.7)	
Fatigue	2 (16.7)	
Pyrexia	2 (16.7)	
Vomiting	2 (16.7)	

EFFICACY

- Of the 8 patients who were evaluable for efficacy, a best overall response of PR was reported in 2 patients (1 with nonsquamous NSCLC, which lacked actionable genomic alterations, and 1 with ER+, HER2– BC; **Table 3**; **Figure 3**), and 1 additional patient achieved SD
- Observation of anti-cancer activity in these patients is notable given prior treatment history and disease context; details above and right

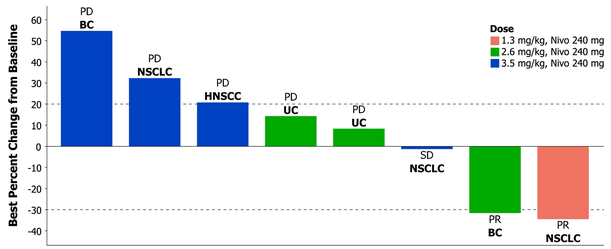
TABLE 3. CONFIRMED BEST OVERALL RESPONSE IN PATIENTS WITH NECTIN-4–ASSOCIATED ADVANCED SOLID TUMORS TREATED WITH BT7480 + NIVOLUMAB

Best overall response in response-evaluable patients, n (%)	Patients (N=8)
Confirmed ORR, n (%) [95% CI]	**2 (25.0)** [3.2–65.1]
Complete response	0
Partial response	2 (25.0)
Stable disease	1 (12.5)
Progressive disease	5 (62.5)
CBR,[a] n (%) [95% CI]	3 (37.5) [8.5–75.5]

[a]CBR defined as complete + partial responses + stable disease (>8 weeks)

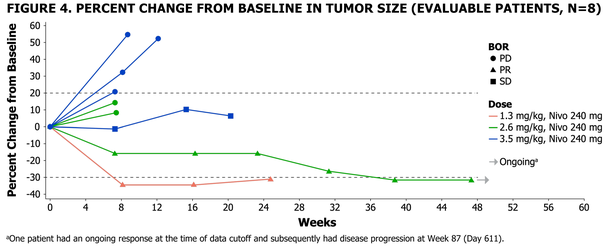
- The patient with NSCLC (wildtype for *EGFR* and *ALK*) who achieved PR had previously received 3 lines of therapy, including multiple lines of ICI treatment
  - 1L: Nivolumab + ipilimumab + platinum-based chemotherapy with complete response and subsequent disease progression at about 5 months of treatment
  - 2L: Investigational SMARCA2 degrader with PD as best response
  - 3L: Immunotherapy rechallenge with durvalumab + tremelimumab + platinum-based chemotherapy with PD as best response
- The ability to achieve PR in a patient with ER+, HER2– BC is notable as responses to immuno-oncology (IO) agents such as nivolumab are not typically seen with immunologically cold tumors
- The duration of the 2 PRs and SD were all >20 weeks, including in the patient with ER+, HER2– BC (responding and on treatment for >45 weeks at time of analysis), demonstrating significant reduction of total tumor burden (**Figure 4**)

FIGURE 3. MAXIMUM PERCENT REDUCTION FROM BASELINE IN TARGET LESION BY DOSE AND TUMOR TYPE (EVALUABLE PATIENTS, N=8)[a]



[a]For patients designated NE (n=4), 3 lacked at least 1 valid post-baseline assessment and 1 achieved SD for less than 6 weeks and thus was designated as NE per RECIST 1.1 criteria.

FIGURE 4. PERCENT CHANGE FROM BASELINE IN TUMOR SIZE (EVALUABLE PATIENTS, N=8)



[a]One patient had an ongoing response at the time of data cutoff and subsequently had disease progression at Week 87 (Day 611).

CASE STUDY

- A patient with ER+, HER2– breast cancer achieving PR with the 2.6 mg/kg QW dose of BT7480 + nivolumab demonstrated resolution of bone metastases and return of bone marrow fat, consistent with no active disease (**Figure 5**)

FIGURE 5. PATIENT CASE

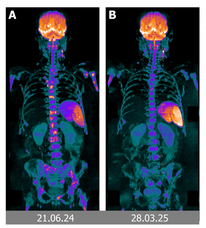


Figure 5A–B. WBMRI showing significant reduction in areas of abnormal DWI (diffusion-weighted imaging)

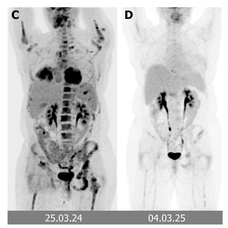


Figure 5C–D. FDG PET-CT showing significant reduction in areas of abnormal FDG uptake

FIGURE 5. PATIENT CASE *(continued)*

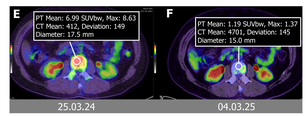


Figure 5 E–F. Representative bone metastasis at L2 showing high SUV (SUV max 8.63) and resolution of FDG avidity (SUV max 1.37)

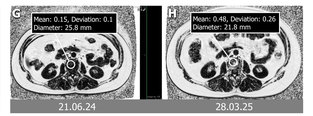
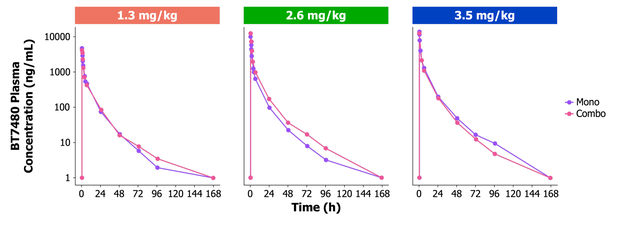


Figure 5 G–H. Low fat fraction (0.15) at baseline and patchy return of bone marrow fat (fat fraction 0.48) in keeping with scarring and no active disease

PHARMACOKINETICS

- PK was approximately dose proportional across the tested dose range at Cycle 1 Day 1
- Terminal half-life of BT7480 at 1.3–3.5 mg/kg was 11–16 hours with minimal BT7480 accumulation at steady state (Cycle 1 Day 15) after once weekly dosing (monotherapy and combination data combined)
- BT7480 PK profiles and parameters (AUC and C_{max}) were similar between monotherapy and combination, suggesting no PK interaction for the combination

FIGURE 6. BT7480 MEAN PLASMA CONCENTRATION-TIME PROFILES AT CYCLE 1 DAY 1 FOR BT7480



CONCLUSIONS

- The combination of BT7480 + nivolumab demonstrated the ability to reduce tumor burden in multiple Nectin-4–associated solid tumor types while maintaining a well-tolerated safety profile, including no reported liver toxicity
  - Responses were observed in ER+, HER2– BC and IO-resistant NSCLC, raising the possibility that BT7480 may have the ability to prime immune responses in patients not otherwise expected to respond to existing IO-based strategies
- BT7480 exhibited a dose-dependent increase in PK with minimal accumulation at steady-state with a once weekly dosing regimen; no PK interaction was observed between BT7480 and nivolumab

ABBREVIATIONS

1L, first line; 2L, second line; 3L third line; AE, adverse event; AUC, area under the curve; BC, breast cancer; Cmax, maximum serum concentration; CBR, clinical benefit rate; CR, complete response; CRS, cytokine release syndrome; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5; DLT, dose-limiting toxicity; DWI, diffusion-weighted imaging; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, HER2–, estrogen receptor-positive HER2-negative; FDG PET-CT, fluorodeoxyglucose positron emission tomograph- computed tomography; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; IO, immuno-oncology; IV, intravenous; MW, molecular weight; NE, not evaluable; Nivo, nivolumab; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PEG3, trimeric polyethylene glycol; PK, pharmacokinetics; PR, partial response; Q2W, once every 2 weeks; QW, once weekly; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SAE, serious adverse event; SD, stable disease; SUV, standardized uptake value; TEAE, treatment-emergent adverse event; TICA, tumor-targeted immune cell agonist; TNF, tumor necrosis factor; TRAE, treatment-related AE; TRSAE, treatment-related SAE; UC, urothelial carcinoma; WBMRI, whole-body magnetic resonance imaging.

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