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Quantifying Patient Preferences for Bacillus Calmette-Guérin (BCG) and PD-(L)1 Inhibitors in High-risk Non-muscle Invasive Bladder Cancer (NMIBC): A Discrete Choice Experiment

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Objective

The objective of the study was to quantify patient benefit and risk preferences for attribute levels relating to investigational PD-(L)1 regimens used in combination with BCG as alternatives to SOC (BCG alone) to treat patients with HR-NMIBC.

Key Findings: HR-NMIBC patient preferences

Patients have a strong preference for treatments which offer improved event-free survival (EFS) and a prolonged time to potential cystectomy.

Bladder-related adverse events (AEs) associated with BCG therapy were the most important safety risks to avoid, although the risk of experiencing AEs associated with PD-(L)1 inhibitors (i.e., serious immune AEs, chronic endocrine conditions) were also important.

Patients preferred PD-(L)1 inhibitors that were administered subcutaneously (rather than intravenously) and over a shorter time period.

While treatment administration attributes were important to HR-NMIBC patients, the clinical benefit and safety risk outcomes were more important.

Conclusions and implications

This research highlights the value of prolonging EFS and effective clinical management of bladder-related AEs.

Findings indicate a willingness for HR-NMIBC patients to accept more burdensome administration regimens in trade-off for improved efficacy and safety outcomes.

This study contributes insights from the HR-NMIBC patient perspective which can inform future clinical and shared decision-making for PD(L)1 inhibitor + BCG regimens.

Considerations

The findings are applicable only to the specific attributes and levels described in this discrete choice experiment (DCE) and the participant sample recruited in this survey.

Attributes and levels were informed by data available and expert clinical opinion at the time of research. This is subject to change as the clinical development landscape evolves.

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Presented at the 2025 ASCO Annual Meeting, Chicago, IL, May 30 – June 3

Background

- Bladder cancer is the 7th most common cancer in the United States (US).
- In 2023, ~75% of new cases were non-muscle invasive bladder cancer (NMIBC).[1]
- Estimates indicate that disease recurrence is common (31-78%) and progression to muscle-invasive disease occurs in approximately 10-20% of NMIBC patients.[2,3]
- High-risk NMIBC (HR-NMIBC) is diagnosed in ~25% of NMIBC cases[4] and associated with an higher chance of progression than low/intermediate-risk.[5]
- Current clinical guidelines for HR-NMIBC recommend transurethral resection of bladder tumor (TURBT), followed by intravesical Bacillus Calmette-Guerin (BCG) induction + maintenance for up to 3 years.[6-10]

– Several studies are investigating combinations of programmed cell death-1/programmed death-ligand 1 (PD-[L]1) inhibitors + BCG as means to improve treatment outcomes in BCG naive HR-NMIBC.

– Investigational PD-(L)1 inhibitor + BCG combination regimens may increase treatment burden while providing benefits. There is value in understanding the trade-offs that HR-NMIBC patients are willing to make among benefit, risk, and administration attributes.

– Evidence on patient preferences for these combination regimens is limited, particularly in a BCG-naive patient population.

Materials and Methods

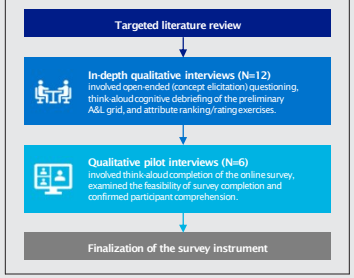
A discrete choice experiment (DCE) was conducted, with DCE being an accepted methodology for quantifying preferences for treatment attributes in a healthcare setting.[11]

STUDY DESIGN

Qualitative research to inform survey development

- In line with good research practice[12-14] and regulatory guidance,[15] evidence-based methods and qualitative research were used to develop[13,16] and pre-test[17] attributes, levels and the survey instrument.
- A targeted literature review (TLR) of patient-focused and clinical literature identified 11 preliminary attributes as being potentially differentiating among investigational PD-(L)1 inhibitor +/- BCG therapy regimens.
- The refinement of patient-relevant attributes and development of survey training and materials was informed by qualitative research with patients (**Figure 1**).
- Feedback from clinical experts, a patient advocate, and regulators, in conjunction with HR-NMIBC patient insights, informed the final list of attributes, levels (**Table 1**) and supplementary images/reference material included in the survey instrument.

Figure 1. Research conducted to develop the survey instrument



Discrete choice experiment (DCE)

- The sample of patients was recruited in the US utilizing clinician-referrals by a third-party recruitment agency (Global Perspectives).
- The DCE experimental design,[18] analysis[19] and model validation[20] were conducted in line with good research practice guidelines.
- Survey participants completed a series of hypothetical choice tasks which described the administration mode and frequency for PD-(L)1 inhibitors and BCG, median event-free survival (EFS) and adverse events (**Table 1**).
- Each choice task included two hypothetical treatment options (alternatives) and participants selected their most preferred treatment plan. (e.g., **Table 2**).
- Participants responded to 10 choice tasks from an experimental design (Figure 2), as well as 2 holdout prediction tasks and 2 practice tasks.

– Alternative-specific (conditional) rules[21] were used to prohibit implausible combinations of attributes and levels. Rules were governed by the *Therapy* attribute in the background that was not shown to participants in any choice tasks.

Table 1. Attributes and levels included the DCE experimental design

#	Attribute name	Patient-facing language		Attribute levels
1	Therapy[a]	Not applicable[a]	a	PD-(L)1 inhibitor only
			b	BCG only
			c	PD-(L)1 inhibitor + BCG
2	PD-(L)1 inhibitor administration route	How patients take ICI therapy	a	Intravenous (IV) infusion lasting between 30 and 60 minutes[d]
			b	Subcutaneous injection lasting between 7 and 10 minutes[d]
			c	Subcutaneous injection lasting less than 1 minute[d]
			d	This treatment plan does not include ICI therapy[b,e]
3	PD-(L)1 inhibitor frequency	How often patients take ICI therapy	a	Every 3 weeks[d]
			b	Every 4 weeks[d]
			c	Every 6 weeks[d]
			d	This treatment plan does not include ICI therapy[b,e]
4	BCG administration and schedule	How often and how long patients take BCG	a	Once a week for the first 6 weeks. Then once a week for 3 weeks at month 3, 6 and 12 (and could continue at month 18 until month 24). This is sometimes called the "maintenance" phase.[f]
			b	Once a week for 6 weeks only. This is sometimes called the "induction" phase.[f]
			c	This treatment plan does not include BCG[b,e]
5	Event-free survival (EFS)	How long the treatment plan will work for	a	22 months until the cancer returns or worsens, after which time patients may need surgery to remove their bladder (called a cystectomy).
			b	27 months until the cancer returns or worsens, after which time patients may need surgery to remove their bladder (called a cystectomy).
			c	36 months until the cancer returns or worsens, after which time patients may need surgery to remove their bladder (called a cystectomy).
6	Bladder-related AEs	Patients who experience bladder problems while taking treatment	a	75% of patients (75 out of 100 patients)
			b	35% of patients (35 out of 100 patients)
			c	No patients (0 out of 100 patients)
7	Chronic endocrine conditions	Patients who develop a chronic condition while taking treatment that needs lifelong management	a	10% of patients (10 out of 100 patients)
			b	5% of patients (5 out of 100 patients)
			c	No of patients (0 out of 100 patients)
8	Serious immune-related AEs	Patients who experience serious immune side effects while taking treatment	a	20% of patients (20 out of 100 patients)
			b	10% of patients (10 out of 100 patients)
			c	No patients (0 out of 100 patients)

a: The *Therapy* attribute governed conditional rules and was not shown to participants in choice tasks (Table 2). b: Null levels were shown for ease of completion but were not designated as a level in the preference (utility) estimation. d: Not shown with 1b, e: Not shown with 1a/c; f: Not shown with 1a; AE: adverse event; ICI: immune checkpoint inhibitor (patient-friendly alternative phrasing for PD-[L]1 inhibitors)

STATISTICAL ANALYSIS

- DCE data was analyzed using a Hierarchical Bayesian (HB) model to estimate individual-level preference weights (PW) for every attribute level (summarized as mean preference weights in **Figure 2**).[22]
- Relative attribute importance (RAI) was derived using predicted choice probabilities:
  1. A base-case lowest utility profile (LUP) was constructed by selecting the combination of attribute levels that had the lowest mean preference weights and included all attributes relating to PD-(L)1 inhibitors + BCG included (no conditional rules).
  2. A sensitivity analysis was conducted by constructing a scenario comprising two identical profiles (base-case LUP and an alternative LUP) then systematically varying a single attribute level in the alternative LUP while other levels remained unchanged.
  3. Individual-level preference weights were used to predict choice probabilities for the base-case LUP and alternative LUP. Changes in the alternative LUP predicted choice probability (maximum-minimum) for each participant was calculated for each attribute.
- RAI is ratio-scaled, enabling proportionate comparison between attributes (e.g., RAI: 20% is twice as important than RAI: 10%). The higher the RAI, the more influential an attribute was to treatment choice in the given scenario.

Table 2. Example of a choice task in the DCE survey

Attribute	Treatment Plan A	Treatment Plan B
How patients take ICI therapy	Intravenous (IV) infusion lasting between 30 and 60 minutes	Subcutaneous injection lasting less than 1 minute
How often patients take ICI therapy	Every 3 weeks	Every 4 weeks
How often and how long patients take BCG	This treatment plan does not include BCG	This treatment plan does not include BCG
How long the treatment plan will work for	22 months until the cancer returns or worsens, after which time patients may need surgery to remove their bladder (called a cystectomy).	36 months until the cancer returns or worsens, after which time patients may need surgery to remove their bladder (called a cystectomy).
Patients who experience bladder problems while taking treatment	No patients (0 out of 100 patients)	35% of patients (35 out of 100 patients)
Patients who develop a chronic condition while taking treatment that needs lifelong management	5% of patients (5 out of 100 patients)	10% of patients (10 out of 100 patients)
Patients who experience serious immune side effects while taking treatment	No patients (0 out of 100 patients)	20% of patients (20 out of 100 patients)
	◎	◎

Results

SURVEY SAMPLE (**Table 3**)

- 150 US adults with completed the online survey between January-June 2024.
- Participants were eligible if they had a diagnosis HR-NMIBC and received TURBT; ineligible if BCG-unresponsive.
- All participants were recruited via clinician referral subject to pre-screening, meaning a clinician-confirmed diagnosis is assumed. Additional diagnostic evidence (HCP-completed form) was collected for 26/150 (17.3%) participants.

Table 3. Summary of participant characteristics (N=150)

Description		N=150
Age (years)	Mean	62.6
	Median	63
	Min-Max	49-74
Gender, n (%)	Male	76 (50.7%)
	Female	72 (48.0%)
	Prefer not to answer	2 (1.3%)
Race, n (%)	Caucasian	69 (46.0%)
	Black/African American	41 (27.3%)
	Native Hawaiian or Other Pacific Islander	13 (8.7%)
	American or American Indian	7 (4.7%)
	Asian	6 (4.0%)
	Prefer not to answer	14 (9.3%)
Ethnicity, n (%)	Hispanic, Latino or Spanish origin (of any race)	31 (20.7%)
	Not Hispanic, Latino or of Spanish origin	119 (79.3%)
Region of the US, n (%)	West	116 (77.3%)
	Northeast	13 (8.7%)
	South	12 (8.0%)
	Midwest	9 (6.0%)
Education level, n (%)	High school or less	45 (30.0%)
	College education/degree	96 (64.0%)
	Prefer not to answer	9 (6.0%)
Health literacy[a] n (%)	Possibility of limited literacy	32 (21.3%)
	Adequate literacy	118 (78.7%)
Time since diagnosis (months)	Mean	3.6
	Median	2
	Min-Max	0-22
BCG status	BCG naive	77 (51.3%)
	BCG experienced	73 (48.7%)
Number of BCG administrations received[b]	Mean	8
	Median	8
	Min-Max	3-14
Time since last BCG treatment (weeks)[b,c]	Within the last 3 weeks	31 (43.1%)
	3-6 weeks	21 (29.2%)
	6-12 weeks	12 (16.7%)
	More than 12-18 weeks	8 (11.1%)

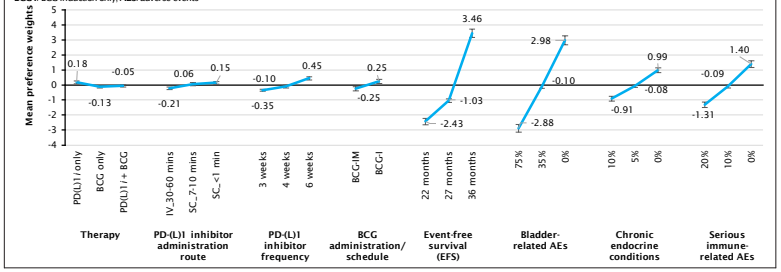
a: Assessed using the Newest Vital Sign[23]; b: Applicable to BCG-experienced (n=77/150) participants; c: Total n=72/73; n=1 had completed BCG.

PATIENT PREFERENCES AND RELATIVE ATTRIBUTE IMPORTANCE

- Preference weights were ordered as expected, with better safety/survival outcomes or less burdensome regimens being preferred to worse safety/survival outcomes or more burdensome regimens (**Figure 2**).

Figure 2. Mean preference weights for each attribute level (N=150)

Key: **PD(L)1***i* : anti-programmed cell death protein-1/programmed death-ligand 1 *inhibitor*; **SC**: subcutaneous injection; **IV**: intravenous infusion; **BCG-IM**: BCG induction + maintenance; **BCG-I**: BCG induction only; **AE**s: adverse events



- RAI scores (shown in **Figure 3**) indicate *EFS* (22 months to 36 months) as the most important attribute (RAI: 17.2%) to HR-NMIBC participants completing this DCE.

– The possibility of experiencing bladder-related AEs due to treatment was the most important safety risk (RAI:16.4%); followed by the risk of experiencing *serious immune-related AEs* (RAI: 14.0%) and *chronic endocrine conditions* (RAI: 12.6%).

- While the attributes describing the administration of PD-(L)1 inhibitors and BCG administration were less important relative to *event-free survival* and safety-related attributes (**Figure 3**), the varying options (levels) in the administration attributes were found to have impacted treatment choice differently:

– The most important administration attributes were *PD-(L)1 inhibitor frequency* (9.9%) and *PD-(L)1 inhibitor administration route* (9.5%).

– The *BCG administration/schedule* attribute (9.0%) was the least important administration-related attribute and the least important attribute overall.

– Per **Figure 2**, participants preferred a *subcutaneous injection* lasting either *<1-minute* (PW: 0.15) or *7-10 minutes* (PW: 0.06) relative to a *30-60 minute IV infusion* (PW: -0.21).

- RAI scores were largely consistent when stratified by clinical and demographic subgroups (including BCG-naive [n=77] and BCG-experienced [n=73]), with *EFS* and *bladder-related AEs* remaining the most important attributes among subgroups.

Figure 3. Conditional relative attribute importance (RAI)* (N=150)

* Estimated using the impact of changes in attribute levels on predicted choice probabilities

Key: *Blue*: Administration attribute; *Green*: Benefit attribute; *Purple*: Safety/risk attribute. Error bars show the 95% confidence interval