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Treatment and disease management patterns for bacillus Calmette-Guérin unresponsive nonmuscle invasive bladder cancer in North America, Europe and Asia: A real-world data analysis

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Abstract

Background: This study examined real-world treatment and management of bacillus Calmette-Guérin (BCG)-unresponsive patients across 3 continents, including patients unable or unwilling to undergo cystectomy.

Materials and methods: Physicians actively involved in managing patients with nonmuscle invasive bladder cancer completed online case report forms for their 5 consecutive patients from the broad BCG-unresponsive population and a further 5 consecutive BCG-unresponsive patients who did not undergo cystectomy (in Japan, physicians provided a total of 5 patients across both cohorts).

Results: Most patients had received 1 (37%) or 2 (24%) maintenance courses of BCG. Five or more maintenance BCG courses were received by patients in Japan (59%) and China (31%), while in Germany 76% of patients received only 1 course. Most patients became BCG-unresponsive during their first (44%) or second (22%) treatment course; in Germany, 77% became BCG-unresponsive during their first treatment course. Most countries did not provide another course of BCG after a patient first became unresponsive, whereas unresponsive patients in Japan and China were most likely to be retreated with BCG. "Untreated - on watch and wait" was the main treatment/management approach received post-BCG treatment for 42% or more of patients in most countries except China (39%) and the United States (36%). "Following treatment guidelines" was consistently the top reason for post-BCG treatment selection across all treatment options.

Conclusions: This study confirmed the global unmet need for patients with nonmuscle invasive bladder cancer, and found that many patients experienced periods of no treatment after not responding to BCG therapy.

Keywords: Bacillus Calmette-Guérin; Bladder cancer; Cystectomy; Treatment failure; Urinary tract

1. Introduction

Nonmuscle invasive bladder cancer (NMIBC) represents approximately 80% of all newly diagnosed bladder cancers.[1] Intravesical bacillus Calmette-Guerin (BCG) is the gold-standard treatment for highrisk NMIBC, but approximately 40% of patients do not respond to treatment, including patients suboptimally treated with BCG or who did not tolerate treatment, as well as patients with true BCG-unresponsive disease[2]

Although radical cystectomy remains the standard of care for BCG-unresponsive patients with high-risk and intermediate-risk tumors, many patients have contraindications including poor health and comorbidities or do not consent to undergo surgery.[3,4] Moreover, cystectomy carries a heavy burden of perioperative morbidity,

hospital readmission and mortality, and has a detrimental effect on a patient's quality of life.[5,6]

There is no known optimal therapy for patients who do not respond to BCG therapy but are unable or unwilling to undergo cystectomy; no salvage medical or intravesical treatments have shown durable efficacy in true BCG-unresponsive patientsd[3,4] A recent systematic review reported that bladder-sparing treatments in patients with only papillary tumors show rapidly declining median recurrence-free rates of 67% at 6 months, 44% at 12 months and only 10% at 24 months; for carcinoma in situ, corresponding median recurrence-free rates were even lower, at 26%, 17%, and 8%, respectively[7]

Current guidelines emphasize the superiority of radical cystectomy over bladder-sparing treatments in BCG-unresponsive patients in all efficacy outcomes and few alternatives to cystectomy are mentioned. Although some interventions may produce responses in some patients, these treatments are considered oncologically suboptimald[8,9]

Little is known about patterns of treatment and management of patients with BCG-unresponsive NMIBC. Given the paucity of treatment options, it is important to know what treatment decisions physicians are making with their patients and the rationale for their choices. This study examined real-world treatment and management of BCG-unresponsive patients in 8 countries in North America, Europe, and Asia by retrospective review of medical records, including patients unable or unwilling to undergo cystectomy.

2. Materials and methods

2.1. Study design

This was a multi-center, retrospective chart review study of BCG-unresponsive patients with NMIBC. The primary study objective was to describe real-world treatment/management, including lines of treatment, as well as duration of therapy received; use of surgery (partial or radical cystectomy), including reasons patients may not undergo cystectomy; choice of subsequent management for BCG-unresponsive patients with reasons for selection, including for patients who may not undergo cystectomy; and next treatment steps. Secondary objectives included demographic and disease characteristics; healthcare resource utilization from the time when a patient became BCG-unresponsive, and physician satisfaction with patients' post-BCG treatment. This paper focuses on treatment and management of BCG-unresponsive patients. Other study outcomes including healthcare resource usage, reasons for cystectomy and use of biomarkers will be reported elsewhere.

The study was conducted in 2 stages. In stage 1, electronic case report forms (eCRFs) were completed for a broad sample of patients defined as BCG-unresponsive for ≥3 months, and in stage 2, eCRFs were completed for an enriched sample of patients defined as BCG-unresponsive for ≥3 months and who did not undergo cystectomy (ineligible/refused patient cohorts). There was no overlap between these 2 cohorts. A study schema is shown in Figure 1.

2.2. Data collection and study populations

Data were collected in the United States, France, Germany, Italy, Spain, the United Kingdom, China, and Japan between January and May 2019, inclusive. Local agencies recruited a geographically representative physician sample in each country comprising urologists and medical/clinical oncologists actively involved in NMIBC management. These physicians abstracted medical record data for BCG-unresponsive patients. A physician pilot (n = 2) was completed to assess the user-friendliness and appropriateness of the eCRF; study materials were updated on the basis of physicians' feedback. Questions asked in the eCRF are presented in supplementary Table 1 of the online appendix, http://links.lww.com/CURRUROL/A7.

Physicians completed eCRFs based on medical chart reviews of their last 5 consecutive patients from the broad BCG-unresponsive population and a further 5 consecutive patients from the population of BCG-unresponsive patients who did not undergo cystectomy; physicians in Japan provided a total of 5 patients across the 2 cohorts, reflecting a smaller universe size versus other countries. The consecutive patient selection approach was stressed to each participating physician to remove the element of selection bias. Patients with NMIBC were defined as BCG-unresponsive (according to FDA criteria) if they had at least 1 of the following: persistent or recurrent carcinoma in situ alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy, recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy, and T1 high-grade disease at the first evaluation after an induction course of BCG.[10]

Eligibility criteria for patients in both cohorts included being ≥18 years of age; physician-confirmed diagnosis of NMIBC; BCG unresponsiveness for ≥3 months before data abstraction, and having undergone adequate BCG therapy (defined as meeting at least 1 of the following: ≥5/6 doses of an initial induction course plus ≥2/3 doses of maintenance therapy; ≥5/6 doses of an initial induction course plus ≥2/6 doses of a second induction course). To qualify for
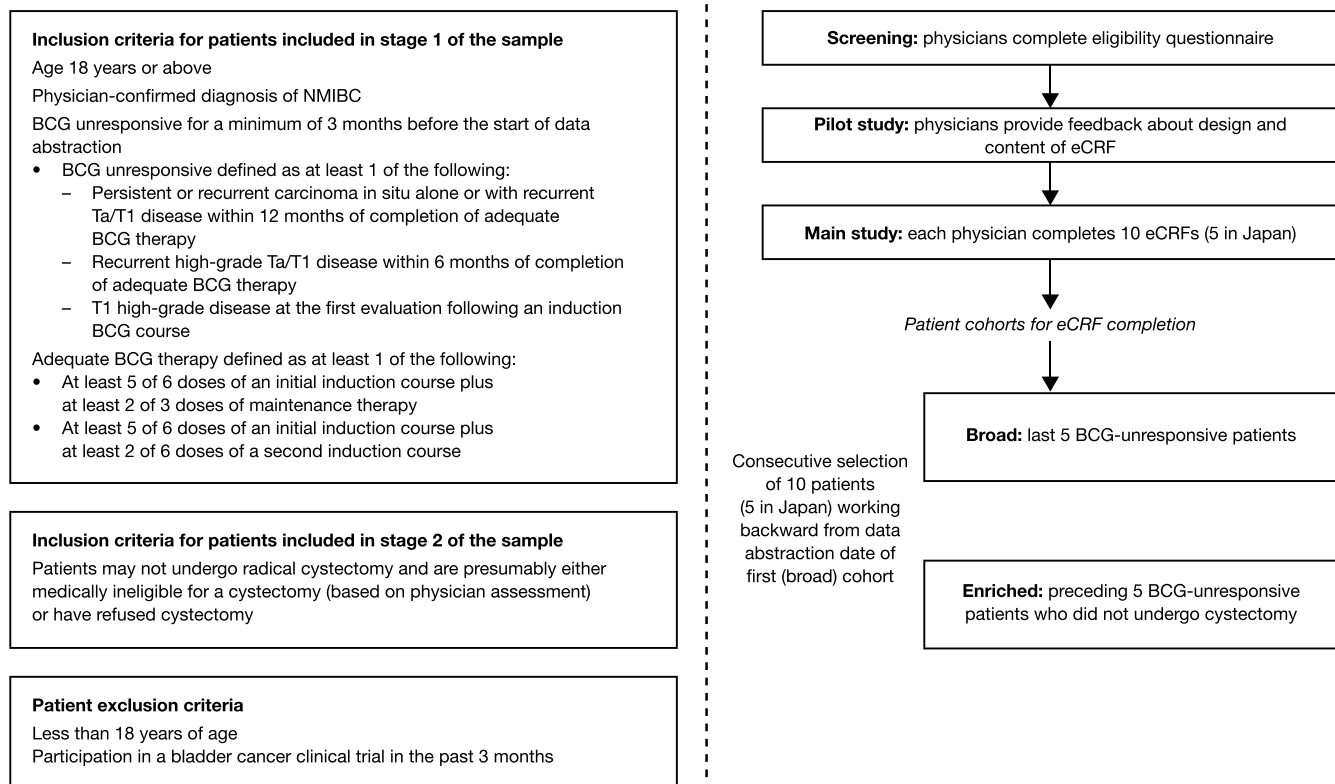

Figure 1. Study design. BCG = bacillus Calmette-Guerin; NMIBC = nonmuscle invasive bladder cancer; eCRF = electronic case report form.

Table1

Patient demographics by country.

	Overall	DE	IT	ES	FR	UK	USA	JP	CN
Number	2554	300	301	301	304	300	600	145	303
Sex, male, %	77	69	74	84	87	72	78	80	77
Mean age (SD), yr	71.5 (9.9)	72.9 (9.2)	69.8 (9.2)	74.6 (8.7)	74.3 (7.8)	74.3 (8.3)	70.2 (10.2)	73.4 (10.7)	64.5 (10.2)
Mean time from diagnosis (SD), yr	1.9 (2.5)	2.1 (2.3)	1.4 (1.1)	2.1 (2.1)	1.9 (2.6)	1.3 (1.0)	2.0 (3.5)	3.0 (3.5)	1.5 (1.1)
Risk classification at diagnosis, %									
High	49	42	38	66	54	51	54	59	28
Intermediate	51	58	62	34	46	49	46	41	72
ECOG PS at initial NMIBC diagnosis, %									
0	48	62	60	49	50	27	43	66	44
1	32	25	29	32	36	41	32	17	38
≥2	19	13	12	19	14	31	24	17	18

CN = China; DE = Germany; ECOG PS = Eastern Cooperative Oncology Group performance status; ES = Spain; FR = France; IT = Italy; JP = Japan; UK = United Kingdom; USA = United States of America. Higher ECOG PS scores indicate a greater degree of disability.

inclusion, patients in the second (enriched) cohort should not have undergone cystectomy either because of physician-assessed ineligibility or patient refusal. In clinical practice, patients are grouped into risk classification (low, intermediate, high) based on tumor grade,[11] defined by European Association of Urology (France, Germany, Spain, and Italy), American Urological Association (United States, China, and Japan) and National Institute for Health and Care Excellence (UK) guidelines.[12]

The protocol and study materials were approved by the Western Institutional Review Board. Physicians provided anonymized patient data and no personal identifiable information were collected; therefore, this study did not require informed consent. The study conformed to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines, guidelines for data processing and protection, and country-specific research guidelines.

2.3. Analysis

This was an exploratory study, and the analysis was primarily descriptive and dependent on the type of variable: continuous variables were summarized by the number of non-missing values, mean, standard deviations, median, and minimum and maximum, while categorical variables were summarized as the number and percentage of patients in each category. Respondents had to complete each question before they could continue to the next; thus there were no missing data as "don't know" or "unknown" were valid responses.

3. Results

3.1. Data completeness

All of the 2554 eCRF surveys issued were completed and there were no missing responses within surveys (mutually exclusive questions did not count as missing responses).

3.2. Study populations

The study recruited a total of 508 physicians. Of these, 56% were urologists, 27% were medical oncologists, 15% were urooncologists, and 2% were clinical oncologists. The overall patient population included 2554 patients, of whom 77% were male; 2066 patients did not undergo cystectomy. Mean age (± standard deviation [SD]) of the overall population was 71.5 (9.9) years and mean time since diagnosis (±SD) was 1.9 (2.5) years; risk classification at diagnosis (n = 2448) was high (49%) and intermediate (51%). Most patients for whom Eastern Cooperative Oncology Group performance status (ECOG PS) score was available (n = 2502; 52 unknown) had a score

of 0 (48%) or 1 (32%) at initial NMIBC diagnosis. Patient demographic information by country is shown in Table 1.

3.3. BCG treatment

Of 2309 patients for whom data were available (245 unknown), most had received 1 or 2 maintenance courses of BCG (37% and 24%, respectively). In Japan, nearly two-thirds of patients received 5 or more maintenance BCG courses (24% between 5 and 7 courses, 35% 8 or more), in China, 31% received 5 or more courses, while in Germany over three-quarters of patients received only 1 course (76%) (Fig. 2). Most patients (n = 2264 evaluable; 290 don't know) became BCG-unresponsive during their first (44%) or second (22%) treatment course; in Germany, over three-quarters of patients (77%) became BCG-unresponsive during their first treatment course. Physicians in most countries did not provide another course of BCG after a patient first became unresponsive, notably in Germany (94%), the United Kingdom (91%), and Italy (90%); physicians in Japan and China, however, were most likely to retreat unresponsive patients with BCG (data not shown). Overall, the most common strains of BCG administered were TICE (16%), Pasteur (14%), and Glaxo (14%); the most common strains per country are presented in Figure 3.

3.4. Treatment post-BCG

"Untreated - on watch and wait" was the main treatment/ management approach received post-BCG across all countries except China and the
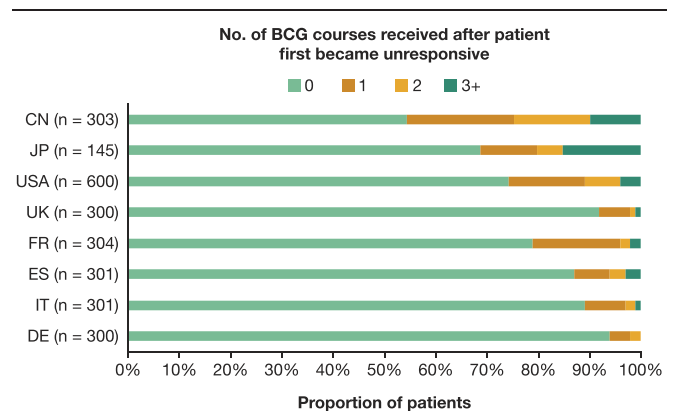

Figure 2. Differences between countries in proportions of patients who received multiple BCG courses. BCG = bacillus Calmette-Guérin.
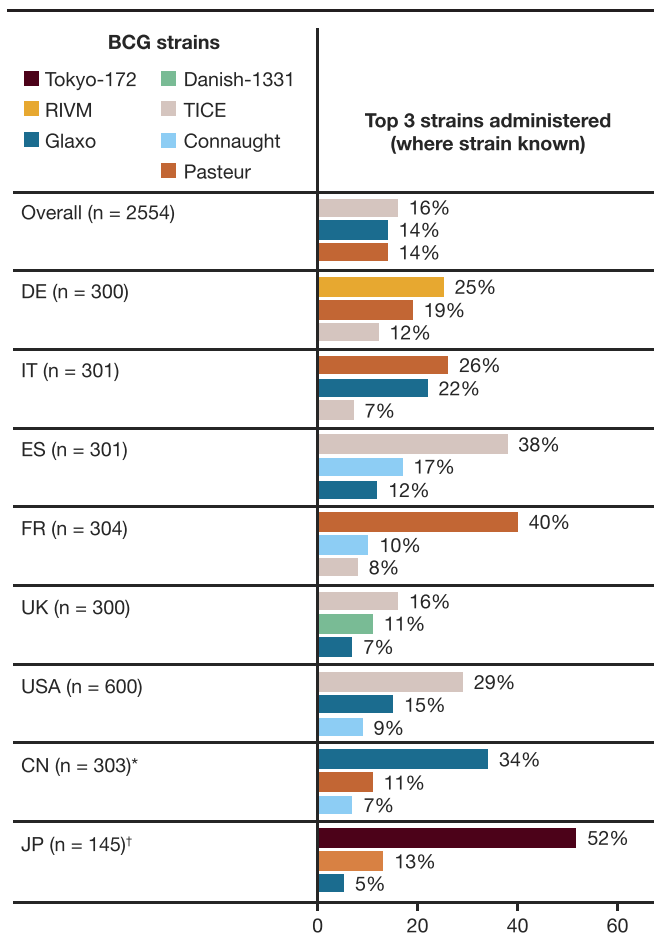
Figure 3. Most common strains of BCG administered. "Don't know" strain: Overall (32%), DE (27%), IT (33%), ES (23%), FR (37%), UK (46%), USA (32%), CN (35%), JP (19%). *7% "Other" in top 3. [†]10% "Other" in top 3. BCG = bacillus Calmette-Guerin.

4. Discussion

The study revealed some similarities and differences in patient characteristics among the 8 countries. In particular, mean patient age was 71.5 years and ranged from 64 to 74 years across the countries, with the lowest mean patient age being observed in China (64.5 years; range, 39–89). The comparatively young age of patients in China could help explain why the lowest rates of radical cystectomy were also seen in China, although this could also be explained by cultural factors, as reflected in a Chinese database study showing that NMIBC patients are mostly (89%) treated with transurethral resection in favor of cystectomy.[13] Time from diagnosis was relatively greater in Japan (3.0 years) and lower in Italy, the United Kingdom, and China (1.4, 1.3, and 1.5years, respectively), although worse outcomes and/or more radical treatment was not observed in Japan, despite the longer period of disease. The United Kingdom had a lower proportion of patients with ECOG PS of 0 (27% vs. overall mean 48%), and greater proportion with ECOG PS of 2 or higher (31%). The United States also had a high population of patients with ECOG PS of 2 or higher (24%). Greater impairment as measured by higher ECOG PS scores could indicate lower quality of life in these patients from the United Kingdom and the United States, however, quality of life was not assessed as an outcome; this may be of interest in future studies.

The majority of patients across most countries became unresponsive to BCG therapy after 1 or 2 courses with the exception of Germany, where most patients became BCG- unresponsive during their first treatment course. Patients in Germany were also most likely to undergo radical cystectomy, presumably related to high rates of BCG unresponsiveness developing during first-line therapy. Conversely, China reported the lowest rate of radical cystectomy alongside the highest frequency of intravesical therapy post-BCG. There is still a lack of clinical trial evidence to support the use of intravesical chemotherapy as an alternative to radical cystectomy.[14]

"Untreated - on watch and wait" was the main treatment/ management approach received post-BCG across most countries, with the top reason being adherence to treatment guidelines. Current US and European guidelines, however, do not advocate a "watch and wait" approach for BCG-unresponsive patients, even for patients who are ineligible for cystectomy.[9,15] Both guidelines strongly advocate immediate cystectomy in this setting; US guidelines include a checkpoint inhibitor as a bladder-sparing option while European guidelines mention intravesical chemotherapy, chemotherapy, and microwave-induced hyperthermia (all based on limited evidence). Transurethral resection of the bladder tumor was also a frequent option used for patients with BCG-unresponsive NMIBC, despite not being supported by guidelines at this stage of treatment.[8,9] "Following treatment guidelines" also was the top reason for post-BCG treatment selection across all treatment options. Overall, other top reasons for choosing post-BCG therapy were similar per treatment option and were mostly patient request or risk-based; current guideline recommendations consider all BCG-unresponsive patients as being high-risk cases with a poor prognosis.[8,9]

A recent systematic review found that guideline adherence is low in NMIBC including for radical cystectomy, where the overall adherence rate is only 33%; the authors noted that there can be discrepancy between stated and actual medical practice patterns, especially in situations where guideline adherence is lacking.[16] Current guidelines are not especially helpful for physicians who have BCG-unresponsive patients, with few options listed and no gold-standard care.[8,9]

Checkpoint inhibitors, notably agents blocking the programmed death 1 (PD-1) signaling pathway, have started to emerge as a possible bladder-sparing option for BCG-unresponsive NMIBC; 5
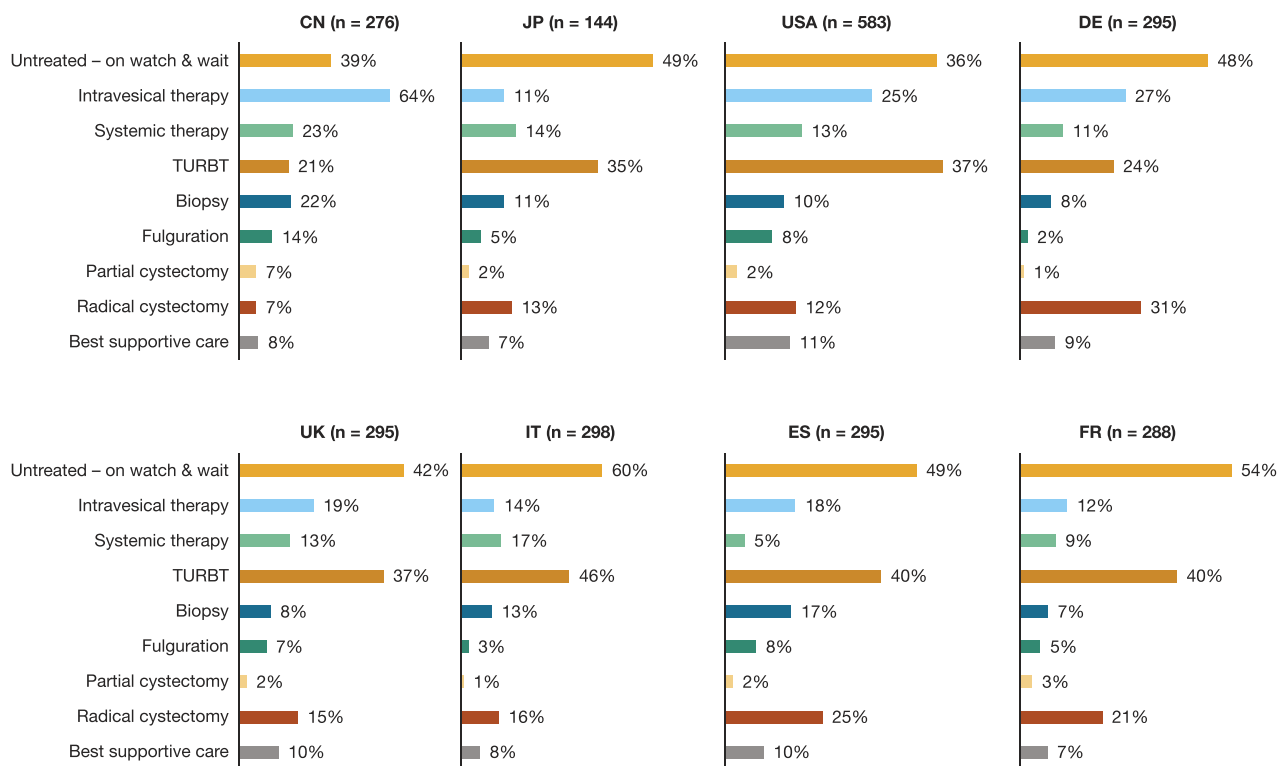
United States (Fig. 4); this option was selected for 42% or more of patients in most countries. Transurethral resection of the bladder tumor (TURBT) was frequently performed post-BCG in all countries (21%–46%), with the lowest frequencies in China (21%) and Germany (24%). Germany, Spain, and France reported the highest rates of radical cystectomy (31%, 25%, and 21%, respectively). China was most conservative in offering patients radical cystectomy (7%) but reported the highest frequency of intravesical therapy post-BCG (64%), with doxorubicin (34%), epirubicin (37%), and gemcitabine (26%) being the agents most commonly given.

"Following treatment guidelines" was consistently the top reason reported by physicians for post-BCG treatment selection across all treatment options (Table 2). "Risk stratification," "patient request," "progression risk score," and "tumor grade" comprised nearly all of the other top reasons per option for post-BCG treatment selection.

3.5. Physicians' satisfaction

Physicians in Germany had the highest satisfaction ratings with their patients' current treatment (Table 3), with approximately two-thirds being satisfied overall including approximately one-quarter of physicians who were "extremely satisfied." In most other countries, approximately one-third of physicians were satisfied with their patients' current treatment (mostly, only "quite satisfied") except for China, where nearly half of physicians were "quite satisfied" (none were "extremely satisfied").

Figure 4. Treatments received at any time post-BCG in the overall study population by country. Note, this question was not asked if respondents had selected "ongoing re-treatment with BCG" in response to question DQ1c in the eCRF. BCG = bacillus Calmette-Guérin; eCRF = electronic case report form; TURBT = Transurethral resection of the bladder.

have already been approved in the United States for first- or second-line use in metastatic urothelial carcinoma and are undergoing active clinical trial investigations for both BCG-unresponsive and first-line high-risk NMIBC settings, including intravesical administration and in combination with BCG or radiotherapy.[17,18] The anti-PD-1 checkpoint inhibitor nivolu- mab has been shown to have a favorable tolerability and efficacy profile, and is currently undergoing clinical trials in BCG-unresponsive NMIBC.[19] Pembrolizumab has been added to the latest version of US guidelines as an option for select BCG-unresponsive patients unable or unwilling to undergo cystectomy.[8] Other potential bladder-sparing options currently in late-stage clinical development include several antibody-drug conjugates (including oportuzumab monatox, or Vicinium) and the intravesical gene therapy nadofaragene firadenovec (Adstiladrin, formerly known as Instiladrin).[11,20,21]

Only approximately one-third of physicians were satisfied with their patients' current treatment; this is unsurprising given the gold-standard choice is radical cystectomy (which may be unsuitable for, or undesired by many patients) with only suboptimally effective bladder-sparing alternatives. There could be reasons for satisfaction outside the effectiveness and availability of therapies, however, these were not considered as part of the objectives of the study.

This study has several limitations. There was potential bias due to its retrospective design, which was minimized by asking physicians to abstract case notes for consecutive eligible patients; quality and completeness of original case notes and respondent veracity, however, could not be confirmed. The study requested the same number of cases per study site irrespective of the number of presenting patients per site, which may have introduced bias based on practices from smaller sites; however, a relatively large number of physicians were recruited to minimize any clustering effect around

Table 2

Top 3 reasons for each post-BCG treatment choice in the overall study population.

Post-BCG treatment (no. of patients)	Top 3 reasons (proportion of physicians)
Untreated - on watch and wait (n = 827)	• Following treatment guidelines (43%) • Patient request (39%) • Based on patient's risk stratification (22%)
Intravesical therapy (n = 379)	• Following treatment guidelines (42%) • Patient request (37%) • Based on patient's progression risk score (31%)*
Systemic therapy (n = 246)	• Following treatment guidelines (49%) • Based on patient's progression risk score (26%) • Patient request (26%)
TURBT (n = 345)	• Following treatment guidelines (36%) • Patient request (29%) • Based on patient's tumor grade (29%)
Biopsy (n = 92)	• Following treatment guidelines (63%) • Based on patient's tumor grade (40%) • Based on patient's risk stratification (35%)
Fulguration (n = 76)	• Following treatment guidelines (37%) • Based on patient's risk stratification (32%) • To minimize/avoid side effects (30%)
Partial cystectomy (n = 25)	• Following treatment guidelines (44%) • Based on patient's tumor grade (32%) • Based on patient's progression risk score (20%)†
Radical cystectomy (n = 257)	• Following treatment guidelines (83%) • Based on patient's tumor grade (28%) • Based on patient's progression risk score (26%)
Best supportive care (n = 167)	• Patient request (50%) • Following treatment guidelines (29%) • Based on patient's risk stratification (23%)

*Intravesical therapy: "based on patient's risk stratification" (31%) also in top 3. †Partial cystectomy: "patient request" (20%) and "as a last resort treatment" (20%) also in top 3. TURBT = Transurethral resection of the bladder. BCG = bacillus Calmette-Guérin.

Table 3

Physicians' satisfaction with patients' current treatment (post-BCG).

Total (n = 508)	CN (n = 35)	JP (n = 91)	USA (n = 180)	UK (n = 36)	IT (n = 39)	ES (n = 49)	FR (n = 39)	DE (n = 39)
Extremely dissatisfied, %	0.3	4.4	2.0	2.1	7.0	3.4	1.1	4.6
Quite dissatisfied, %	12.2	15.3	14.8	25.4	23.5	24.1	19.7	10.3
Neither, %	39.2	45.2	44.5	32.9	35.5	40.6	47.5	21.5
Quite satisfied, %	48.3	30.7	34.3	37.5	30.0	26.3	25.9	37.5
Extremely satisfied, %	0.0	4.4	4.4	2.1	4.0	5.6	5.8	26.1

BCG = bacillus Calmette-Guérin.

a smaller number of sites, and physicians seeing small numbers of patients were excluded. Study strengths included the large study population, representative real-world physician and patient samples, and clear definition of BCG-unresponsive NMIBC.

5. Conclusions

Patterns of treatment and management of BCG-unresponsive patients were broadly similar across different countries, with a notable exception that patients in China and Japan were more likely to continue on BCG treatment. Only approximately one-third of physicians were satisfied with their patients' current treatment. Outcomes from this large real-world study examining treatment and management practices for BCG-unresponsive NMIBC across 3 continents confirmed the unmet need for this patient group as a large percentage of patients experienced periods of no treatment after failing on BCG.

Statement of ethics

The protocol and study materials were approved by the Western Institutional Review Board. Physicians provided anonymized patient data and no personal identifiable information were collected; therefore, this study did not require informed consent. The study conformed to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines, guidelines for data processing and protection, and country-specific research guidelines

Conflict of interest statement

EB and KMG are employees of and have stock ownership in Bristol Myers Squibb.
DSC reports financial support for tuition and graduate stipend from Bristol Myers Squibb; and is currently an employee of and has stock ownership in Takeda.
KLM, IR, and GT-S are employees of Adelphi Real World who received consultancy fees from Bristol Myers Squibb.

Author contributions

EB contributed to the conception or design, analysis and interpretation of data, drafting and revising the article, providing intellectual content of critical importance to the work described and final approval of the version to be published.
DSC was involved in study design, drafts and revisions of the article, contributed to the intellectual integrity of the manuscript, was involved in data analysis, journal selection and approved all drafts including final version of the manuscript.
KMG contributed to study design, reviewed and provided feedback for the manuscript drafts, provided input in data analysis and approved final version of the manuscript.
KLM, IR, and GT-S contributed to all aspects of the manuscript, including design, analysis, interpretation of data, drafting manuscript, intellectual content, and approval of final version.

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