

Assessing Bladder Cancer Risk in Type 2 Diabetes Clinical Trials: the Dapagliflozin Drug Development Program as a ‘Case Study’

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ABSTRACT

Introduction: Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, decreases plasma glucose levels by suppressing renal glucose reabsorption and increasing urinary glucose excretion. Previously published pre-clinical data suggest that dapagliflozin lacks carcinogenic potential. This article reviews data on bladder cancer with dapagliflozin to illustrate the challenges in assessing bladder cancer in drug development programs in patients with type 2 diabetes mellitus (T2DM).

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Methods: Clinical cases of bladder cancer were analyzed in a pooled population of >9000 patients in 21 phase 2b/3 dapagliflozin clinical trials of up to 208 weeks' duration.

Results: In the 21-study pool, demographic and baseline characteristics were generally consistent between dapagliflozin and comparator groups. The overall incidence of malignancies was also balanced between the treatment groups, with an incidence rate ratio (IRR) of 1.035 [95% confidence interval (CI): 0.724, 1.481]. Nine of 5936 dapagliflozin-treated patients and 1 of 3403 comparator-treated patients reported bladder cancer, with an IRR of 5.168 (95% CI: 0.677, 233.55). All of these patients had clinical attributes typical of bladder cancer in the general population (≥ 60 -year-old males; 8 of the 10 patients were current/former smokers). All cases of bladder cancer were reported within 2 years of starting study treatment. There was an absence of detailed workup of hematuria prior to randomization, and no hematuria workup data were collected proactively in the dapagliflozin trials, which is typical of clinical practice. Failure to exclude bladder cancer prior to randomization increases the chance of

recruiting patients with pre-existing bladder cancer in clinical trials and may delay the final diagnosis. Of the nine dapagliflozin-treated patients with bladder cancer, eight had microscopic hematuria prior to start of treatment or within 6 months of initiating study treatment.

Conclusion: The assessment of bladder cancer data illustrates the challenges of characterizing cancer risk in T2DM drug development programs. The totality of evidence to date does not suggest a causal relationship between dapagliflozin and bladder cancer.

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Keywords: Bladder cancer; Dapagliflozin; Hematuria; SGLT2 inhibitor; Type 2 diabetes mellitus

INTRODUCTION

Epidemiologic data suggest that people with diabetes are at a significantly higher risk of many forms of cancer [1]. However, it is not clear if diabetes itself is an independent risk factor for cancer, or if the association can be explained by common risk factors such as obesity and a sedentary lifestyle shared between diabetes and several forms of cancer. Specifically, data show that type 2 diabetes mellitus (T2DM) may be associated with an increased risk of bladder cancer, with a meta-analysis showing 35% increased risk in patients with diabetes versus a healthy population, [2, 3], although this positive association may be limited to patients with longstanding diabetes and/or to insulin users [4, 5]. One study reported increased odds of bladder cancer in patients with T2DM of ≥ 16 years' standing versus non-diabetics [odds ratio 3.6; 95% confidence interval (CI): 1.1, 11.2] [5].

Against this background, the influence of glucose-lowering drugs on cancer risk is of great interest, and several therapies have been under scrutiny because of signals for potential increased cancer risk. Due to the relative infrequency of cancer events, detecting a cancer signal in pre-marketing clinical development programs is very difficult. Therefore, assessment should be based on the totality of evidence, including pre-clinical and clinical data, individual case reports, as well as continued monitoring for any potential signals in post-marketing surveillance and longer-term clinical studies.

Data suggest that long-term use of insulin glargine (>5 years) may increase the risk of breast cancer [6]. However, findings from the ORIGIN trial (Outcome Reduction with Initial Glargine Intervention; ClinicalTrials.gov #NCT00069784) [7], which enrolled 12,537 patients and followed them for a median of 6.2 years, found no increased breast cancer risk with insulin glargine versus standard therapy [8, 9]. Further, a potential link between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and pancreatic carcinoma and thyroid cancer has also been of concern in recent years. However, no clear conclusions have been drawn regarding a causal relationship with pancreatic disease (pancreatic cancer and pancreatitis) [10–13]. With regard to thyroid cancer, clinical data have not shown any association between GLP-1 RAs and thyroid cancer in patients with T2DM [14].

There have also been some concerns about the potential association between the thiazolidinedione pioglitazone [a peroxisome proliferator-activated receptor (PPAR) γ agonist] and bladder cancer [15, 16], which was evaluated in a 10-year epidemiologic study. Although a 5-year interim analysis of this

study showed a statistically significant increased risk of bladder cancer among patients on pioglitazone for ≥ 2 years [17], the 10-year final analysis did not show any statistically significant increases [18]. Reflecting this, the updated American Diabetes Association/European Association for the Study of Diabetes position statement states that earlier concerns about the association of pioglitazone and bladder cancer have been dismissed by evidence provided by recently published clinical studies [19, 20].

More recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a novel class of oral medications for T2DM. Dapagliflozin works by suppressing renal glucose reabsorption and increasing urinary glucose excretion via SGLT2 inhibition, thereby leading to decreases in plasma glucose levels [21]. Dapagliflozin is approved for adults with T2DM in the USA as an adjunct to diet and exercise [22], and in Europe for use as monotherapy or add-on combination therapy [23]. A fixed dose combination of dapagliflozin and metformin is also approved in the USA and Europe as an adjunct to diet and exercise when treatment with both dapagliflozin and metformin is appropriate [24, 25]. Bladder cancer concerns were raised with dapagliflozin due to the observed numerical imbalance between treatment groups in the new drug application submitted to the Food and Drug Administration in 2011; 9 out of 5478 patients on dapagliflozin and 1 out of 3156 patients on control reported bladder cancer in the pooled dapagliflozin studies [26]. Bladder cancer occurrences have not been reported in humans with other SGLT2 inhibitors; while they have been shown to induce tumors (although not urothelial tumors of the kidney pelvis, ureters, or bladder) in rats [27] and male mice [28], the

associated mechanisms are not considered relevant to humans.

This article reviews data on bladder cancer with dapagliflozin to illustrate the methodologic challenges in assessing cancer risk in drug development programs in T2DM. The article further highlights complications in the assessment of bladder cancer in the case of SGLT2 inhibitors due to their glucosuric mechanism of action.

PRE-CLINICAL STUDIES OF DAPAGLIFLOZIN

The potential for SGLT2 inhibition and exposure to dapagliflozin to induce tumors or enhance tumor growth have been examined in pre-clinical studies. This includes studies of cancers in general, as well as bladder cancer in particular.

Pharmacologically, dapagliflozin does not raise any concerns as SGLT2 is not expressed in bladder tissue [29], and the action of dapagliflozin is highly specific to SGLT2, with no off-target effects observed across an in vitro screen of >330 receptors, enzymes, ion channels, and transporters [30]. The presence of glucosuria did not enhance background hyperplastic effects, or lead to or enhance bladder tumors in in vivo or in vitro models. Dapagliflozin induced extensive glucosuria in both rodents and dogs that exceeded human urinary glucose concentrations (166 mM) and did not lead to bladder proliferative or tumor development [30, 31]. Furthermore, there was no evidence of hyperplasia or neoplasia in the kidney or bladder of SGLT2 knockout mice with glucosuria of ~ 2000 mg/dL, compared with its wild-type counterpart with no glucosuria [32].

There was also no evidence of carcinogenic potential for dapagliflozin in toxicology studies. A recent study showed that the exposure of

CD-1 mice and Sprague–Dawley rats to dapagliflozin for up to 2 years at ≥ 100 -fold human clinical exposure did not increase tumor incidence or bladder proliferative/preneoplastic lesions [33]. No proliferative or hyperplastic changes were observed in dogs (a species that has been shown to be highly predictive of human bladder carcinogens [34]) over 1 year at >3000 -fold human clinical exposure of dapagliflozin. In summary, these pre-clinical data suggest that dapagliflozin lacks carcinogenic potential.

CLINICAL DATA FOR DAPAGLIFLOZIN

Methods

Cancer cases were analyzed in a pooled population of >9000 patients taking part in 21 phase 2b/3 dapagliflozin clinical trials ranging from 12 to 208 weeks' duration (five phase 2b studies of 12 weeks' duration, and 16 phase 3 studies of 24–208 weeks' duration) (see Table S1 in the Electronic Supplementary Material). Treatment groups included dapagliflozin (2.5, 5, 10, 20, and 50 mg) versus comparator (placebo with or without background medications or active control including benchmark treatments). Overall, only 59 and 56 patients received 20 and 50 mg doses of dapagliflozin, respectively, for 12 weeks, with the remainder receiving dapagliflozin 2.5, 5 and 10 mg.

Hematuria was measured at baseline and during clinic visits. The frequency of patient visits during the treatment period was different in individual studies, varying from weekly visit in the beginning to every 4th week in short-term studies, and every 12th week in long-term studies. Urine dipstick analyses were

performed at all visits, and samples with positive dipstick underwent microscopic urinalysis.

Events were identified according to the Standardized MedDRA Query of 'malignant or unspecified tumors'.

The analysis reported in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Statistical Analyses

Incidence rate ratio (IRR) and Kaplan–Meier estimates of events were calculated. Due to the small number of bladder cancer cases, analyses of IRR were estimated using the Cox proportional hazard ratio model stratified by study [35].

Clinical Findings

The number of patients in the dapagliflozin group ($n = 5936$) was much higher than in the comparator group ($n = 3403$). Demographic and baseline characteristics were generally consistent between the two groups (Table 1). Most patients were <65 years of age and were overweight or obese; almost 90% of patients in both groups had a body mass index (BMI) ≥ 25 kg/m², while approximately half of all patients had a BMI ≥ 30 kg/m². Mean duration of T2DM was 7.0 and 7.6 years in the dapagliflozin and comparator groups, respectively, and mean baseline glycated hemoglobin (HbA1c) values were 8.21% and 8.14%, respectively. Overall, 43.3% and 46.3% of patients in the dapagliflozin and comparator groups, respectively, had a history of smoking. The pooled analysis included patients from an add-on to pioglitazone study ($n = 420$) and

Table 1 Demographic and baseline characteristics

	Dapagliflozin (<i>n</i> = 5936)	Comparator (<i>n</i> = 3403)
Age, years		
Mean ± SD	56.9 ± 10.44	58.1 ± 10.33
Age categorization, years, <i>n</i> (%)		
<65	4512 (76.0)	2424 (71.2)
≥65 and <75	1217 (20.5)	859 (25.2)
≥75	207 (3.5)	120 (3.5)
Gender, <i>n</i> (%)		
Male	3243 (54.6)	1964 (57.7)
Female	2693 (45.4)	1439 (42.3)
Race, <i>n</i> (%)		
White	4505 (75.9)	2644 (77.7)
Black/African American	208 (3.5)	125 (3.7)
Asian	1050 (17.7)	513 (15.1)
Other	173 (2.9)	121 (3.6)
BMI, kg/m ² , <i>n</i> (%)		
≥25	5214 (87.8)	2998 (88.1)
≥30	3368 (56.7)	1949 (57.3)
Smoking history, <i>n</i> (%)		
Current	998 (16.8)	562 (16.5)
Former	1572 (26.5)	1014 (29.8)
Duration of T2DM, years		
Mean ± SD	6.95 ± 7.49	7.59 ± 7.68
Median (range)	4.50 (0.0, 54.4)	5.20 (0.0, 48.0)
HbA1c, % (mmol/mol)		
Mean ± SD	8.21 ± 1.03 (66 ± 11.3)	8.14 ± 1.02 (65 ± 11.1)
FPG, mg/dL (mmol/L)		
Mean ± SD	167.21 ± 48.78 (9.28 ± 2.71)	165.27 ± 46.48 (9.17 ± 2.58)
Seated systolic blood pressure, mmHg		
Mean ± SD	130.4 ± 15.66	131.1 ± 14.88
Seated diastolic blood pressure, mmHg		
Mean ± SD	78.8 ± 9.10	78.8 ± 8.94

Table 1 continued

	Dapagliflozin (<i>n</i> = 5936)	Comparator (<i>n</i> = 3403)
GFR, mL/min/1.73 m ² , <i>n</i> (%)		
<30	9 (0.2)	6 (0.2)
≥30 to <60	668 (11.3)	387 (11.4)
≥60 to <90	3113 (52.4)	1793 (52.7)
≥90	2146 (36.2)	1216 (35.7)

Includes all treated patients from 21 phase 2b/3 dapagliflozin clinical trials ranging from 12 to 208 weeks' duration (five phase 2b studies of 12 weeks' duration and 16 phase 3 studies with 24–208 weeks' duration)

BMI body mass index, *FPG* fasting plasma glucose, *GFR* glomerular filtration rate, *HbA1c* hemoglobin A1c, *SD* standard deviation, *T2DM* type 2 diabetes mellitus

from four studies with background insulin and/or oral antidiabetic drugs (*n* = 3017).

Malignant or Unspecified Tumors

The overall incidence rate of malignancies was balanced between dapagliflozin and comparator groups; 89/5936 (1.5%) patients treated with dapagliflozin and 51/3403 (1.5%) patients treated with comparator had malignant or unspecified tumors. The IRR for overall malignant and unspecified tumors was 1.035 (95% CI: 0.724, 1.481; *p* = 0.849). The time-to-first-event analyses of malignant and unspecified tumors (Kaplan–Meier estimates) were also similar between patients treated with dapagliflozin and comparator (Table 2).

When different cancer types were analyzed, the incidence rates were numerically lower in the dapagliflozin group versus comparator for some organ categories (e.g., renal, female reproductive), and greater in the dapagliflozin group versus comparator for other organ categories (e.g., bladder, breast) (Fig. 1). There was no obvious pattern to the distribution of various tumor types, with no clear pathophysiologic link between the tumor types favoring dapagliflozin or comparator. The CIs for the incidence rate for all

specific tumor types included unity, indicating that there was no statistically significant difference between treatment groups. The majority of patients with cancer were diagnosed within 1 year of initiating study drug treatment (72% and 63% in the dapagliflozin and comparator groups, respectively).

Bladder Cancer

Nine of 5936 dapagliflozin-treated patients (0.15%) and 1 of 3403 comparator-treated patients (0.03%) reported bladder cancer events (Table 3). This corresponds to an unstratified incidence rate of 135 events per 100,000 patient-years for dapagliflozin-treated patients and 26 events per 100,000 patient-years for comparator-treated patients, with an IRR of 5.168 (95% CI: 0.677, 233.55) (Table 4).

All patients reporting bladder cancer were male, most were ≥60 years old, and had clinical attributes typical of bladder cancer in the general population; the pattern of urothelial cell carcinomas detected during the study period was typical of the general population [36], with approximately 50% being low-grade non-invasive cancer at first diagnosis. Furthermore, 8/10 patients with events of

Table 2 Cumulative proportion of patients with malignant and unspecified tumors (Kaplan–Meier analysis)

Week	Dapagliflozin (<i>n</i> = 5936)			Comparator (<i>n</i> = 3403)		
	<i>n</i>	<i>N</i> #	Proportion, % (95% CI)	<i>n</i>	<i>N</i> #	Proportion, % (95% CI)
<18	24	5347	0.42 (0.25–0.59)	11	3070	0.34 (0.14–0.54)
<26	31	4846	0.57 (0.37–0.77)	15	2771	0.48 (0.24–0.73)
<52	64	3245	1.50 (1.13–1.88)	31	1911	1.25 (0.80–1.70)
<104	85	1552	2.69 (2.06–3.32)	45	774	2.69 (1.81–3.57)
<208	89	156	3.93 (2.27–5.59)	50	135	5.76 (2.97–8.54)
<216	89	3	3.93	51	2	6.46

Including data after rescue

n Number of patients with an event of malignant cancer, *N* number of treated patients, *N*# number of patients at risk at the beginning of the period, *CI* confidence interval

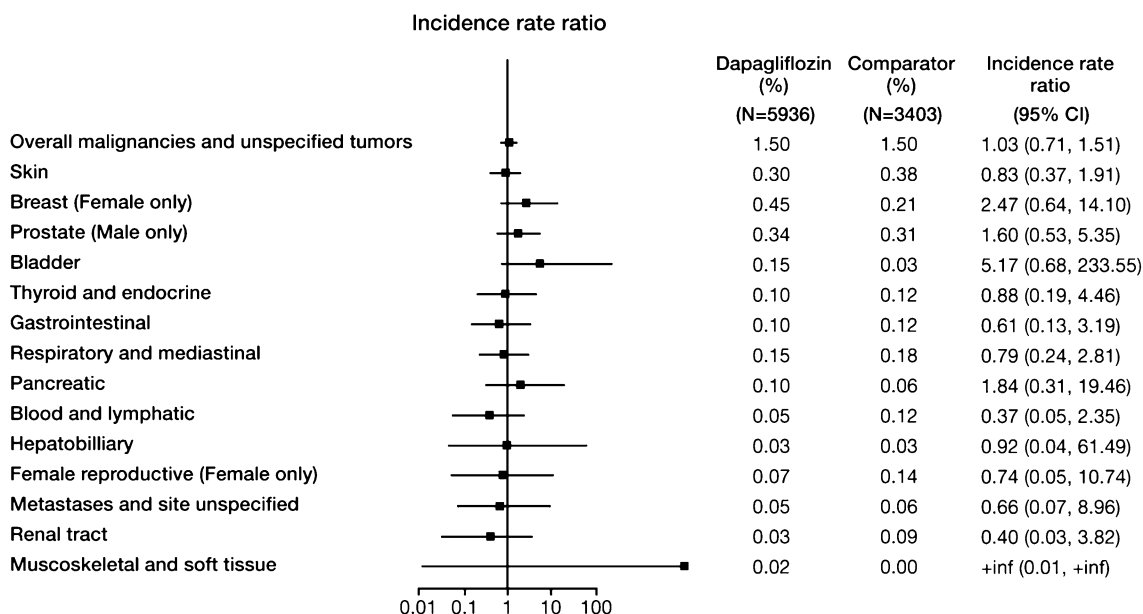


Fig. 1 Incident rate ratio of malignant and unspecified tumors by organ category from the dapagliflozin clinical trials. *N* is the number of treated patients. Only trials with at least one selected event contributed to the analysis. Confidence intervals are based on an exact method.

Includes serious and non-serious adverse events on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment +30 days (or up to follow-up visit whichever was first) or +4 days

bladder cancer were current or former smokers. These findings are consistent with data from previous studies reporting bladder cancer predominance in smokers [37, 38]. It should be noted that history of smoking in patients

who reported bladder cancer was higher than in the overall study population of male dapagliflozin- and comparator-treated patients (58.5% and 61.1%, respectively, were current or former smokers).

Table 3 Summaries of bladder cancer cases

Study/age/ gender/country	T/t group	Study day for bladder cancer diagnosis	Histology ^b	Smoking, other risk factors	Hematuria		Reason for bladder cancer workup	Additional clinical information
					Within 6 months prior to rand.	After rand.		
NCT00972244 [54]/75/male/ Japan	DAPA 2.5 mg	43	Type: class 4 malignant cells TNM classification: T2N0MX Grade: 2	20 cigs/day for 50 years, stopped 2007	Yes	Yes	AE 'occult blood positive' on day 36	Continued positive urine occult blood since day 215; hematuria × 6 in 1.5 months; symptoms of anorexia and weight loss; metastases to the lung at diagnosis
NCT01031680/ 48/male/ United States	DAPA 10 mg + MET + SU	74	Type: urothelial Grade: low	20 cigs/day for 34 years, stopped 2008 Hematuria and renal stones reported in 2008	Yes	No	Hospitalized for coronary artery disease; CT scan showed possibility of lesion in bladder	History of hematuria and renal stones ~2 years prior to randomization

Table 3 continued

Study/age/ gender/country	T/t group	Study day for bladder cancer diagnosis	Histology ^b	Smoking, other risk factors	Hematuria		Reason for bladder cancer workup	Additional clinical information
					Within 6 months prior to rand.	After rand.		
NCT00683878 [55]/67/male/ Argentina	DAPA 5 mg + PIO	144	Type: urothelial cell with areas of squamous differentiation TNM classification: T2 Grade: 3	Family h/o of bladder cancer PIO 45 mg used on day -223 to -16 AE of UTI reported on day 84	Yes	Yes	AE 'hematuria' on day 130 and AE 'urinary bladder polyp' on day 144	Trace blood in urine on day 1; multiple positive urines for blood; UTI on day 84. Gross hematuria on day 130. Urinary urgency and frequency prior to day 144; 80 × 60 mm mass at diagnosis
NCT01031680/ 55/male/ Taiwan	DAPA 10 mg + MET + SU	169	Type: urothelial cell Grade: 1	Current smoker— 5 cigs/day for 36 years	Yes	Yes	Intermittent hematuria for 3 months and persistent hematospermia	Trace blood on day 36 and day 1 Trace + blood in urine in 5 of 8 tests during the study
NCT00673231 [56]/63/male/ Austria	DAPA 5 mg + INS	358 (AE of bladder neoplasm) 393 (SAE of bladder cancer)	Type: G2 TNM classification: pTa Grade: unknown	Current smoker— 40 cigs/day for 50 years	No	Yes	Recurring microscopic hematuria since ~day 165 (according to the investigator)	Microscopic hematuria noted on day 165

Table 3 continued

Study/age/ gender/country	T/t group	Study day for bladder cancer diagnosis	Histology ^b	Smoking, other risk factors	Hematuria		Reason for bladder cancer workup	Additional clinical information
					Within 6 months prior to rand.	After rand.		
NCT00673231 [56]/67/male/ Hungary	DAPA 10 mg + INS	399	Type: urothelial cell Grade: 2	Never smoked	Yes	Yes	AE 'hematuria' on study day 372	Hematuria 1+ on day 13; 3+ on day 1; 7 of 9 urines positive for blood in study months 1–12
NCT00528879 [57]/60/male/ Canada	DAPA 5 mg + MET	512	Type: urothelial cell TNM classification: pT _a , pN0, M0 Grade: low	25 cigs/day for 25 years, stopped 1989	Yes	Yes	AE 'calculus ureteric' on day 509	Hematuria 2+ on day 15, trace hematuria on day 34
NCT00673231 [56]/66/male/ United States	DAPA 10 mg + INS	581	Type: urothelial Grade: low	30 cigs/day for 42 years, stopped 2001	No	Yes	AE 'hematuria' on day 577	Hematuria on days 56, 84, 118 and 377 prior to diagnostic evaluation
NCT00660907 [58]/76/male/ Germany	DAPA 10 mg ^a + MET	727	Type: urothelial with partial squamous cell differentiation TNM classification: pT1, M0 Grade: high (G3)	20 packs, stopped 1980	No	Yes	AE 'benign prostatic hyperplasia' on day 727	Urine blood 3+ on day 726 Eleven prior urines negative for blood

Table 3 continued

Study/age/ gender/country	T/t group	Study day for bladder cancer diagnosis	Histology ^b	Smoking, other risk factors	Hematuria		Reason for bladder cancer workup	Additional clinical information
					Within 6 months prior to rand.	After rand.		
NCT01042977 [59]/66/male/ Canada	Placebo + INS + MET	136	Type: urothelial Grade: high	20 cigs/day for 50 years; cystitis reported as AE on day 32	Yes	Yes	Painless macroscopic hematuria for a few weeks	History of hematuria and positive dipstick results for blood in urine before and at randomization

AE adverse event, *cigs* cigarettes, *DAPA* dapagliflozin, *INS* insulin, *MET* metformin, *PIO* pioglitazone, *SAE* serious adverse event, *SU* sulfonylurea, *TNM* tumor, node, metastasis

^a The dapagliflozin dose for this patient was up-titrated from 2.5 to 5 to 10 mg. At the time of event, the dose was 10 mg

^b Current accepted terminology is urothelial cell carcinoma, although transitional cell carcinoma is still commonly used. These are different names for the same malignancy

Table 4 Adverse events of bladder cancer, including data after rescue

	Dapagliflozin (<i>n</i> = 5936)	Comparator (<i>n</i> = 3403)
Exposure, patient-years	6650	3864
Patients with events, <i>n</i> (%)	9 (0.15)	1 (0.03)
Incident rate per 100 patient-years	0.135	0.026
Incident rate ratio vs comparator (95% CI) ^a	5.168 (0.677, 233.55)	–

^a One additional case of bladder cancer in a patient treated with dapagliflozin 10 mg has been reported since database lock. The subject is a female, <60 years of age and a current smoker (20 cigarettes/day for 40 years). Bladder cancer was diagnosed within 3.5 months of starting treatment with dapagliflozin suggesting that the cancer was pre-existent. The incidence rate ratio in the dapagliflozin total group versus comparator including this additional event is 6.111 (95% CI: 0.827, 272.02)

The hypothesis that symptoms related to increased urinary volume and increased events of urinary tract infections (UTIs) with dapagliflozin treatment led to increased bladder cancer detection bias has not been fully tested. In clinical studies of dapagliflozin, three patients had urinary events prior to bladder cancer diagnosis: one dapagliflozin-treated patient had a UTI on day 84 of the study (bladder cancer was detected on day 144), the second dapagliflozin-treated patient had an adverse event (AE) of benign prostatic hypertrophy on day 727 (the same day as cystoscopy workup for benign prostatic hypertrophy; bladder cancer was detected as an incidental finding), and the third comparator-treated patient had cystitis on day 32 (bladder cancer was detected on day 136).

Eight of the nine bladder cancer patients who received dapagliflozin were treated with background glucose-lowering medications: insulin (*n* = 3), metformin (*n* = 2), metformin and sulfonylurea (*n* = 2), and pioglitazone (*n* = 1). The patient in the comparator group who reported bladder cancer received insulin and metformin background therapy (Table 3).

All ten cases of bladder cancer were reported within 2 years of starting study treatment

(range 43–727 days) (Fig. 2). The bladder cancer events were diagnosed in the dapagliflozin-treated patients in <6 months (*n* = 4), 6 to <12 months (*n* = 1), 12 to <18 months (*n* = 2), and 18 to <24 months (*n* = 2) of starting the study drug, which is a relatively short amount of time when considering the latency period for human bladder carcinogenesis [39, 40].

Hematuria and Bladder Cancer

Hematuria, microscopic or macroscopic, is the most common symptom of bladder cancer. In addition to being a manifestation of bladder cancer, hematuria can also be a sign of carcinoma in situ and may be associated with bladder cancer detected up to 6 years later [41].

Of the nine dapagliflozin-treated patients with bladder cancer, eight had microscopic hematuria prior to start of treatment or within 6 months of initiating study drug treatment (Fig. 3) and one reported hematuria 6 months after initiating study treatment. The patient with bladder cancer in the comparator-treated group had evidence of hematuria prior to start of treatment. It should be noted that in the

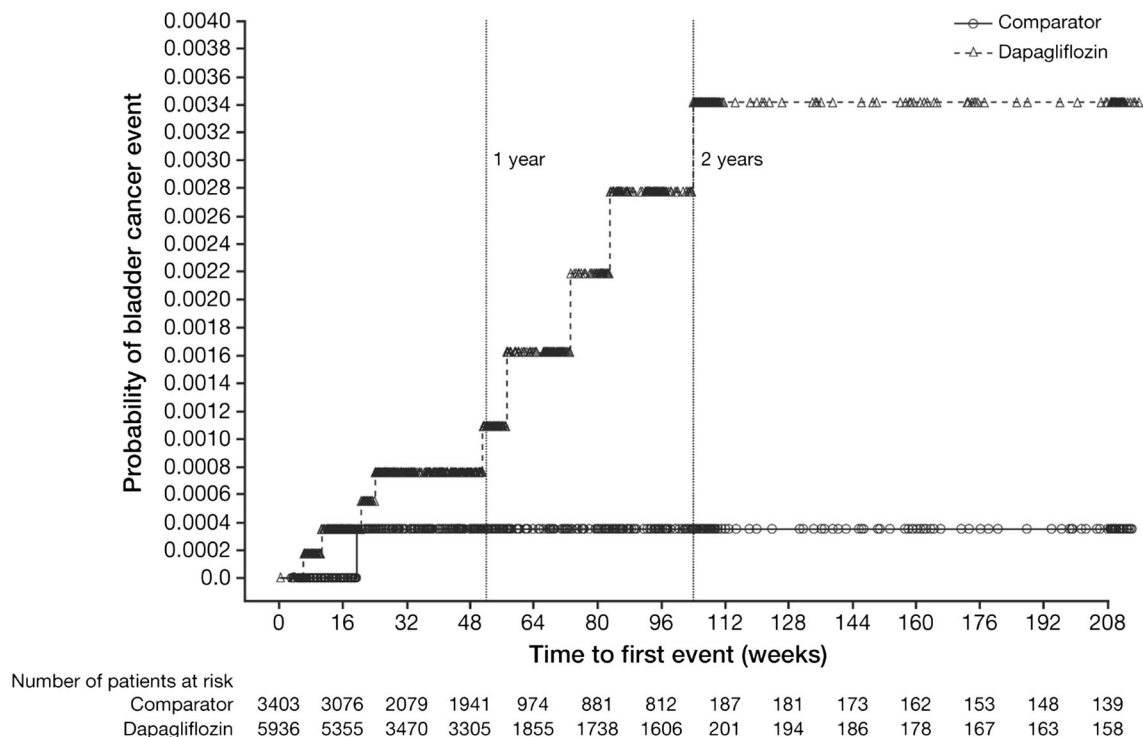
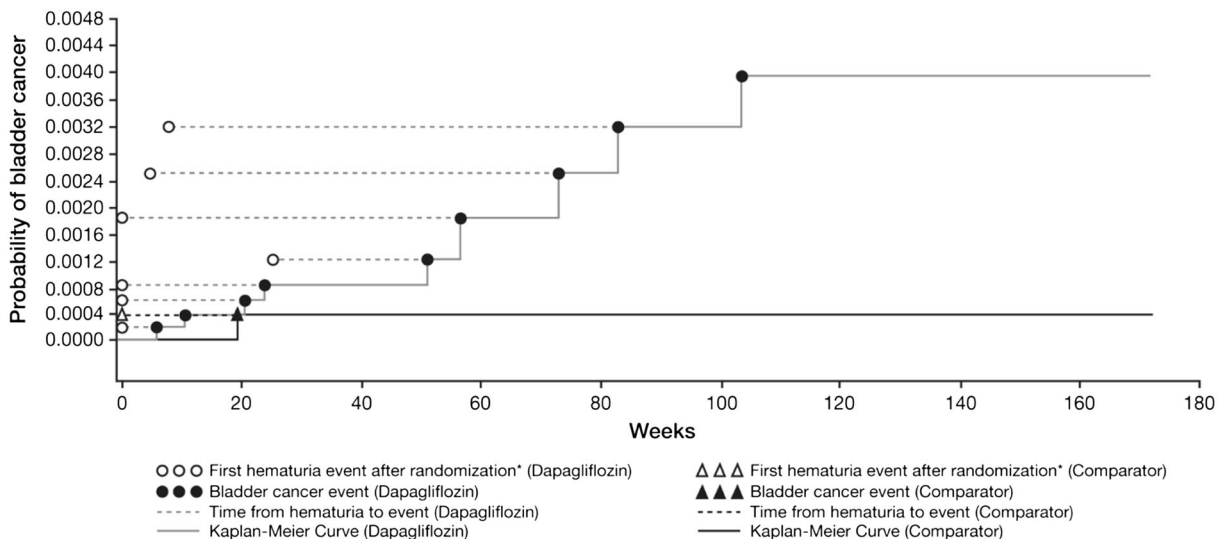


Fig. 2 Kaplan–Meier plot of time to first event of bladder cancer. Includes data after rescue. Week is not scheduled week visit, but actual days from the first dose of

double-blind study medication divided by 7. The number of patients at risk is the number of patients at risk in the beginning of the period



*Presence of hematuria before randomization is not shown in this analysis

Fig. 3 Relationship between first hematuria event after randomization and time to first bladder cancer event

overall pool of >9000 patients, the prevalence of hematuria at baseline was similar in patients receiving dapagliflozin and comparator [8.5% of patients on dapagliflozin (3.7% of men and 14.2% of women) versus 8.1% on comparator (4.2% of men and 13.4% of women)].

DISCUSSION

The assessment of bladder cancer data from the dapagliflozin drug development program illustrates the challenge of characterizing cancer risk in T2DM, particularly individual cancer types where the number of cases is low and statistical conclusion is not possible. Pre-clinical studies indicated that dapagliflozin is not carcinogenic. In addition to rigorously demonstrating that dapagliflozin is not an initiator of tumor development, neither the drug, its primary metabolite, nor drug-induced glucosuria have been found to enhance the growth of human bladder cancer cells *in vitro* or in a mouse xenograft model [30, 33]. Further, exposure to dapagliflozin in the presence of extensive glucosuria did not lead to the conversion of hyperplastic cells to bladder tumors. Therefore, the possibility of tumor cells being more susceptible to the potential growth effects of glucosuria seems unlikely.

These findings are in contrast with studies of known carcinogenic agents such as estrogen, for which several mechanisms are postulated and where there is a clear link to breast cancer in humans [42]. Pre-clinical data have shown an association between pioglitazone exposure and bladder tumors in male rats; tumor formation was considered secondary to the formation of urinary solids with subsequent irritation and hyperplasia [43]. A similar rat-specific mode of action for urinary bladder tumors was demonstrated by the PPAR γ/α agonist,

muraglitazar [44, 45]. Further, as described earlier, other less selective SGLT2 inhibitors have been shown to induce tumors (although not urothelial tumors of the kidney pelvis, ureters, or bladder) in animal studies [27, 28], but the associated mechanisms are considered irrelevant to humans. Such findings therefore bring SGLT2 inhibitors under increased scrutiny for their carcinogenic potential.

This post hoc pooled analysis of dapagliflozin clinical trials showed no obvious pattern in the distribution of various tumors, with no statistically significant differences between treatment groups for any tumor types. The number of bladder cancer cases was small, but numerical imbalances were noted between treatment groups [46]. It should be noted that the characteristics of patients reporting urothelial cell carcinomas during the study period were ≥ 60 years old, male, and most were current or former smokers and typical of the general population. Although it does not explain the greater number of cancer cases in patients treated with dapagliflozin versus comparator, these data highlight that some well-established and potent risk factors of bladder cancer in patients with T2DM were present, which cannot be ignored.

The assessment of incidence rates in a clinical trial versus real-world population has its own challenges. The dapagliflozin trials were not large enough and were not designed to assess the risk of bladder cancer (as noted by the wide 95% CIs), and it is questionable whether data reported in the dapagliflozin trials can be extrapolated to a larger, “real life” population of patients with bladder cancer. Furthermore, the incidence rates for bladder cancer in the general population vary among different countries and between databases—this could potentially be related to an absence of routine screening for bladder cancer detection.

The assessment of bladder cancer with dapagliflozin may also potentially be confounded because of the drug-induced diuresis and symptomatology associated with genitourinary infections. This could have possibly prompted more rigorous investigations in the dapagliflozin treatment groups, leading to detection of pre-existing bladder cancers. However, this hypothesis cannot be confirmed because of the absence of systematic collection of data for medical procedures related to cancer diagnosis in these trials.

Previous studies have shown an association between recurrent UTIs and bladder cancer [47, 48], and therefore one important question was whether the bladder cancer cases with dapagliflozin were related to increased rates of UTIs. However, of the ten patients reporting bladder cancer in the dapagliflozin clinical development program, seven were not preceded by urinary events. Furthermore, other SGLT2 inhibitors, which are associated with very similar patterns of infection, were not associated with bladder cancer imbalances in clinical trials. Hence, these observations do not support a causal relationship between UTIs in dapagliflozin-treated patients and bladder cancer.

Bladder carcinomas usually have a latency period of several years [34]. In one study, cyclophosphamide, a well-described bladder carcinogen, was administered to patients with Wegener's syndrome with a median drug exposure of 2.7 years. The estimated incidence of bladder cancer after the first exposure to cyclophosphamide was 5% at 10 years [49]. In contrast, the time from initiation of dapagliflozin to bladder cancer development was much shorter, making it unlikely that the exposure to dapagliflozin in studies to date would have been long enough to produce a

quantifiable effect on bladder tumor development or growth.

Unlike in daily practice, urinalysis is often conducted in clinical trials, making the detection of hematuria more likely. However, there was an absence of detailed workup of hematuria prior to randomization in the dapagliflozin trials, which is typical of clinical practice [50]. No specific direction was provided and no hematuria workup data were collected proactively until later studies, where local guidance was followed. The management and follow-up of hematuria are often ambiguous due to lack of clarity surrounding definitions, diagnosis, and referral criteria. Studies have suggested that most patients with hematuria are not appropriately referred to urologists for evaluation [51–53]. Failure to exclude bladder cancer prior to randomization increases the likelihood of recruiting patients with pre-existing bladder cancer in clinical trials or may delay the final diagnosis to after the study initiation. In the present analysis, all except one patient had hematuria prior to the start of treatment or within 6 months of initiating the study drug, and it took several additional weeks or months to establish the final diagnosis of bladder cancer. Such findings highlight an unmet need for improved guidance regarding a complete workup of hematuria or any other potential indicators of pre-existing cancers for clinical trials conducted in patients with T2DM. It is important to note that in clinical practice, the use of dapagliflozin should not be precluded in patients presenting with hematuria, and neither is it necessary to routinely screen for hematuria before or during dapagliflozin treatment.

In summary, the totality of evidence to date does not suggest a causal relationship between dapagliflozin and bladder cancer, and the observed effect in clinical trials may be a

chance finding. However, given the observed imbalances, any firm conclusion cannot be made without additional clinical data, and as such accruing bladder cancer events are being carefully investigated in ongoing trials of dapagliflozin.

CONCLUSION

The case of dapagliflozin illustrates the challenges of interpreting bladder cancer events with a drug associated with urinary symptoms and in a disease where the background incidence of bladder cancer is elevated. An important learning from the dapagliflozin experience is the need for improved and comprehensive follow-up of hematuria in clinical trials at baseline and throughout the study period, and in real-world populations.

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Bristol-Myers Squibb. EJ and KJ are employees of AstraZeneca.

Compliance with ethic guidelines. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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