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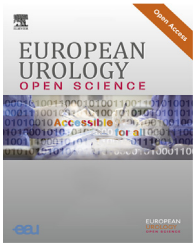

European Association of Urology

Brief Correspondence

Treatment Patterns and Use of Immune Checkpoint Inhibitors Among Patients with Metastatic Bladder Cancer in a Dutch Nationwide Cohort

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Abstract

Since 2017, two immune checkpoint inhibitors (ICIs) have become the standard of care for the treatment of metastatic urothelial carcinoma in Europe: pembrolizumab as second-line therapy and avelumab as maintenance therapy. Our aim was to describe the use of ICIs as first and later lines of treatment in patients with metastatic bladder cancer (mBC) in the Netherlands. We identified all patients diagnosed with primary mBC between 2018 and 2021 in the Netherlands from the Netherlands Cancer Registry (NCR). NCR data were supplemented with data from the Dutch nationwide Prospective Bladder Cancer Infrastructure (ProBCI) collected from medical files, with follow-up until death or end of data collection on January 1, 2023. A total of 1525 patients were diagnosed with primary mBC between 2018 and 2021 in the Netherlands. Of these, 34.7% received at least one line of systemic treatment with chemotherapy or ICI. After first-line platinum-based chemotherapy, 34.1% received second-line ICI and 3.9% received maintenance ICI. Among patients who completed or discontinued first-line cisplatin- or carboplatin-based chemotherapy after approval of maintenance ICI in the Netherlands, 40.7% and 19.7% received second-line ICI, and 9.3% and 14.1% received maintenance ICI, respectively. ICI use for mBC treatment has not increased considerably since their introduction in 2017. Future research should assess whether the introduction of maintenance avelumab (available since April 2021 in the Netherlands) has led to increases in the proportion of patients with mBC patients receiving systemic treatment and the proportion receiving ICI.

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Patient summary: We assessed the rate of immunotherapy use for patients with metastatic bladder cancer in the Netherlands. Since its introduction, immunotherapy has been used in a minority of patients, mostly as second-line treatment after platinum-based chemotherapy.

The European Medicines Agency has issued several approvals for immune checkpoint inhibitors (ICIs) for patients with advanced urothelial cancer since 2017. In November 2017, pembrolizumab was introduced as standard second-line care for patients with advanced urothelial cancer of the bladder and upper urinary tract in the Netherlands following a positive recommendation from the Dutch medical oncology association [1]. In June 2018, pembrolizumab was also approved as a first-line option for patients who are ineligible for cisplatin-based combination chemotherapy (CTx) and whose tumors have sufficient PD-L1 expression [2]. In 2021, avelumab was approved for maintenance treatment (Tx) after first-line palliative platinum-based CTx [3]. Before the availability of ICIs, many patients with metastatic bladder cancer (mBC) remained untreated because of CTx ineligibility, comorbidities, short life expectancy, or patient preference [4]. The aim of this study was to describe the use of ICI in the Netherlands for first- and later-line Tx for patients with mBC.

We identified all patients with primary mBC (metastatic disease at first BC diagnosis) between 2018 and 2021 in the Netherlands from the Prospective Bladder Cancer Infrastructure (ProBCI) [5]. Clinical data were collected for all patients within the framework of the Netherlands Cancer Registry (NCR). Standard NCR data were supplemented with longitudinal information on Tx determinants (eg, performance status, laboratory results, metastatic locations), initial and subsequent Tx, and oncologic follow-up until death or the end of data collection on January 1, 2023, ensuring at least 1 yr of follow-up for all patients. Median follow-up was calculated as the time from diagnosis until the end of data collection. Best supportive care (BSC) was defined as any management that did not include systemic therapy, radical surgery, or radiotherapy to the bladder (total dose $\leq$20 Gy or $\leq$5 fractions was considered as BSC).

A total of 1536 patients with primary mBC were identified. Eleven patients were excluded from further analyses because Tx took place abroad and detailed Tx information was lacking, leaving 1525 patients in the final cohort for analysis. The median age at diagnosis was 74 yr (interquartile range [IQR] 67–81) and 68% were men (Table 1). Lung, liver, bone, and distant lymph-node metastases were present in 33%, 21%, 33%, and 50% of patients, respectively. Patients were followed over time until death or the end of the study. Twenty-one patients were lost to follow-up (7 patients shortly after diagnosis, 2 patients at $\geq$3 mo after diagnosis without receiving systemic Tx, 9 patients after receiving first-line Tx, and 3 patients after receiving later-line systemic Tx). The remaining patients had complete follow-up until death (90.8%) or January 1, 2023 (9.2%). Median follow-up among those still alive at January 1, 2023 was 27 mo (IQR 11–39).

In total, 529 patients (34.7%) received systemic Tx with CTx or ICI (Table 2). Twenty-one patients (1.4%) underwent radical cystectomy, of whom all but three received induction CTx; none received systemic Tx afterwards. Seventeen patients (1.1%) underwent radiotherapy to the bladder (>5 fractions and >20 Gy), of whom two received subsequent carboplatin-based CTx followed by ICI. The remaining 62.8% of patients received BSC only.

Among patients treated with at least one line of systemic Tx, the most common first-line systemic Tx was carboplatin-based CTx (16.7% of all patients; 48.0% of patients who received systemic Tx; Table 2). First-line cisplatin-based CTx was given in 13.9% of patients overall (40.1% of the systemic Tx group) and ICI in 3.6% of patients overall (10.4% of the systemic Tx group).

Of the patients receiving first-line systemic Tx, the cisplatin-based CTx group had the highest proportions of patients aged $\leq$60 yr (32%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 (52%), Charlson comorbidity index of 0 (69%), and an adequate hemoglobin (Hb) level (79%; Table 1). Patients receiving BSC with no tumor-directed Tx were predominantly older (38% aged >80 yr), had metastases in locations other than the lymph nodes (80%), and more often had inadequate Hb (27%) and nonurothelial histology (31%).

After first-line cisplatin-based CTx, 42.5% of patients received a second-line ICI and 2.8% received maintenance ICI. After first-line carboplatin-based CTx, the corresponding percentages were 27.2% and 4.7%. Overall, 34.1% of patients treated with platinum-based CTx received a second-line ICI and 3.9% received maintenance ICI.

Among patients who completed or discontinued first-line cisplatin or carboplatin-based CTx after the introduction date of maintenance ICI, 40.7% and 19.7% received a second-line ICI, and 9.3% and 14.1% received maintenance ICI, respectively (Table 2).

ICI as first-line Tx was applied in 3.2% of all patients diagnosed with primary mBC in 2018, in 3.6% of those diagnosed in 2019, 3.4% of those diagnosed in 2020, and 4.2% of those diagnosed in 2021 (3.6% across all diagnosis years). Among patients treated with first-line platinum-based CTx, ICI was used as second-line or maintenance Tx in 30.9% of patients diagnosed in 2018, 41.5% of those diagnosed in 2019, 39.6% of those diagnosed in 2020, and 39.4% of those diagnosed in 2021 (38.0% across all diagnosis years). Overall, ICIs were used in any setting in 15.5% of patients diagnosed with primary mBC in 2018, and 17.2%, 17.1%, and 17.5% of those diagnosed in 2019, 2020, and 2021, respectively (16.9% across all diagnosis years).

Table 1 – Patient and disease characteristics at the time of diagnosis of primary metastatic bladder cancer in 2018–2021 for the overall cohort and by first-line treatment

Parameter	Patients, *n* (%)					
	Overall cohort	First-line treatment				
		ICI	Chemotherapy		BSC[b]	RC/RT
			Cisplatin[a]	Other CTx		
Patients, *n* (%)	1525 (100)	55 (3.6)	212 (13.9)	262 (17.2)	958 (62.8)	38 (2.5)
Year of diagnosis, *n* (%)						
2018	375 (25)	12 (22)	49 (23)	63 (24)	242 (25)	9 (24)
2019	389 (26)	14 (25)	59 (28)	61 (23)	247 (26)	8 (21)
2020	356 (23)	12 (22)	48 (23)	66 (25)	220 (23)	10 (26)
2021	405 (27)	17 (31)	56 (26)	72 (27)	249 (26)	11 (29)
Age category, *n* (%)						
0–60 yr	209 (14)	12 (22)	67 (32)	37 (14)	83 (9)	10 (26)
61–70 yr	363 (24)	14 (25)	84 (40)	83 (32)	173 (18)	9 (24)
71–80 yr	559 (37)	19 (35)	61 (29)	130 (50)	337 (35)	12 (32)
>80 yr	394 (26)	10 (18)	–	12 (5)	365 (38)	7 (18)
Median age, yr (IQR)	74 (67–81)	72 (62–79)	66 (59–71.5)	71 (65–76)	78 (70–83)	70.5 (59–76)
Sex, *n* (%)						
Male	1035 (68)	36 (65)	151 (71)	187 (71)	638 (67)	23 (61)
Female	490 (32)	19 (35)	61 (29)	75 (29)	320 (33)	15 (39)
CCI, *n* (%)						
0	696 (46)	30 (55)	147 (69)	117 (45)	384 (40)	18 (47)
1	366 (24)	9 (16)	44 (21)	64 (24)	238 (25)	11 (29)
2	251 (16)	9 (16)	14 (7)	45 (17)	179 (19)	4 (11)
≥3	212 (14)	7 (13)	7 (3)	36 (14)	157 (16)	5 (13)
Performance status, *n* (%)						
ECOG 0	365 (24)	25 (45)	111 (52)	112 (43)	103 (11)	14 (37)
ECOG 1	286 (19)	13 (24)	61 (29)	82 (31)	125 (13)	5 (13)
ECOG 2	173 (11)	6 (11)	4 (2)	22 (8)	138 (14)	3 (8)
ECOG 3/4	100 (7)	1 (2)	–	–	99 (10)	–
Unknown	601 (39)	10 (18)	36 (17)	46 (18)	493 (51)	16 (42)
Renal function, *n* (%)						
0–29 ml/min/1.73 m^2	206 (14)	4 (7)	–	16 (6)	184 (19)	2 (5)
30–49 ml/min/1.73 m^2	348 (23)	11 (20)	8 (4)	86 (33)	236 (25)	7 (18)
50–59 ml/min/1.73 m^2	199 (13)	10 (18)	25 (12)	37 (14)	121 (13)	6 (16)
≥60 ml/min/1.73 m^2	692 (45)	25 (45)	168 (79)	112 (43)	366 (38)	21 (55)
Unknown	80 (5)	5 (9)	11 (5)	11 (4)	51 (5)	2 (5)
Hb category, *n* (%)						
<10 g/dl	318 (21)	6 (11)	14 (7)	34 (13)	257 (27)	7 (18)
≥10 g/dl	990 (65)	41 (75)	167 (79)	193 (74)	566 (59)	23 (61)
Unknown	217 (14)	8 (15)	31 (15)	35 (13)	135 (14)	8 (21)
Metastasis location, *n* (%)[c]						
Lung	500 (33)	19 (35)	56 (26)	79 (30)	339 (35)	7 (18)
Liver	325 (21)	8 (15)	32 (15)	48 (18)	234 (24)	3 (8)
Bone	503 (33)	13 (24)	65 (31)	80 (31)	335 (35)	10 (26)
Other visceral organ	292 (19)	9 (16)	31 (15)	43 (16)	205 (21)	4 (11)
Distant LNs	762 (50)	35 (64)	127 (60)	147 (56)	436 (46)	17 (45)
Distant LNs only	388 (25)	21 (38)	78 (37)	80 (31)	193 (20)	16 (42)
Histology, *n* (%)						
UCC	1,167 (77)	54 (98)	189 (89)	228 (87)	664 (69)	32 (84)
Non-UCC	358 (23)	1 (2)	23 (11)	34 (13)	294 (31)	6 (16)

ICI = immune checkpoint inhibitor; CTx = chemotherapy; BSC, best supportive care; RC = radical cystectomy; RT = radiotherapy to the bladder; IQR - interquartile range; CCI = Charlson comorbidity index; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; LN = lymph node; UCC = urothelial carcinoma.

[a] Including patients who started with first-line cisplatin-based CTx who switched to carboplatin-based CTx.

[b] Including RT of ≤5 fractions or ≤20 Gy.

[c] The categories are not mutually exclusive.

We conclude that in the years following ICI availability for mBC in the Netherlands, CTx remained the mainstay in the first-line setting. Neither the proportion of patients treated with systemic Tx nor the proportion of patients who received ICI substantially increased over time in this cohort. In particular, patients with poor prognosis [6,7] (eg, aged >80 yr, ECOG ≥2, Hb ≤10 g/d) and/or with nonurothelial histology appear to be underserved by the current Tx options, in line with findings for a German cohort [8]. Future analyses will show whether more recently introduced maintenance ICIs will lead to more frequent ICI use after first-line CTx. In the current cohort, an increase in the use of maintenance ICI after CTx was observed after the introduction of maintenance avelumab, but this was partly offset by a decrease in second-line ICIs after CTx, resulting in only a small increase in overall ICI use after CTx. This increase was greatest for patients treated with first-line carboplatin.

Approved ICIs are available for all patients in the Netherlands regardless of their insurance plan. Hence, ICI use is

Table 2 – First and later treatments for patients with primary metastatic bladder cancer diagnosed in 2018–2021

First-line and second-line treatments	Patients, *n* (%)	
	Overall cohort (*n* = 1525)	PAA subgroup[a] (*n* = 125)
Best supportive care	958 (62.8)	–
First-line cisplatin-based chemotherapy[b]	212 (13.9)	54
Subsequent treatment		
None	95 (44.8)	23 (42.6)
Maintenance immunotherapy	6 (2.8)	5 (9.3)
Second-line immunotherapy	90 (42.5)	22 (40.7)
Second-line cisplatin-based chemotherapy	4 (1.9)	0 (0)
Second-line carboplatin-based chemotherapy	15 (7.1)	4 (7.4)
Second-line other chemotherapy	2 (0.9)	0 (0)
First-line carboplatin-based chemotherapy	254 (16.7)	71
Subsequent treatment		
None	155 (61.0)	43 (60.6)
Maintenance immunotherapy	12 (4.7)	10 (14.1)
Second-line immunotherapy	69 (27.2)	14 (19.7)
Second-line cisplatin-based chemotherapy	3 (1.2)	0 (0)
Second-line carboplatin-based chemotherapy	13 (5.1)	4 (5.6)
Second-line other chemotherapy	2 (0.8)	0 (0)
First-line other chemotherapy	8 (0.5)	–
Subsequent treatment		
None	7 (87.5)	–
Second-line immunotherapy	1 (12.5)	–
First-line immunotherapy	55 (3.6)	–
Subsequent treatment		
None	44 (80.0)	–
Second-line immunotherapy	4 (7.3)	–
Second-line cisplatin-based chemotherapy	1 (1.8)	–
Second-line carboplatin-based chemotherapy	5 (9.1)	–
Second-line other chemotherapy	1 (1.8)	–
Radical cystectomy	21 (1.4)	–
Radiotherapy to the bladder	17 (1.1)	–

PAA = post-avelumab approval.
[a] The PAA subgroup comprises only the patients who received first-line chemotherapy which was discontinued after the introduction of maintenance avelumab in the Netherlands.
[b] Including patients who started with cisplatin-based chemotherapy but switched to carboplatin.

predominantly based on the perceived tolerability and effects of the Tx as discussed during the decision-making process between the clinician and the patient. However, there is a short window of opportunity for mBC Tx, with median survival of 2.5 mo for untreated patients [4] and median post-CTx survival of 3 mo for patients not starting subsequent therapy.

Uptake of immunotherapy in first-line, second-line, and maintenance settings differs markedly from the uptake observed in the USA, where ICIs account for 39–49% of first-line Tx options [9,10] (vs 10% in the Netherlands) and more than a quarter of patients treated with first-line platinum-based CTx receive maintenance ICI [10] (vs 9–14% in the Netherlands). However, with ICIs mostly playing a role after CTx in Europe, the large proportion of cases not receiving CTx in the first-line setting precludes many patients from reaching subsequent lines of therapy. The high proportion of patients not receiving systemic Tx is comparable to results reported for other cohorts not based on insurance data. In comparison to results from insurance databases, the proportion of untreated patients is higher in the Netherlands, as untreated patients are likely to be under-represented in those databases [11]. Both US and German cohort studies and international interventional studies with crossover options show that only a minority (approx. 30–40%) of patients treated with first-line CTx are able to receive second-line therapy [8,11–13].

No other studies on ICI uptake in nationwide population-based cohorts in European countries have been published so far. A strength of our study is the availability of detailed data on Tx determinants and first-line and later-line Tx approaches for a contemporary, nationwide, prospective cohort of patients with primary mBC. This allowed a comprehensive characterization of Tx patterns and assessment of changes over time, without any selection (eg, according to insurance status, referral patterns, or initial Tx). A limitation is the lack of data for patients with metachronous (secondary) mBC. Inclusion of the latter population would require longitudinal data collection for all BC patients, which is not available yet, but such follow-up was initiated for BC patients diagnosed from 2020 onwards in ProBCI. Hence, future analyses of these data will be able to assess whether Tx patterns are similar for patients with metachronous mBC. While the ICI indication for metastatic urothelial carcinoma also includes urothelial tumors of the upper urinary tract, these were not included in the current study because they are not covered by the ProBCI data collection. PD-L1 expression was not reported here because this was not routinely determined in the standard care setting over the period described in this paper.

Future updates of these analyses will reveal the impact of maintenance ICI availability on the rate of ICI use for management of mBC in the Netherlands.

Author contributions: Anke Richters had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Richters, Aben.
Acquisition of data: Richters, Aben.
Analysis and interpretation of data: Richters, Robbrecht, Meijer, Van der Heijden, Kiemeney, Van den Bosch, Suelmann, Özdemir, Mehra, Aben.
Drafting of the manuscript: Richters.
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Ethics statement: This study was approved by the privacy review board of the Netherlands Cancer Registry (reference K22.317) and the ProBCI Steering Group. No written informed consent from patients was required.

Data sharing statement: All data from the Netherlands Cancer Registry and the Prospective Bladder Cancer Infrastructure are available from the authors on request (www.iknl.nl/en/ncr/apply-for-data).

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