Insights into second-line systemic treatment selection in patients with metastatic urothelial carcinoma: results of a retrospective observational study in Germany

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CONCLUSIONS

- This real-world study using data from two German statutory health insurance claims databases (N=4,290) found that a significant portion of treated patients with metastatic urothelial carcinoma (mUC; n=1,779) did not receive second-line (2L) systemic anti-cancer treatment (60.7%)
  - Of those who received 2L treatment (39.3%), patients were typically younger and healthier, having slightly lower Charlson Comorbidity Index (CCI) scores and with fewer non-UC primary malignancies compared with those who did not receive 2L treatment
- The number of patients with incident mUC who later received 2L treatment increased over time (index year 2015, 78 [11.2%]; 2020, 132 [18.9%]; 4.4% and 7.4% of all treated patients with mUC, respectively)
  - However, treatment rates may be underestimated due to unaccounted therapies administered as part of clinical trials
- High attrition across lines of treatment was observed, consistent with previous studies
- Further research is needed to clarify barriers to accessing 2L treatment in this patient population to ensure that more patients can benefit from advancements in mUC
- Guidance is needed to determine how the expanding range of 2L therapies can be optimally deployed as part of a treatment sequencing strategy, stratified by the class of first-line (1L) therapies received

PLAIN LANGUAGE SUMMARY

- In this study, researchers looked at medical records of people receiving treatment for advanced urothelial cancer in Germany
- Of 4,290 people diagnosed with advanced urothelial cancer, only 1,779 (41.5%) received drug treatment
- 699 (39.3%) people received a different drug treatment when their first treatment stopped working (called second-line treatment)
  - People who received second-line treatment were likely to be younger and healthier
- In people who received any treatment, the use of second-line treatment increased over the study period, from 4.4% in 2015 to 7.4% in 2020
  - The most common types of second-line treatment were immunotherapies followed by chemotherapies
- More studies are needed to investigate the reasons why eligible people with advanced urothelial cancer sometimes do not receive drug treatment so that more people can benefit from available treatments

BACKGROUND

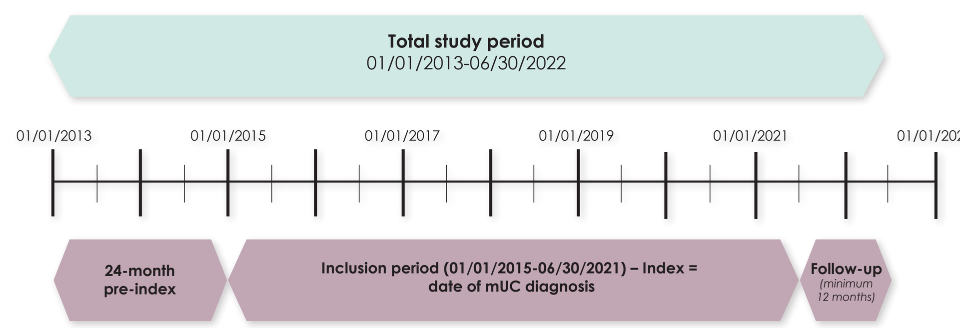
- The treatment landscape in mUC is rapidly evolving, with novel therapeutic advances being incorporated into guidelines and clinical practice[1-3]
- Limited real-world data are available regarding the proportion of eligible patients who receive 2L treatment following progression on 1L systemic therapy for mUC
  - Previous estimates of 2L treatment rates in mUC vary widely, with a median of 43% (range, 8%-87%)[4]
  - Factors influencing selection of 2L agents are also not well understood
- Understanding real-world treatment patterns and patient outcomes is crucial for improving care and developing treatment guidelines for mUC[5]
- The objective of this retrospective, observational cohort study was to determine the prevalence and predictors of receipt of 2L treatment among patients with mUC in Germany and to identify potential gaps in the mUC care pathway

METHODS

Data source and study design

- This was a retrospective, non interventional cohort analysis of data from January 1, 2013, to June 30, 2022 (9.5 years), using 2 German anonymized claims databases (**Figure 1**)[6]:
  - **AOK PLUS:** covers approximately 3.5 million insured individuals in the German federal states of Saxony and Thuringia, representing approximately 4%-5% of the overall statutory insured population in Germany
  - **GWQ ServicePlus AG:** covers approximately 5 million insured persons from several regions throughout Germany
- Adults with incident mUC were identified using ICD-10 codes C65-68 and C77-79, from January 1, 2015, to June 30, 2021
- Patients were followed up for ≥12 months post incident mUC diagnosis (index) until the end of the study period (June 30, 2022) or until censorship (death or end of continuous insurance)

Figure 1. Study schematic



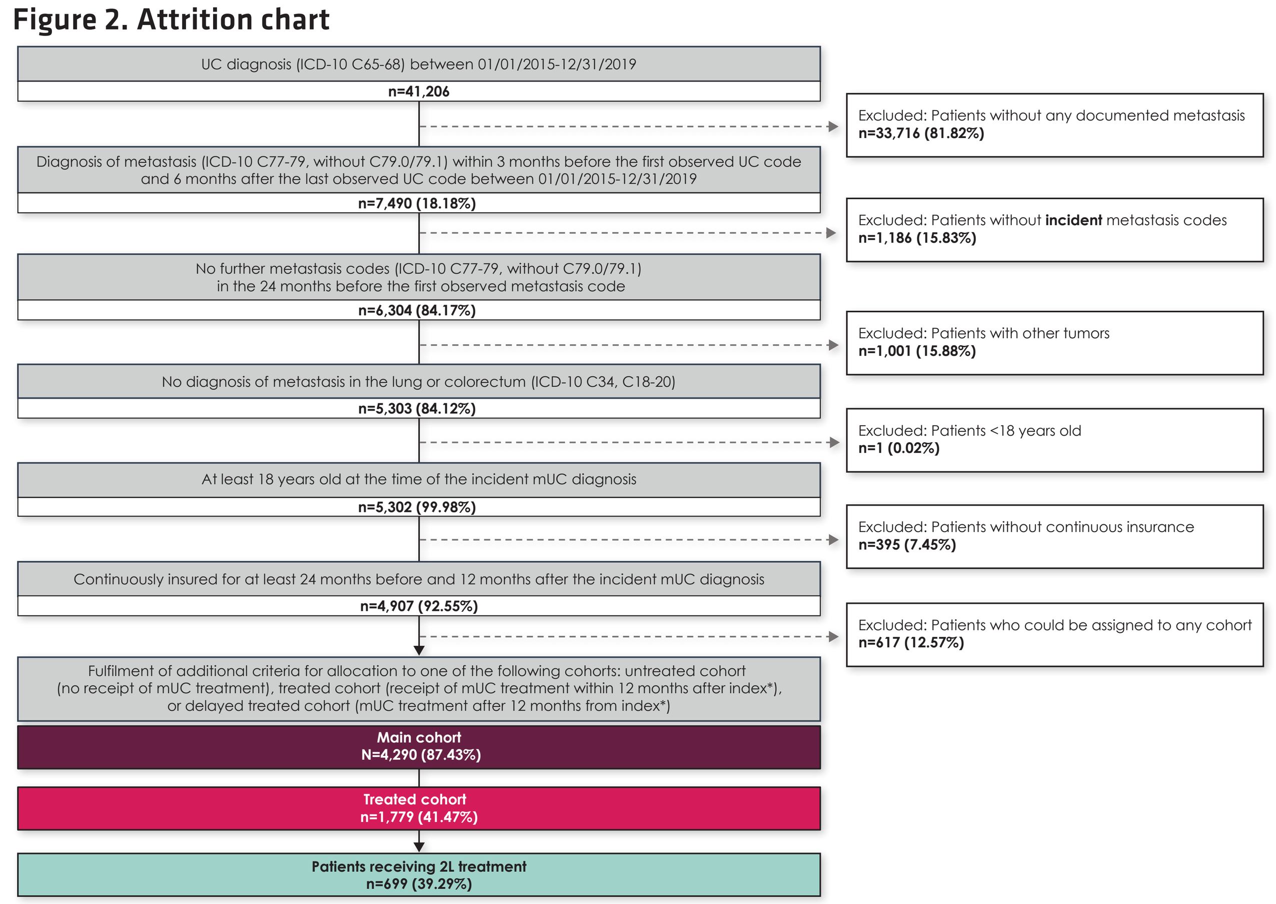
Statistical analysis

- Baseline characteristics were identified 24 months before the index and were analyzed using descriptive statistics
- Treatment regimens in 2L were categorized as either platinum-based chemotherapy (PB-CT), immune checkpoint inhibitors (ICIs), or other non–PB-CT using identification codes (**Supplementary Table 1**)
- A 30-day treatment window (90-day window for PB-CT regimens) was used to identify combination therapies, considering all agents prescribed within this period as part of the combination
- 2L regimens were defined as either a switch to another systemic agent following 1L treatment or a therapy initiated after discontinuation of 1L treatment, indicated by a treatment gap of ≥60 days
- Multivariable logistic regression was used to analyze factors associated with receiving 2L treatment

RESULTS

- Of 4,290 patients with mUC identified,1,779 (41.5%) received 1L systemic anticancer treatment (**Figure 2**)
  - Of these, 699/1,779 patients (39.3%) received 2L treatment (16.3% of all patients with mUC)
- Among treated patients, the mean age at index was 69.1 years, 74.2% were male, mean CCI score was 5.6, and mean follow-up was 19.6 months (**Table 1**)
- Patients who received 2L treatment had a mean age at index of 67.6 years, 75.3% were male, mean CCI score was 5.3, and mean follow-up was 22.8 months (**Table 1**)
- The number of patients with incident mUC who later received 2L treatment increased over time (index year 2015, 78/699 [11.2%]; 2020, 132/699 [18.9%]). This represents 4.4% (78/1,799) and 7.4% (132/1,799) of all treated patients with mUC or 1.8% (78/4,290) and 3.1% (132/4,290) of all patients with mUC, respectively
- The most common 2L treatments were ICIs (66.1%), followed by non–PB-CT (17.3%) and PB-CT (16.6%) (**Table 2**)
- Younger patients and those without other primary malignancies at baseline were more likely to receive 2L treatment (**Table 3**)

Figure 2. Attrition chart



ICD, International Classification of Diseases; **mUC**, metastatic urothelial carcinoma; **UC**, urothelial carcinoma.
*Index = date of mUC diagnosis.

Table 1. Baseline characteristics of patients who received 1L and 2L therapy

	1L treatment (n=1,779)	2L treatment (n=699)
Age at index, mean (SD) [range], year	69.14 (10.28) [23-93]	67.62 (10.05) [35-90]
Sex, n (%)		
Female	459 (25.80)	173 (24.75)
Male	1,320 (74.20)	526 (75.25)
Index year of first mUC diagnosis, n (%) [% of all treated patients]		
2015	211 (11.86)	78 (11.16) [4.38]
2016	259 (14.56)	84 (12.02) [4.72]
2017	272 (15.29)	112 (16.02) [6.30]
2018	230 (12.93)	99 (14.16) [5.56]
2019	312 (17.54)	130 (18.60) [7.31]
2020	335 (18.83)	132 (18.88) [7.42]
2021 (until June 30)	160 (8.99)	64 (9.16) [3.60]
Year of 2L treatment initiation, n (%) [% of all treated patients]		
2015	-	16 (2.29) [0.90]
2016	-	54 (7.73) [3.04]
2017	-	100 (14.31) [5.62]
2018	-	113 (16.17) [6.35]
2019	-	98 (14.02) [5.51]
2020	-	140 (20.03) [7.87]
2021	-	148 (21.17) [8.32]
2022 (until June 30)		30 (4.29) [1.69]
mUC index diagnosis setting, n (%) [% of all treated patients]		
Inpatient metastasis diagnosis	1,334 (74.99)	518 (74.11) [29.12]
Outpatient metastasis diagnosis	445 (25.01)	181 (25.89) [10.17]
Charlson Comorbidity Index, mean (SD)*	5.62 (3.56)	5.26 (3.39)
Elixhauser Comorbidity Index, mean (SD)*	13.92 (10.63)	13.06 (10.27)
Most common UC-related procedures/interventions, n (%) [% of all treated patients]*		
Transurethral resection of the bladder (OPS 5-573.4)	1,220 (68.58)	487 (69.67) [27.37]
Continuous irrigation of bladder (OPS 8-132.3)	993 (55.82)	401 (57.37) [22.54]
Cystoscopy (OPS 5-576)	629 (35.36)	261 (37.34) [14.67]
Ureter splint (OPS 8-137)	421 (23.66)	167 (23.89) [9.39]
Transfusions (EBM 02100, EBM 01211, OPS 8-80)	262 (14.73)	95 (13.59) [5.34]
Follow-up duration, mean (SD), months	19.6 (18.40)	22.8 (16.20)

1L, first line; **2L**, second line; **BL**, baseline; **EBM**, Einheitlicher Bewertungsmaßstab (uniform assessment standard); **mUC**, metastatic urothelial carcinoma; **OPS**, Operationen und Prozeduren Schlüssel (operation and procedures key).
*Baseline period = 24 months before index.

Table 2. Patients who received 2L treatment by treatment group and regimen

2L treatment regimens	All 2L patients (n=699)	AOK PLUS (n=319)	GWQ (n=380)
Group 1: PB-CT, n (%)			
Gemcitabine + cisplatin or carboplatin	27 (3.86)	7 (2.19)	20 (5.26)
Paclitaxel + carboplatin	3 (0.43)	0	3 (0.79)
Paclitaxel + carboplatin + gemcitabine	0	0	0
Gemcitabine + oxaliplatin	3 (0.43)	3 (0.94)	0
Cisplatin or carboplatin (mono)	7 (1.00)	2 (0.63)	5 (1.32)
Oxaliplatin (mono)	7 (1.00)	4 (1.25)	3 (0.79)
MVAC	5 (0.72)	1 (0.31)	4 (1.05)
OPS 8-543 (MVAC or gemcitabine + cisplatin)	64 (9.16)	37 (11.60)	27 (7.11)
Total	**116 (16.60)**	**54 (16.93)**	**62 (16.32)**
Group 2: ICI, n (%)			
Atezolizumab	52 (7.44)	29 (9.09)	23 (6.05)
Pembrolizumab	250 (35.77)	109 (34.17)	141 (37.11)
Nivolumab	115 (16.45)	46 (14.42)	69 (18.16)
Avelumab*	45 (6.44)	22 (6.90)	23 (6.05)
Total	**462 (66.09)**	**206 (64.58)**	**256 (67.37)**
Group 3: other non–PB-CT			
Gemcitabine	12 (1.72)	8 (2.51)	4 (1.05)
Vinflunine	56 (8.01)	25 (7.84)	31 (8.16)
Paclitaxel	6 (0.86)	3 (0.94)	3 (0.79)
Docetaxel	3 (0.43)	2 (0.63)	1 (0.26)
Gemcitabine + paclitaxel	2 (0.29)	1 (0.31)	1 (0.26)
Gemcitabine + vinflunine	1 (0.14)	0	1 (0.26)
OPS 8-542 (gemcitabine/paclitaxel or gemcitabine + paclitaxel)	41 (5.87)	20 (6.27)	21 (5.53)
Total	**121 (17.31)**	**59 (18.50)**	**62 (16.32)**

1L, first line; **2L**, second line; **MVAC**, methotrexate, vinblastine, doxorubicin, cisplatin; **OPS**, Operationen und Prozeduren Schlüssel (operation and procedures key).
*Avelumab was approved as a 1L maintenance treatment by the European Medicines Agency as of January 21, 2021.[7] The risk of misclassification of the 1L maintenance and 2L treatment is possible as response rates to PB-CT are not available in the databases.

Table 3. Predictive factors associated with receipt of 2L treatment: multivariate model results

Variable	Odds ratio (95% CI)	p value
Age at index (continuous)	0.98 (0.97-0.99)	<0.001
Diagnosis of non-UC primary malignant carcinomas (24-month BL, binary)	0.81 (0.66-1.00)	0.028
Year of 1L treatment initiation (reference year, 2015; categorical)	1.04 (0.99-1.10)	0.153
CCI (24-month BL; continuous)	0.98 (0.95-1.01)	0.188
Female (binary)	0.87 (0.70-1.10)	0.203
Outpatient diagnosis setting (binary)	1.13 (0.92-1.37)	0.258
UC-related treatment, surgeries, and interventions (24-month BL; binary)	1.14 (0.90-1.45)	0.318

Multivariable logistic regression using 2L treatment receipt as dependent variable.
1L, first line; **2L**, second line; **BL**, baseline; **UC**, urothelial carcinoma.

LIMITATIONS

- The administrative claims data used in this study were intended for billing purposes, potentially causing measurement errors due to coding inaccuracies influenced by reimbursement needs rather than research priorities
- Both the AOK PLUS and GWQ datasets include information from routine medical practice but lack essential clinical data, such as vital signs and laboratory test results; therefore, the datasets may not capture all relevant aspects of a patient's medical history, leading to an incomplete patient profile
- The study inclusion period was limited to January 1, 2015, to June 30, 2021. Since that period, the approval of novel therapeutics for mUC may have increased 2L treatment rates
- Due to database regulations in Germany and data accessibility constraints, the AOK PLUS and GWQ patient cohorts were analyzed independently. The results were then combined using meta-analysis methods and presented in aggregate form

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Supplementary data can be accessed through this QR code

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DISCLOSURES G. Niegisch has participated in talks and symposia for Astellas, AstraZeneca, Bristol Myers Squibb, MEDAC, Pfizer, and Roche; has participated in advisory boards for Bristol Myers Squibb, Ipsen, Janssen, Merck, Pfizer, Roche, and Sanofi; and has received travel and congress registrations from Merck, Pfizer, and Roche. **M. Kearney** is an employee of Merck and holds stock and other ownership interests in Novartis, Merck, and UCB. **J. Krieger** was an employee of Cytel at the time of study and has served in a consulting or advisory roles for Merck. **U. Osowski** is an employee of Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA, and holds stock and other ownership interests in Merck. **B. Deiters** is an employee of GWQ ServicePlus AG. **U. Maywald** was an employee of AOK PLUS at the time the study was conducted. **T. Wilke** is an employee of IPAM, which received financial support from Cytel to conduct the claims data analyses. **M.-O. Grimm** has served in consulting or advisory roles for Astellas Pharma, AstraZeneca, Bayer/Vital, Bristol Myers Squibb, Eisai, EUSA Pharma, Gilead, Ipsen, Merck, MSD, Novartis, Pfizer, Roche Pharma AG, and Takeda; has received travel, accommodations, and expenses from Bristol Myers Squibb and Merck; has received honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, EUSA Pharma, Ipsen, MSD, and Pfizer; and has received research funding from Bristol Myers Squibb and Intuitive Surgical. **ACKNOWLEDGMENTS** This study was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between Merck and Pfizer. Editorial support was provided by Nucleus Global and was funded by Merck.

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Supplementary Table 1. Identification of 2L treatment regimens by group

Treatment regimens	Outpatient care (ATC codes)	Inpatient care (OPS codes)
Group 1: PB-CT		
Gemcitabine + cisplatin	L01BC05 + L01XA01	8-543*
Gemcitabine + carboplatin	L01BC05 + L01XA02	None
Gemcitabine + carboplatin + paclitaxel	L01BC05 + L01XA02 + L01CD01	None
Gemcitabine + oxaliplatin	L01BC05 +L01XA03	None
MVAC	L01BA01 + L01CA01 + L01DB01 + L01XA01	8-543*
Methotrexate + cisplatin	L01BA01+L01XA01	None
Paclitaxel + carboplatin	L01CD01+L01XA02	None
Group 2: ICI		
Atezolizumab	L01XC32, L01FF05	6-00a.1
Pembrolizumab	L01XC18, L01FF02	6-009.3
Nivolumab	L01XC17, L01FF01	6-008.m
Avelumab	L01XC31, L01FF04	6-00a.2
Group 3: other non-PB-CT		
Gemcitabine	L01BC05	6-001.1, 8-542†
Paclitaxel + gemcitabine	L01CD01 + L01BC05	6-001.f + 6-001.1; 8-542†
Paclitaxel	L01CD01	6-001.f; 8-542†
Docetaxel	L01CD02	6-002.h
Vinflunine	L01CA05	6-005.b
Gemcitabine + vinflunine	L01BC05 + L01CA05	6-001.1 + 6-005.b
Pemetrexed	L01BA04	6-001.c

ATC, Anatomical Therapeutical Chemical classification system; **ICI**, immune checkpoint inhibitor; **MVAC**, methotrexate, vinblastine, doxorubicin, cisplatin; **OPS**, Operationen und Prozeduren Schlüssel (operation and procedures key); **PB-CT**, platinum-based chemotherapy.
*8-543: moderately complex and intensive block chemotherapy. †8-542: non-complex chemotherapy.