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ORIGINAL ARTICLE

Implementation and outcome of personalized treatment strategies in advanced genitourinary cancers

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Background: Outcome is dismal in patients with advanced genitourinary (GU) cancers refractory to standard treatments. Molecular analyses and subsequent discussion of cases in specialized molecular tumor boards (MTBs) are increasingly incorporated into clinical management to facilitate personalized treatment. Data on this approach are lacking for GU malignancies.

Methods: We conducted a retrospective analysis of patients with GU cancers discussed in the MTB at the Charité between 2016 and 2023. Ethics approval was obtained for prospective follow-up of patients after written informed consent and for retrospective data analysis. Clinical benefit was defined as complete response (CR), partial response (PR) or stable disease (SD) >6 months or a progression-free survival (PFS) ratio between molecularly matched therapy (MMT) and previous non-MMT >1.3. Outcome was assessed by the investigators.

Results: Among 126 identified MTB patients, most patients had a rare tumor type ($n = 59$), followed by adenocarcinoma of the prostate ($n = 45$), urothelial carcinoma ($n = 17$) and clear-cell renal carcinoma ($n = 5$). Molecular profiling included immunohistochemistry ($n = 80$), panel sequencing ($n = 110$) and/or whole-exome/-transcriptome sequencing ($n = 21$). Eleven patients died before the final MTB discussion. At least one treatment option for MMT was identified for 78/115 patients (68%). Twenty-five patients were treated with an MMT (22%), three of whom subsequently received a second MMT. Eighteen MMTs were given in an off-label setting and two within clinical trials. A clinical benefit was observed in 8/28 (28.6%) applied MMTs. A PFS-ratio >1.3 was achieved in eight patients. Among patients with rare entities discussed ($n = 54$), 42 patients had at least one MMT option (78%), with 19 patients receiving at least one MMT (35%).

Conclusion: For a majority of GU cancer patients an MMT was identified and responses were seen in heavily pretreated patients. Additional controlled trials and integration of comprehensive molecular analyses and subsequent personalized therapy should be considered for patients with GU cancers, especially those with rare histologies.

Key words: molecular tumor board, targeted therapy, precision oncology, genitourinary cancer, real-world data

BACKGROUND/INTRODUCTION

The identification of molecular alterations in cancers and subsequent targeted treatment is expected to improve outcome for a subset of patients. This concept of personalized tumor treatment requires a multistep process. Currently, approved personalized treatment options are limited for patients with genitourinary (GU) malignancies.

Molecularly matched treatment in GU malignancies

Available molecularly matched therapies (MMTs) in GU cancers comprise different therapeutic mechanisms. Efficacy of poly (ADP-ribose) polymerase (PARP)-inhibitors has been demonstrated in the treatment of metastatic prostate cancer with *BRCA1/2* mutations.[1-3] Fibroblast growth factor receptor (FGFR) inhibitors are recommended in urothelial carcinoma with *FGFR* alterations.[4] Additional data exist for the use of belzutifan in renal-cell carcinoma in particular

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with von Hippel–Lindau (*VHL*) disease.[5] In recent years, a number of tumor agnostic approvals have been granted. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved larotrectinib and entrectinib for the treatment of *NTRK* fusion-positive tumors and selpercatinib for *RET* fusion-positive tumors. Data and FDA approvals exist for additional predictive biomarkers such as high tumor mutational burden (TMB), mismatch-repair deficiency/high microsatellite instability (dMMR/MSI-h), *HER2* positivity and *BRAF* p.V600E.[6]

Comprehensive molecular analyses in GU malignancies

There is a rationale to integrate comprehensive molecular profiling for patients with advanced solid tumors. ESMO already recommends next generation sequencing (NGS) explicitly for several tumor types, including advanced cancer of the lung, prostate, bowel, biliary tract, ovary, breast, thyroid and cancer with unknown primary and gastrointestinal stromal tumors. Additionally, NGS is recommended for patients where access to a matched treatment is available.[7] GU cancers apart from prostate cancer lack similar consensus despite the presence of actionable alterations.[7,8] Thus, there is need for more evidence on molecular alterations and clinical impact in these tumor types.

Molecular tumor board and personalized treatment

Due to the complexity of results from comprehensive molecular profiling, molecular tumor boards (MTBs) have been established to facilitate the translation of molecular findings into personalized treatment. This concept of precision oncology aims at identifying and initiating molecularly matched treatment of cancer patients. An improved survival has been demonstrated with the integration of molecular profiling and personalized treatment in other cancer types including non-small-cell lung cancer or sarcoma.[9-11] In contrast, data are limited for GU malignancies, and GU cancers were underrepresented in the recent pan-tumor ROME trial, that demonstrated an improved response rate and progression-free survival (PFS) with molecularly matched treatment.[12] The multistep process of molecular testing, MTB discussion and personalized treatment initiation is limited by geographic and socioeconomic disparities, which also limits data availability from resource-constrained settings where advanced GU malignancies are prevalent.[13]

Rationale for this study

Because of this lack of data on personalized treatment in GU malignancies, this study aims to assess the impact of molecular tumor analyses and personalized treatment initiation in a real-world cohort and evaluate signals of activity of MTB-guided therapies in this specific patient population.

MATERIAL AND METHODS

Patient identification

We searched the MTB database for patients with GU cancers discussed in the institutional MTB of Charité Comprehensive Cancer Center between January 2016 and December 2023. Retrospective analysis of the patient cohort was approved by local ethics committee (EA4/070/24). Due to their frequency, urothelial carcinomas with squamous cell differentiation were analyzed as common tumors together with prostate adenocarcinomas, urothelial carcinomas and clear-cell renal-cell carcinomas.[14] The remaining tumors including rare histologies of common tumor sites like rare variants of urothelial carcinoma and prostate cancer were classified as rare tumors.

Molecular diagnostics

Gene panel sequencing as well as immunohistochemistry was carried out by molecular pathology following routine workflows. The MH IVD 600+ gene panel (Agilent Technologies, Santa Clara, CA, designed by Molecular Health) enables the detection of mutations [i.e. single nucleotide variants (SNVs), small indels] in 617 genes. Sequencing was carried out on a NextSeq 550 instrument (Illumina, San Diego, CA) with a mean coverage $>300\times$ and a minimum of $100\times$ coverage for 96% of target bases. Variant allele frequency threshold was set to 5%. The Oncomine Focus RNA assay (Thermo Fisher Scientific, Waltham, MA) interrogated known gene fusions in 23 genes.

Whole-transcriptome and whole-exome sequencing was carried out within the German Cancer Consortium MASTER (Molecularly Aided Stratification for Tumor Eradication) program as previously described.[15] Molecular analyses were carried out by external academic or commercial laboratories for a subset of patients and discussed in the MTB if complete sequencing information were available.

Molecular tumor board

Patients with advanced cancer were referred to the Charité precision oncology clinic to evaluate molecular tumor analyses and MTB presentation by primary caregivers (i.e. uro-oncologists) after exhaustion of standard therapies. Early referral to the precision oncology clinic was offered for patients with rare tumor types or uncommon presentation of common tumor types (i.e. young patient age). Molecular testing, clinical interpretation of molecular findings and MTB presentation were organized by the precision oncology team. Patients with available sequencing data were directly referred to the MTB if additional clinical interpretation of molecular findings was deemed necessary by the attending physician. The MTB convened weekly with participation by hematology/oncology, molecular pathology, pathology, genetics, molecular biology, bioinformatics and attendance by additional disciplines such as uro-oncology, as required. Clinical interpretation of molecular alterations was carried out using prespecified evidence levels according to National Center for Tumor Diseases (NCT)/Centers for Personalized Medicine (ZPM), as previously reported.[16] MTB consensus was required to recommend personalized treatment. In the event of divergent opinions, these were listed as alternative treatment options, highlighting the missing consensus.

Table 1. Clinicopathological characteristics of the cohort and information on extended testing

	n	Age (years, median)	Male *(n)*	Prior systemic therapies (median)	Adv./met. disease[a] *(n)*	Panel-seq *(n)*	WES ± RNA-seq *(n)*	IHC[b] *(n)*
All patients	126	61.5	103	2[c]	119[c]	110	21	80
Entities								
Prostate cancer								
Adenocarcinoma (ADC)	45	70	45	3[c]	42[c]	44	1	23
Neuroendocrine carcinoma (NEC)/mixed adenoneuroendocrine carcinoma (MANEC)[d]	6	64	6	2	6	5	1	4
Basal cell adenocarcinoma[d]	1	57	1	2	1	1	1	1
Bladder and upper urinary tract								
Urothelial carcinoma (UC)	17	62	11	2	17	16	2	13
Sarcomatoid UC[d]	3	61	2	2	3	3	0	3
Plasmacytoid UC[d]	1	57	0	2	1	1	0	1
Squamous cell carcinoma (SCC)[d]	1	41	0	1	1	0	1	1
Adenocarcinoma[d]	2	66.5	1	3.5	2	2	0	2
NEC, mixed UC and NEC[d]	3	53	1	2	3	3	0	1
Urachal carcinoma[d]	6	47	4	1	5	4	2	4
Noninvasive papillary UC (low grade)[d]	1	28	1	0	0	1	0	0
Renal-cell carcinoma								
Clear-cell	5	43	2	5	5	4	1	2
Papillary[d]	9	62	8	1	9	9	0	6
Medullary[d]	1	24	1	0	1	1	0	1
Ductus bellini[d]	1	55	1	2	1	1	0	1
Germ cell tumor/testicular stromal tumors								
Mixed germ cell tumor[d]	6	32.5	6	4	6	3	6	2
Non-seminoma[d]	2	34.5	2	2.5	2	2	0	2
Growing teratoma syndrome[d]	1	33	1	2	1	0	1	1
Malignant Sertoli cell tumor[d]	1	59	1	0	0	0	1	1
High-grade serous carcinoma[d]	1	55	1	5	1	1	0	1
Penile cancer[d]	5	46	5	1	5	3	2	4
Urethral cancer								
Adenocarcinoma[d]	2	63	0	1.5	1	2	0	2
Mixed UC and SCC[d]	1	59	1	2	1	1	0	1
SCC[d]	2	62.5	2	2	2	1	1	1
Other[d,e]	3	40	0	2	3	2	1	2

IHC, immunohistochemistry; Panel-seq., panel sequencing; RNA-seq, whole-transcriptome sequencing; WES, whole-exome sequencing.
[a]Advanced or metastatic disease with indication for systemic therapy.
[b]*EGFR*, Estrogen receptor, HER2 (*ERBB2*), INI1 (*SMARCB1*), Mismatch repair, *PDL1 (CD274)* and/or *MET*.
[c]Missing data for three patients.
[d]Rare tumors.
[e]Primary renal neuroendocrine tumor (NET) $n = 2$, SCC at the transition bladder/colon interposition $n = 1$.

Follow-up

Follow-up of patients was carried out until December 2023. Prospective follow-up was carried out for patients after written informed consent was given within the MTB registrational study (NCT05926284, ethics committee approval EA1/021/16). Additional retrospective information was collected for patients outside of the registrational study (ethics committee approval EA4/070/24) using discharge letters, medical notes, radiological findings, entries in the electronic medical records and tumor conference protocols. Response was assessed by the investigators. A clinical benefit was defined as complete response (CR), partial response (PR) or stable disease (SD) >6 months. Progression-free survival (PFS) and the ratio of PFS with MMT and prior non-MMT was calculated. A PFS rate >1.3 was considered beneficial following previous publications.[17,18]

Statistical analysis and visualization

IBM SPSS Statistics version 30 (SPSS, Chicago, IL) was used for descriptive analysis, calculation of the PFS-ratio and Kaplan—Meier analysis. Molecular alterations and therapy recommendations were visualized using OncoPrint using JupyterLab 3.4.4 (Project Jupyter, Berkeley, CA) with a modified version of the PyOncoPrint library (script available on request).[19] Readability of the legend was improved using Inkscape 3.1.2 (Inkscape Project, Boston, MA).

RESULTS

Cohort and workflow

We identified 126 patients with GU cancers and molecular tumor profiles from the period of January 2016 to December 2023 in our MTB database. Median age was 61.5 years (range 24-85 years) and the majority of patients ($n = 103$) were male. The most common primary tumor sites were the prostate, followed by the bladder and the upper urinary tract.

Patients were pretreated with a median of two lines of systemic therapy before MTB discussion. In four patients, there was no indication for systemic therapy at the time of the MTB discussion. In these cases, analyses were carried out due to rare disease and a high risk of disease recurrence. Eleven patients died before a final MTB discussion took place.

Clinicopathological characteristics of the cohort at the time of MTB discussion and information on extended testing are summarized in Table 1.

Molecular alterations and recommendations for MMT

Different molecular analyses were carried out in the 126 patients. NGS-based panels were carried out in 110 patients. The most frequently used NGS panel was the MH IVD 600+ gene test in 69 patients. Whole-exome sequencing ± whole-transcriptome sequencing was carried out in 21 patients with additional panel sequencing in 5 of these patients. A summary of utilized gene panels is provided in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105497.

A final MTB discussion was carried out for 115 patients. No pathogenic or likely pathogenic alterations were identified in 10 cases.

Following interdisciplinary discussion, a recommendation for MMT was made for 78 patients.

The median number of treatment recommendations was one. Recommendations included off-label treatment for 64 patients and in-label treatment for 8 patients. Clinical trial screening was recommended for 28 patients and a compassionate use/expanded access program for 3 patients. A summarizing CONSORT diagram is depicted in Figure 1. Molecular alterations leading to recommendations for MMT are summarized in Figure 2. Biomarkers used for recommendation comprised several layers including gene mutations, fusions, copy number variations, messenger RNA (mRNA) expressions, immunohistochemical tests, homologous recombination deficiency score, TMB, dMMR/MSI-h, mutational signatures (AC3 and AC13) either alone or in combination. Immune checkpoint inhibition was the most frequent treatment recommendation followed by PARP and mTOR inhibition (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105497). Combination therapies were recommended in individual cases.

Efficacy of MMT

MMT was initiated in 25 patients. Twenty MMTs were given as off-label treatment ($n = 18$) or within clinical trials ($n = 2$). The most used MMT regimen was an immune checkpoint inhibition (pembrolizumab $n = 7$, nivolumab $n = 3$, nivolumab ± ipilimumab $n = 2$), followed by HER2 inhibition (trastuzumab deruxtecan $n = 1$, trastuzumab $n = 1$, trastuzumab + tucatinib $n = 1$), PARP inhibition (olaparib $n = 3$) and mTOR inhibition (temsirolimus $n = 2$, everolimus $n = 1$).

Best response included CR achieved in one patient and PR in seven patients for a clinical benefit of 32%. SD and mixed response (MR) were achieved in one patient each.

Median PFS was 3 months with MMT. A Kaplan–Meier curve showing PFS is provided in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105497.

Median time to first radiological staging was 2 months. The PFS-ratio comparing PFS with MMT to the immediate prior non-MMT was >1.3 in eight patients.

Detailed data on treatment type, response and underlying evidence levels are provided in Table 2.

In three patients, therapy had to be discontinued because of toxicity. One patient with urothelial carcinoma with squamous cell differentiation and complete remission with pembrolizumab developed an immune-associated nephritis

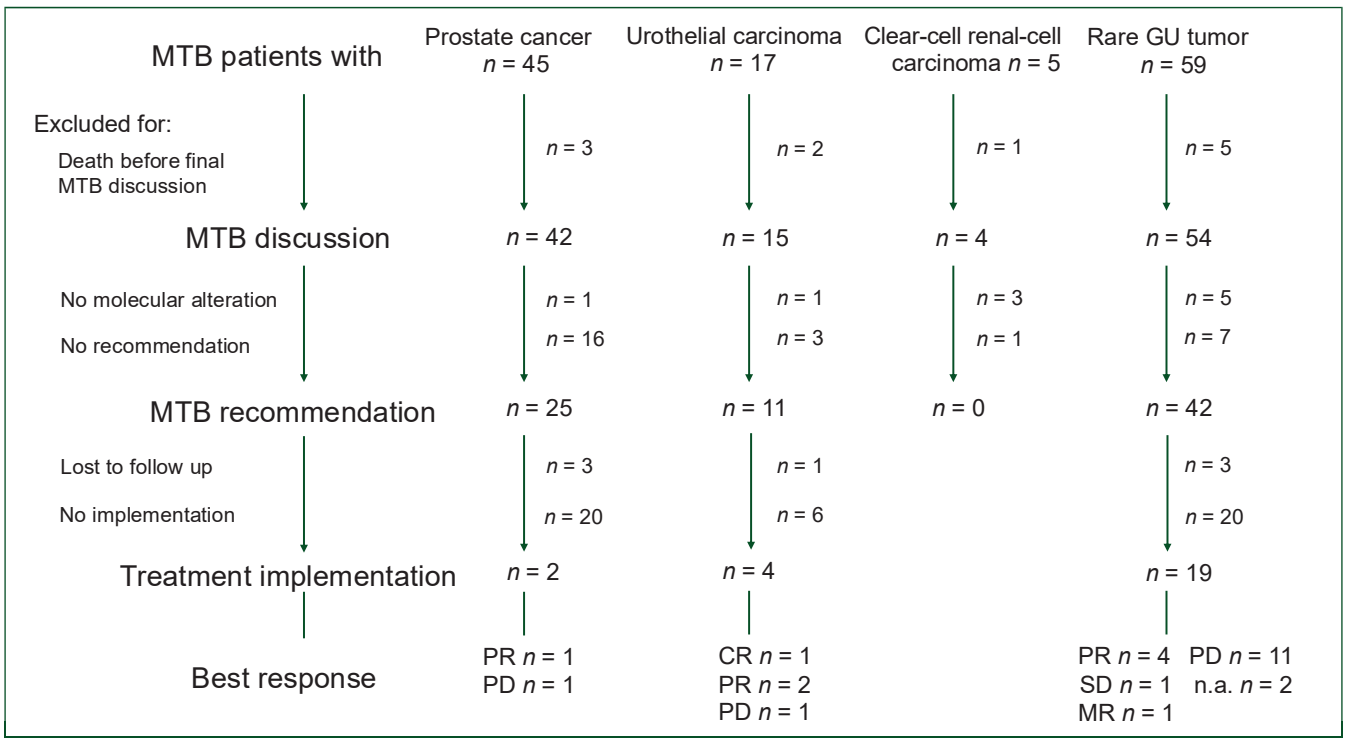

Figure 1. CONSORT diagram of the patient cohort.
CR, complete response; GU, genitourinary; MR, mixed response; MTB, molecular tumor board; n.a., not available; PD, progressive disease; PR, partial response; SD, stable disease.

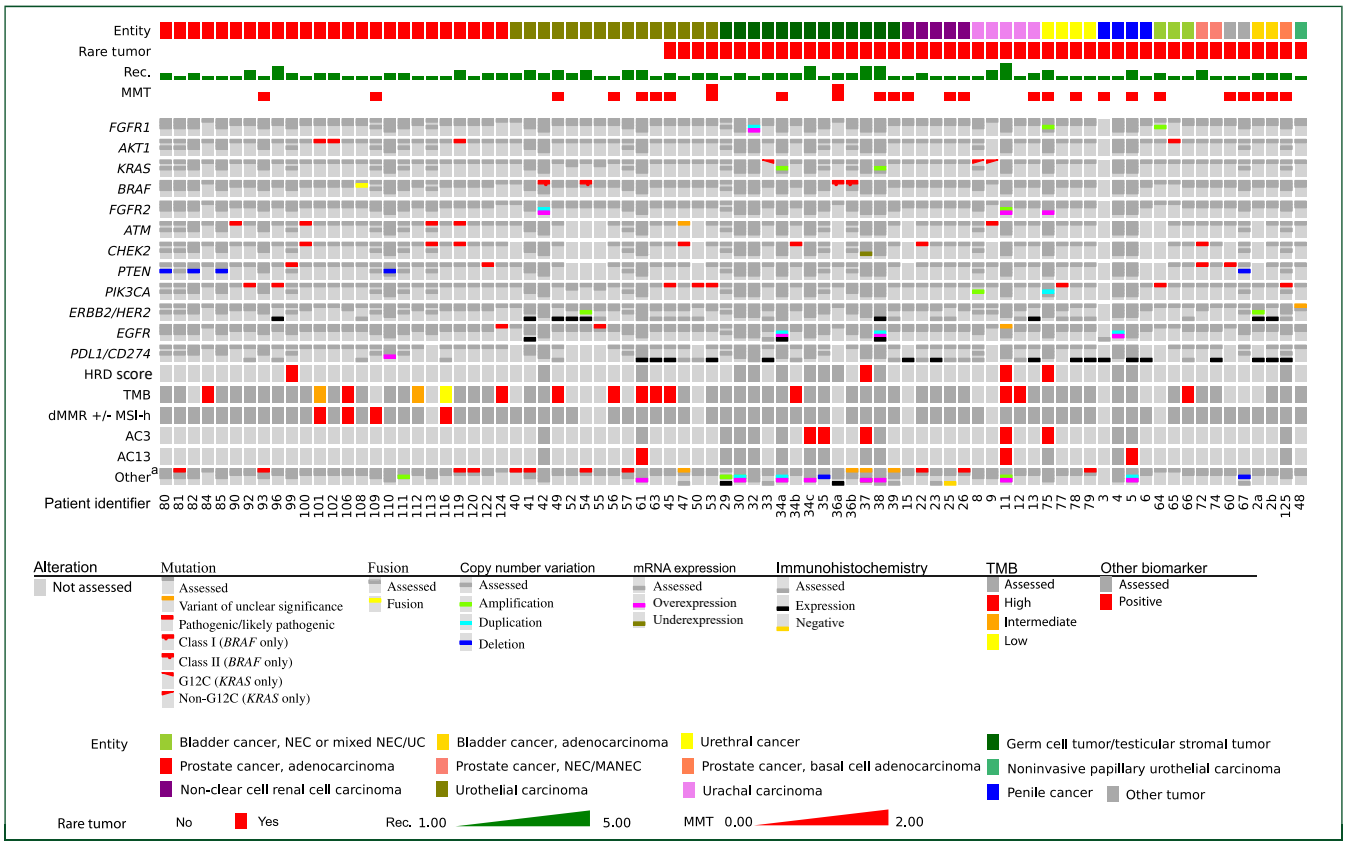

Figure 2. Molecular characteristics. Molecular alterations leading to matched treatment recommendations were summarized in this figure together with tumor entity, number of recommendations (rec.) and implementation of MMT. Rebiopsy and resequencing after prior systemic therapy with MTB discussion was carried out in three patients (i.e. 2a, 2b; 34a, 34b, 34c; 36a, 36b).
AC3/AC13, mutational signatures; dMMR, mismatch-repair deficiency; HRD, homologous recombination deficiency score; MANEC, mixed adenoneuroendocrine carcinoma; MMT, molecularly matched therapy; mRNA, messenger RNA; MSI-h, high microsatellite instability; MTB, molecular tumor board; NEC, neuroendocrine carcinoma; TMB, tumor mutational burden; UC, urothelial carcinoma.
[a]*BARD1, BRCA1, BRCA2, CCND2, CDK4, CDKN2A, CLDN6,* ESR1, *ERBB3, FANCD2, FGFR3, HGF, HRAS, LAG3, MAGEA1/3, MET, MYC, NRG1/2/3, PBRM1, PDGFRA, PRAME, RAD54L, RAF1, RET, SMARCA4, SMARCB1/INI1, SMO, SOX10, SSTR1/2/3/4/5, TACSTD2, TNFRSF18, TSC1, VHL.*

after 8 months. After the end of therapy, the remission lasted for a further 13 months. One patient with a relapse of an embryonal cell carcinoma developed a cough with olaparib. Pancytopenia and intestinal perforation with peritonitis occurred in one patient taking temsirolimus.

Resequencing and sequential use of MMT

Three out of twenty-five patients were discussed several times after resequencing of new tumor material obtained during progression under a previous MTB-recommended MMT with initial response (PR or MR). One of the three patients was sequenced a total of three times, with the second sequencing taking place before any MMT was applied. The other two were sequenced twice in total. Details can be found in Table 3. Treatment options were found for all three patients, one of which was implemented. Best response was progression with a PFS-ratio >1.3 (Table 2, patient 2b).

DISCUSSION

We conducted an analysis of patients with advanced GU cancers discussed in an institutional MTB to assess the impact of a precision oncology workflow for these patients.

Nearly half of the MTB patients showed a rare entity leading to a relative underrepresentation of common GU cancers such as prostate cancer or urothelial carcinoma. Several active standard treatment options exist for patients with common GU cancers, which is also reflected in the high number of prior therapies in the prostate and clear-cell renal-cell carcinoma patients in our cohort. Furthermore, patients with well-known molecular alterations and available standard treatment in these entities will not regularly be presented to the MTB in our clinical routine. Thus, our cohort reflects a poor prognosis subgroup.

In this cohort, 11 patients died before a final MTB recommendation could be made (9%). ∼3%-21% of patients in previously published studies passed away before molecular analysis was finished and personalized treatments could be initiated.[20,21] Thus, an earlier integration of molecular profiling should be considered.

Overall, at least one option for MMT was identified for most cases ($n = 78$, 68%), comprising >37 different treatment types and combination therapies. Clinical trial options were identified for 28 patients. These are comparably high numbers, given the fact that most patients were heavily pretreated and/or without standard treatment options. Similar recommendation

Table 2. Patients receiving molecular tumor board (MTB)-recommended molecularly matched therapy (MMT). Three patients (i.e. 2, 36, 53) subsequently received two MMTs. MMTs were based on the same sequencing results for two patients (i.e. 36, 53) and on separate analyses for one patient (i.e. 2a, 2b)

Pt	Entity	Predictive biomarker	MMT	Evl	Best response	PFS in months	PFS-ratio
93	Prostate cancer	BRCA2 p.N1747fs*1	Olaparib	M1a	PR[a]	6.4[a]	1.1[a]
109	Prostate cancer	MSI high	Pembrolizumab	M1a	PD	4.2	1.2[a]
49	UC of the urinary bladder	HER2 score 3	Trastuzumab + tucatinib	M2a	PR	4.3[b]	1.8
56	UC of the urinary bladder	23 mut/Mb	Nivolumab ± ipilimumab[c]	M2a	PR	8.8	1.5
61	UC of the urinary bladder (with mainly squamous cell differentiation)	PDL1 TC 0%, IC 2%, CPS 2, 149 SNVs, AC13 mutational signature	Pembrolizumab ± chemo[d]	M1c	PD/death	2.3	—
63	UC of the urinary bladder (with mainly squamous cell differentiation)	41 mut/Mb, PDL1 TC 0%, IC 5%, CPS 5	Pembrolizumab	M1c	CR	21	4.3
45	UC of the urinary bladder (with partly sarcomatoid differentiation)	20 mut/Mb, PDL1 TC 80% IC 2% CPS 82	Pembrolizumab	M1c	PD	3.7	1.5
53	Sarcomatoid UC	PDL1 TC 60%-70%, IC 0%	Pembrolizumab ± chemo[d]	M1c	PR	6.2	4.2
53	Sarcomatoid UC	PIK3CA p.Q546E	Alpelisib	M2a	PD/death	1.4	0.9
34a	Mixed germ cell tumor	EGFR dup, exp (IHC, mRNA)	Cetuximab ± cisplatin	[e]	MR	3	1.1
36a	High-grade serous carcinoma testicular/paratesticular	BRAF p.V600E	Dabrafenib + trametinib	M2a	PR	5.8	1.8
36a	High-grade serous carcinoma testicular/paratesticular	ER exp (IHC)	Trabectedin + letrozole	M2a	PD	0.9	0.3
38	Mixed germ cell tumor	EGFR dup, exp (IHC, mRNA)	Cetuximab + irinotecan	[e]	PD	1.1	0.9
39	Embryonal cell carcinoma	FANCD2 p.T914I	Olaparib	M3	—[f]	—	—
15	Papillary renal-cell carcinoma	PDL1 TC 10% IC 20% CPS 30	Nivolumab	[e]	PD	1.4	0.3
25	Renal medullary carcinoma	INI1 negative (IHC)	Bortezomib ± chemo[g]	M3	PR	4.6	—
26	Papillary renal-cell carcinoma	VHL p.V137fs	Cabozantinib	[e]	PD	1.7	0.7
13	Urachal carcinoma	HER2 score 3	FOLFOX + trastuzumab	M2a	PD	5.4	—
75	Urethral cancer (SCC)	HRD score, AC3 mutational signature	Olaparib + trabectedin	M2a	PD	1.9	0.5
78	Urethral cancer (SCC and UC)	PDL1 TC <1% IC 25% CPS 25	Pembrolizumab	M1a	PD[b]	2.3	0.4
3	Penile cancer	PDL1 TC 5%-10% IC 30%	Nivolumab	M1b	PD	2.6	—
5	Penile cancer	PDL1 TC 0% IC 5% CPS 5, AC13 mutational signature	Nivolumab	M1b	PD	3.2	2.3
64	NEC of the urinary bladder	PIK3CA p.E545K	Temsirolimus	[e]	—[f]	—	—
60	SCC at the transition bladder/colon interposition	PTEN p.Q171*	Temsirolimus	[e]	PD	2.5	—
67	Renal NET	PBRM1del, VHLdel, PTENdel	Everolimus	[e]	SD	3.2	0.8
2a	ADC of the urinary bladder	HER2 score 3, HER2 amp	Trastuzumab deruxtecan	M2a	PR	7.9	1.4
2b	ADC of the urinary bladder	PDL1 TC 10% IC n.a. CPS 10	Nivolumab ± ipilimumab	M2a	PD	2.7	1.8
125	Basal cell—ADC of the prostate	PDL1 TC 5% IC 5% CPS 10	Pembrolizumab	M2a	PD	2	0.4

ADC, adenocarcinoma; Amp, amplification; CPS, combined positive score; Del, deletion; Dup, duplication; Evl, evidence level according to NCT/ZPM; Exp, expression; HRD, homologous recombination deficiency score; IC, immune cells; MR, mixed response; MSI, microsatellite instability; Mut/Mb, mutations per megabase; N.a., not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pt, patient; SD, stable disease; SNV, single nucleotide variant; TC, tumor cells.
[a]PSA-based evaluation.
[b]Clinical progression.
[c]Previously PD on nivolumab.
[d]Carboplatin/paclitaxel.
[e]Conflicting data.
[f]No staging, early discontinuation.
[g]Alternating cisplatin/doxorubicin or carboplatin/paclitaxel/gemcitabine.

rates between 47%-78% were previously reported in GU cancer cohorts, although patient characteristics differed between these analyzed cohorts.[20-22]

A total of 28 MMTs were applied in 25 patients (32% of patients with an identified treatment option). This implementation rate is similar to what has been previously reported for MTBs.[16,23,24] However, the results compare favorably with previous retrospective analyses showing treatment implementations between 6%-20% in GU malignancies.[21,22] In particular, we found high implementation rates among patients with rare tumors, most likely due to the lack of approved therapies and number and quality of identified predictive biomarkers.

In an analysis of the impact of MTB discussion in advanced prostate cancer, a treatment initiation rate of 62% has been reported. This high rate is explained by the integration of clinical trials and PARP-inhibitors making up the majority of therapy implementations.[25] Also, in the GU cohort of the PERMED-01 trial with an implementation rate comparable with our study (12/38) the proportion of PARP-inhibitors used in prostate cancer was comparatively high at 33%.[20] These differences again highlight the differences in patient selection, local reimbursement practices, drug approvals and clinical trial availability, limiting the feasibility of a precision oncology approach.

In this cohort, 8/25 patients (32%) achieved an objective response with molecularly stratified treatment regimens. Very different overall response rates with MTB-recommended therapies are known from previous analyses, ranging from 0%-67%, whereby these were particularly high in lung cancer patients.[16,23,26,27] Previous comparable analyses in GU cancer patients did not report objective responses to personalized treatment approaches.[21,22]

Table 3. Resequencing of new tumor tissue after prior molecularly matched therapy (MMT)

Pt	Entity	Prior predictive biomarker	Prior MMT (therapy line)	Prior MMT	Sequencing method	Predictive biomarker	Recommendations	Implementation
2b	ADC of the urinary bladder	HER2 score 3, HER2 amp	Trastuzumab deruxtecan (3)	Trastuzumab deruxtecan	Panel-seq, IHC	HER2 score 3, PDL1 TC 10% IC n.a. CPS 10	ICI, HER2i + chemo	Nivolumab ± ipilimumab
34c	Mixed germ cell tumor	EGFR dup, exp (IHC, mRNA)	Cetuximab + cisplatin (8)	Cetuximab + cisplatin	WES + RNA-seq	AC3 mutational signature, mRNA exp of MAGEA1, MAGEA3, PRAME, CLDN6	PARPi, MAGEAi, PRAMEi, CLDN6i	No
36b	High-grade serous carcinoma testicular/ paratesticular	BRAF p.V600E	Dabrafenib + trametinib (6)	Dabrafenib + trametinib	Panel-seq	BRAF p.V600E, SOX10 VUS	IAPi ± MEKi	No

ADC, adenocarcinoma; Amp, amplification; CPS, combined positive score; Dup, duplication; Exp, expression; IC, immune cells; ICI, immune checkpoint inhibition; IHC, immunohistochemistry; Panel-seq, panel sequencing; Pt, patient; RNA-seq, whole-transcriptome sequencing; TC, tumor cells; VUS, variant of unclear significance; WES, whole-exome sequencing.

In the reported cohort, several promising predictive biomarkers were identified: *HER2* overexpression was identified in two patients; one with adenocarcinoma of the bladder and one with urachal carcinoma. One PR to trastuzumab deruxtecan was observed in the adenocarcinoma of the bladder, whereas progressive disease was seen with FOLFOX/trastuzumab in the patient with urachal carcinoma. These findings highlight the importance of *HER2* testing especially in rare histologies of bladder carcinoma, in line with previous reports.[28] This is also potentially therapeutically relevant in light of the DESTINY-PanTumor02 phase 2 trial data.[29]

A *BRAF* p.V600E mutation was identified in a male patient with a high-grade serous carcinoma of the testicle/paratesticular tissue. This patient achieved PR with dabrafenib and trametinib. *BRAF* mutations were previously described in such histological rarities, thus supporting the diagnosis.[30] The clinical benefit observed in this patient also highlights the therapeutic importance of this finding.

A relevant subset of patients received immune checkpoint inhibitors as MMT. Predictive biomarkers to guide immune checkpoint inhibitors are still lacking in clinical routine. Predictive biomarkers that guided immune checkpoint inhibition in this cohort included programmed death ligand 1 expression, high TMB and/or dMMR/MSI-h, which is supported by previous findings in pan-cancer cohorts.[31,32]

Three patients underwent repeated molecular tumor analyses, identifying additional treatment options. These results underline the possibility of following disease dynamics under therapeutic pressure. However, the number of patients is too small to draw conclusions.

There are several additional limitations, as this is a retrospective real-world analysis of a limited number of patients from a single cancer center. A high degree of heterogeneity in clinical and molecular characteristics is expected in this setting, but limits the applicability of findings. Furthermore, the availability of NGS technologies, drugs and clinical trials limits the application of these findings to different contexts. An assessment of drug availabilities and pretest probabilities for different tumor types could help to improve the cost effectiveness in more resource-constrained settings.[8] Furthermore, the rapidly changing landscape of biomarkers and available treatments warrant frequent reanalyses of testing standards. The exploratory nature of this analysis requires larger studies, ideally in a controlled setting, to validate findings.

Conclusion

In our explorative analysis, molecular analyses and personalized treatment initiation was feasible for patients with GU tumors in a real-world setting. Additional treatment options were identified for most patients and a clinical benefit was observed in heavily pretreated patients. Molecular tumor profiling and personalized treatment should be considered for patients with GU malignancies, especially for those with rare histologies.

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DISCLOSURE

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DATA SHARING

Data supporting the findings of this study are provided in the manuscript and supplementary material. Additional information is available from the corresponding author upon reasonable request.

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