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Real-world clinicogenomic analysis of *FGFR2/3* alterations and treatment response in upper tract urothelial carcinoma

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Abstract

Background

FGFR2/3 alterations are therapeutically relevant in upper tract urothelial carcinoma (UTUC), but their association with conventional treatment response remains uncertain. We characterized the *FGFR2/3* spectrum and examined its association with treatment response in a nationwide registry cohort.

Methods

We retrospectively analyzed the Japanese C-CAT registry, characterizing 1,329 urothelial carcinomas and focusing on 566 UTUC cases. Patients were assigned to study-defined pathogenic variant (PV), variant of uncertain significance, or wild-type (WT) groups. PV comprised four prespecified *FGFR3* hotspot mutations and *FGFR3–TACC3* fusion isoforms V1 or V3 selected on the basis of therascreen. Other evaluated alterations, including amplifications, were assigned to the variant of uncertain significance group in patients without PV. First-line platinum and second-line pembrolizumab responses were assessed using registry treatment histories. Comparisons used Fisher's exact tests and logistic regression adjusted for age and platinum type.

Results

An evaluated *FGFR2/3* alteration was identified in 134/566 patients (23.7%), including 84 PV cases (14.8%). Small variants or fusions occurred in 122 patients (21.6%), including 30 *FGFR3–TACC3* fusions (5.3%). Of the 84 PV cases, 27 (32.1%) had qualifying fusions without a qualifying hotspot mutation. Among 287 patients with evaluable first-line platinum response, objective response rate was 22.4% in PV and 43.5% in WT. The adjusted odds ratio was 0.35 (95% confidence interval, 0.16–0.74; n=283). Among 118

patients with evaluable second-line pembrolizumab response, objective response rate was 11.5% in PV and 15.9% in WT (odds ratio, 0.69; 95% confidence interval, 0.12–2.85). PV was detected across testing contexts.

Conclusions

Selected *FGFR3* PV was associated with lower observed first-line platinum response in UTUC, whereas the second-line pembrolizumab association remained uncertain. This exploratory association requires external validation, including after first-line enfortumab vedotin plus pembrolizumab.

Keywords

Upper tract urothelial carcinoma; *FGFR3*; Comprehensive genomic profiling; Platinum-based chemotherapy; Pembrolizumab; Treatment response; C-CAT

Background

Bladder and upper tract urothelial carcinoma (UC) represent clinically and biologically heterogeneous malignancies [1]. Despite the availability of platinum-based chemotherapy, immune checkpoint inhibitors (ICIs), and antibody–drug conjugates, advanced disease remains a substantial clinical challenge [2]. Upper tract urothelial carcinoma (UTUC) is less common than urothelial carcinoma of the bladder (UCB), but its incidence varies geographically, with a relatively high incidence documented in parts of East Asia, particularly Taiwan [3]. This regional burden reinforces the need for UTUC-focused clinicogenomic studies in Asian populations. Systemic treatment of UTUC has largely been informed by studies combining anatomical sites. Comparative genomic studies have described differences between UTUC and UCB, including the distribution of *FGFR3* alterations and chromatin-modifying genes [4-6].

Comprehensive genomic profiling (CGP) informs molecular characterization and targeted treatment in UC. Among actionable alterations, selected fibroblast growth factor receptor (FGFR) alterations are clinically relevant, and erdafitinib has demonstrated activity in previously treated FGFR-altered disease [7, 8]. However, FGFR2/3 findings encompass hotspot mutations, fusions, and other variants with differing biological and therapeutic implications [9]. Their association with platinum and ICI outcomes remains heterogeneous across studies [10, 11]. The K-MASTER program has already integrated genomic findings and treatment outcomes in 231 metastatic UC patients, including 56 with UTUC [12]. A larger UTUC-focused analysis with explicit variant definitions and assessment of treatment histories can refine this clinical question.

Japan's nationwide C-CAT (Center for Cancer Genomics and Advanced Therapeutics) program provides a resource for evaluating the genomic landscape and treatment histories of patients undergoing CGP [13, 14]. This is a clinically selected population, frequently profiled after systemic treatment, rather than a population-based sample. Testing context and the timing of molecular assessment relative to treatment must therefore be considered when interpreting response associations.

In this study, we first characterized the overall C-CAT UC cohort and compared UTUC with UCB, then focused on *FGFR2/3* architecture, testing context, and treatment response in UTUC. The principal clinical analysis compared study-defined pathogenic variants (PV) with wild-type (WT) for first-line platinum response; variants of uncertain significance (VUS) were retained as a separate category. Second-line pembrolizumab response and survival were supportive analyses, and detailed bladder results were assigned to the Supplementary Materials.

Methods

Study design and data source

CGP assays used in this cohort comprised FoundationOne CDx, FoundationOne Liquid CDx, Guardant360 CDx, the NCC Oncopanel System, and GenMineTOP. Assay selection was determined by the treating physician in routine practice [13, 15]. Tissue and liquid assays were evaluated as distinct testing contexts; assay choice was not randomized.

For this retrospective, exploratory study, genomic and clinical data were obtained from the C-CAT database on August 13, 2025. Clinical characteristics were documented

at CGP or registry enrollment and may not reflect patient status at the start of first-line treatment. Ethics approval is described in the Declarations section.

Case classification

Cases were classified according to primary tumor site and histological diagnosis. Upper tract cancer included renal pelvis and ureter tumors. Of 1,650 bladder or upper tract cancers, 1,329 were UC, comprising 763 UCB and 566 UTUC cases. Non-urothelial tumors were retained only for overall cohort context. UTUC constituted the principal analysis population, and UCB provided the anatomical-site comparison. Clinical, genomic, and detailed treatment information was matched for all UC patients using unique registry identifiers.

Genomic profiling and FGFR2/3 classification

Tumor genomic profiling used next-generation sequencing, with results reviewed by multidisciplinary molecular tumor boards [16]. Patients were assigned to mutually exclusive study-defined PV, VUS, or WT groups. PV was defined by the following prespecified *FGFR3* alterations, selected on the basis of the therascreen FGFR RGQ RT-PCR Kit: R248C, G370C, S249C, or Y373C mutations, and *FGFR3–TACC3* fusions explicitly annotated as V1 or V3. Patients with any qualifying alteration were classified as PV, irrespective of coexisting amplifications or other alterations. Among patients without PV, all other *FGFR2/3* alterations evaluated in this study were classified as VUS, including amplifications, *FGFR3–TACC3* fusions with an unspecified isoform, and alterations annotated in C-CAT's Cancer Knowledge Database (CKDB) as having

potential therapeutic relevance. The study-defined VUS category did not imply uncertain pathogenicity or a lack of therapeutic relevance for every included alteration. WT was defined as the absence of an FGFR2/3 alteration included in these study categories; copy-number losses did not determine group assignment.

The broader genomic analysis included mutations, amplifications, copy-number losses, rearrangements, and variants annotated as germline in the registry; these annotations alone did not establish confirmed germline status. The 30 most frequently altered genes in UTUC were displayed together with their frequencies in UCB (Figure 2). The FGFR-focused oncoprint provides a descriptive overview of registry genomic annotations, with small variants not meeting the PV definition displayed as VUS (Figure 3A). The annotations used in this plot differ from the study-defined patient categories used for quantitative FGFR analyses. For the small-variant and fusion analyses (Figure 3B–C), each patient was counted once for each reported alteration; patients with multiple alterations could contribute to more than one feature. Amino-acid positions were used as reported, and splice variants described only at the cDNA level were not assigned protein coordinates.

Study outcomes and statistics

The main clinical endpoint was objective response rate (ORR) to first-line platinum therapy in UTUC. ORR was defined as complete or partial response (CR or PR), and disease control rate (DCR) additionally included stable disease (SD). Response analyses included patients with a documented best response of CR, PR, SD, or progressive disease (PD). All stable-disease classifications were analyzed together. Patients without

evaluable response data, including those with nonevaluable, missing, or unspecified responses, were excluded from the response analyses; in the second-line pembrolizumab cohort, they were additionally classified as nonresponders in a sensitivity analysis. Best response was based on registry documentation; central review and confirmation according to RECIST could not be verified. Proportions were reported with Wilson 95% confidence intervals (CIs).

First-line platinum-containing treatment was identified from individual treatment histories and matched to detailed treatment information documented before or after molecular tumor board review. Eligibility was assessed using the regimen, constituent drugs, treatment intent, and corresponding best response. Explicitly perioperative or local treatments and entries spanning multiple treatment phases without an attributable response were excluded. Treatment-line assignment relied on the designated first-line regimen rather than numerical treatment-line labels alone, because earlier perioperative therapy could influence the recorded line number. The resulting cohort included 773 eligible UC patients; exclusion of 104 patients without evaluable response data yielded 669 patients for the response analysis. All response estimates were calculated from patient-level treatment data using these eligibility criteria. The primary comparison was selected after preliminary examination of UTUC response data and was therefore exploratory.

The second-line pembrolizumab cohort comprised patients eligible for the first-line platinum cohort who had pembrolizumab monotherapy documented as second-line treatment. Eligibility required agreement between the treatment history, drug regimen, and documented treatment line. Maintenance, perioperative, and combination ICI

treatments and first-line ICI exposure were excluded. Treatment chronology was checked when both initiation dates were available; patients whose ICI treatment began on or before first-line platinum initiation were excluded. Patients with missing initiation dates were retained. Seven eligible patients lacked a first-line initiation date and four lacked an ICI initiation date, limiting verification of treatment chronology. Patients with PV and those with VUS were each compared with patients with WT using two-sided Fisher tests with conditional exact ORs and CIs. Sparse responses precluded a reliable adjusted ICI model.

Unadjusted ORR and DCR comparisons used conditional maximum-likelihood ORs and exact 95% CIs with two-sided Fisher's exact tests. Adjusted first-line platinum ORs were estimated using logistic regression, with WT as the reference and VUS entered as a separate category. The minimal adjusted model included age at CGP per ten years and cisplatin versus carboplatin, with no stepwise selection. Four nedaplatin cases were excluded from the UTUC adjusted model. Adjusted regression CIs and p values were Wald estimates.

FGFR2/3 alteration patterns were compared between UTUC and UCB using conditional exact ORs and 95% CIs and two-sided Fisher tests. Benjamini–Hochberg false discovery rate (FDR) correction covered the 13 FGFR architecture comparisons; the additional amplification and uncharacterized rearrangement rows in Table S2 were descriptive and were not included in this testing family. The frequencies of any *FGFR2/3* alteration included in the study definition and of PV were reported separately. Models evaluating PV detection across testing contexts were adjusted for age and sex; models for tissue origin and CGP timing additionally included assay platform. Liquid samples

were excluded from comparisons of primary and metastatic tissue. Because few patients underwent CGP before first-line therapy, these patients were combined with those tested between first- and second-line therapy to form the early testing group. Patients without documented CGP timing were excluded from regression analyses. These comparisons involved different patients and assessed detection frequencies; they did not evaluate within-patient concordance or analytical sensitivity.

Survival analyses were presented in Fig. S3. Overall survival (OS) was measured from first-line treatment initiation or CGP to death or last contact, with patients alive at last contact censored on that date. Each analysis included patients with an available, nonnegative recorded OS duration and known event status for the relevant time origin. OS from first-line treatment was evaluable in 326 UTUC and 431 UCB patients; OS from CGP was evaluable in 399 and 541 patients, respectively. Survival was estimated using the Kaplan–Meier method and compared across the three FGFR categories using global log-rank tests. Unadjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models with FGFR category as the sole explanatory variable and WT as the reference. The same hierarchical FGFR classification was applied across analyses, but survival analyses were not restricted to patients with evaluable treatment response. These conventional survival analyses did not account for delayed entry. Continuous variables were summarized as medians and interquartile ranges (IQRs) and categorical variables as n (%). All response and testing-context p values were nominal. Data processing and testing-context analyses used Python with pandas, SciPy, and statsmodels. Updated treatment-response, FGFR architecture, patient-characteristic, and survival analyses were performed in R version 4.5.2.

Results

Study population and patient characteristics

The cohort comprised 1,650 cancers: 1,053 bladder and 597 upper tract cancers. Urothelial histology accounted for 763 and 566 cases, respectively, yielding the 1,329-patient UC cohort (Figure 1A). Assay platform, CGP timing, specimen collection site, and histology were described for the 597 upper tract cancers, including 31 non-UC tumors (Figure 1B–C). FoundationOne CDx was the most frequently used tissue assay, and FoundationOne Liquid CDx predominated among liquid assays. Among patients with documented timing, 367/447 (82.1%) underwent CGP after second-line or later therapy. The urinary tract was the most common specimen collection site (415/597, 69.5%), followed by blood for liquid biopsy (99/597, 16.6%) and lymph nodes (36/597, 6.0%). Subsequent principal analyses focused on UTUC. Among 566 UTUC patients, median age at CGP was 70 years (IQR, 63–75), and 395 (69.8%) were male. Tissue and liquid assays were used in 469 (82.9%) and 97 (17.1%) patients, respectively; 383/469 tissue specimens were from primary tumors. CGP timing was not documented for 140 patients, and only three were profiled before first-line therapy (Table 1). Comparative UCB/UTUC characteristics are provided in Table S1.

Genomic landscape of UTUC with a bladder comparison

The UTUC oncoprint and descriptive comparison with UCB are shown in Figure 2A–B. Recorded gene-level alterations were most frequent in *TP53* (355/566; 62.7%), *KMT2D* (271/566; 47.9%), *CDKN2A* (217/566; 38.3%), and *TERT* (199/566; 35.2%). *KMT2D* and *TERT* alterations were identified in 36.7% and 57.3% of UCB cases, respectively. These

descriptive frequencies include copy-number alterations and variants of uncertain significance and do not represent the prevalence of actionable alterations. The bladder oncoprint and the comparison of genomic alterations by tumor site are presented in Fig. S1. Across the UC cohort, 317/1,329 patients (23.9%) had an FGFR2/3 alteration included in the study definition. In UTUC, 134/566 (23.7%) had an evaluated FGFR2/3 alteration, including FGFR3 in 114 (20.1%) and FGFR2 in 23 (4.1%); alterations in the two genes could coexist. The mutually exclusive PV, VUS, and WT categories comprised 84 (14.8%), 50 (8.8%), and 432 (76.3%) patients, respectively. Small variants or fusions were identified in 297/1,329 UC patients (22.3%), including 122/566 UTUC patients (21.6%).

FGFR2/3 alteration spectrum

The FGFR-focused oncoprints, small-variant positions, and fusion spectrum in UTUC are shown in Figure 3A–C. The most frequent *FGFR3* hotspot mutations were S249C (28 patients), Y373C (17), and R248C (eight). *FGFR3–TACC3* fusions were recorded in 30 patients (5.3%): 21 V1, seven V3, and two with unspecified isoform. Of the 84 patients with study-defined PV, 27 (32.1%) had qualifying *FGFR3–TACC3* fusions without a qualifying hotspot mutation. One patient each had a recorded *FGFR3–NOL4*, *FGFR3–ADD1*, or *FGFR2–CCDC6* fusion. Small variants and fusions could coexist. Relative to UCB, *TACC3* fusion frequency was nominally higher in UTUC (30/566 versus 18/763; OR, 2.32; 95% CI, 1.23–4.46; p=0.007) (Table S2). The focused oncoprint displays registry genomic annotations, with non-PV small variants grouped as VUS. Quantitative comparisons use the study-defined patient categories described in Methods.

Amplifications were recorded in 16 UTUC patients, including seven with FGFR2 and nine with FGFR3 amplification; four were classified as PV and 12 as VUS. Seventeen patients in the study-defined VUS group harbored alterations annotated in C-CAT's Cancer Knowledge Database (CKDB) as having potential therapeutic relevance. These annotations overlapped with the alteration types reported above. Additional FGFR2 rearrangements without a defined partner were distinguished from confirmed fusions (Table S2).

Clinical characteristics according to FGFR alteration status are summarized in Table S3. The frequency of recorded lymph node metastases differed nominally across the WT, PV, and VUS groups (69.9%, 60.7%, and 82.0%, respectively; unadjusted global p=0.034). No statistically significant differences were observed in age at CGP, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), other recorded metastatic sites, assay type, CGP panel, tissue specimen source, or CGP timing (all p≥0.184).

Table 2 summarizes the detection of FGFR2/3 alterations included in the study definition across testing contexts in UTUC. Such alterations were identified in 110/469 tissue-profiled patients (23.5%) and 24/97 liquid-profiled patients (24.7%). PV was identified in 71/469 (15.1%) and 13/97 (13.4%), respectively; the liquid-versus-tissue adjusted OR was 0.87 (95% CI, 0.46–1.64). PV frequency was 58/383 (15.1%) in primary and 13/86 (15.1%) in metastatic tissue, with an adjusted OR of 1.02 (95% CI, 0.53–1.96). PV detection was 6/67 (9.0%) in the early profiling category, 22/151 (14.6%) after second-line therapy, and 31/208 (14.9%) after at least third-line therapy (adjusted global

p=0.401). The early category included only three pretreatment cases. Context plots and comparative estimates are provided in Fig. S2 and Table S4.

First-line platinum response in UTUC

The UTUC cohort included 336 eligible platinum-treated patients. After excluding 49 patients without evaluable response data (four PV, four VUS, and 41 WT), 287 patients were included in the response analysis. Characteristics of the eligible cohort, response-evaluable patients, and patients without evaluable response data are summarized in Table S5. Response distributions, ORR, and DCR were evaluated in this same population (Figure 4A–B). ORR was 11/49 (22.4%) in PV, 18/29 (62.1%) in VUS, and 91/209 (43.5%) in WT; DCR was 69.4%, 79.3%, and 75.1%, respectively. Patients with PV had lower odds of response than those with WT (conditional exact OR, 0.38; 95% CI, 0.16–0.80; p=0.009). Adjustment for age and cisplatin versus carboplatin yielded an OR of 0.35 (95% CI, 0.16–0.74; p=0.006) in 283 patients with 117 responses, including ten responses among 47 PV patients (Table S6). The adjusted VUS OR was imprecise (OR, 2.17; 95% CI, 0.97–4.86; p=0.059), and disease control did not differ clearly between patients with PV and those with WT after adjustment (OR, 0.68; 95% CI, 0.34–1.37; p=0.286). Among the 17 VUS patients with CKDB annotations of potential therapeutic relevance, nine had evaluable first-line platinum response and seven responded. These descriptive results were based on a small, molecularly heterogeneous subgroup.

Second-line pembrolizumab response in UTUC

A total of 137 patients met the eligibility criteria for second-line pembrolizumab analysis. Nineteen patients lacked evaluable response data (three PV, three VUS, and 13 WT).

Among 118 patients with evaluable response, there were 26 PV, ten VUS, and 82 WT patients (Figure 4C–D). ORR was 3/26 (11.5%) in PV, 2/10 (20.0%) in VUS, and 13/82 (15.9%) in WT. Response did not differ clearly between patients with PV and those with WT (conditional exact OR, 0.69; 95% CI, 0.12–2.85; p=0.757). DCR was 12/26 (46.2%), 6/10 (60.0%), and 44/82 (53.7%), respectively (PV versus WT: OR, 0.74; 95% CI, 0.28–1.97; p=0.653). Classifying patients without evaluable response data as nonresponders yielded ORR of 3/29 (10.3%) versus 13/95 (13.7%; p=0.761).

Supportive survival analyses

No statistically clear OS differences across FGFR categories were observed in the conventional survival analyses from first-line treatment or CGP in either UTUC or UCB (Fig. S3). In UTUC, the unadjusted HR for PV versus WT was 0.77 (95% CI, 0.47–1.26) for OS from first-line treatment and 0.84 (95% CI, 0.56–1.26) for OS from CGP. The survival-analysis populations and eligibility criteria differed from those used for the response analyses.

Discussion

This nationwide clinicogenomic analysis characterizes *FGFR2/3* alterations in 566 patients with UTUC and identifies an association between *FGFR3* PV and lower first-line platinum ORR. Comparison with UCB places the UTUC molecular findings in context, while analyses of treatment response focus on UTUC. The clinical information derives from 287 patients with evaluable platinum response, including 49 PV cases, rather than

all 566 profiled patients. Second-line pembrolizumab response showed no statistically clear PV association.

The contribution should be considered alongside established evidence. UTUC/UCB genomic differences and *FGFR3* fusion enrichment have already been described [4-6, 17]. K-MASTER combined molecular and clinical analyses in 231 metastatic UC patients, including 56 with UTUC, and reported heterogeneous associations involving *FGFR3* and *FGFR2* [12]. Our 566 profiled UTUC cases provide approximately ten times as many UTUC observations, strengthening descriptive coverage, but the populations and endpoint definitions differ. This ratio does not imply a tenfold increase in treatment-response information. Our study has practical implications for FGFR testing in patients with UTUC undergoing CGP. Among patients with UTUC undergoing CGP, 14.8% harbored study-defined PV, alteration types covered by the US Food and Drug Administration (FDA)-approved companion diagnostic (CDx) for erdafitinib. Of these 84 patients, 27 (32%) had qualifying fusions without a hotspot mutation and would not have been identified as having study-defined PV by testing limited to the four qualifying hotspot mutations. By contrast, the platinum-response association, based on 49 response-evaluable PV patients, is hypothesis-generating.

Our study-defined PV category was restricted to the FGFR3 alterations selected on the basis of therascreen and did not encompass all alterations with potential oncogenic or therapeutic relevance. The study-defined VUS group therefore included molecularly diverse findings, including amplifications and alterations annotated in CKDB as having potential therapeutic relevance, and should not be regarded as a biologically uniform group. Their assignment to VUS reflected the study classification and did not negate

these annotations. Our platinum-response findings should consequently be interpreted in relation to the study-defined PV category and should not be generalized to all pathogenic FGFR2/3 alterations. CKDB annotations alone do not establish sensitivity to erdafitinib. A confirmed partial response to the investigational FGFR3 inhibitor dabogratinib has been reported in a patient with metastatic UC harboring an FGFR3–JAKMIP1 fusion, which is not covered by therascreen [18]. CGP can identify such additional alterations and support evaluation of whether FGFR-targeted treatment eligibility could be extended beyond established CDx targets; this requires alteration-specific clinical evidence, and response to another FGFR inhibitor does not establish sensitivity to erdafitinib.

Platinum-response evidence is inconsistent. Teo et al. reported numerically lower response in *FGFR3*-altered metastatic UC, without a clear PFS or OS difference [10], whereas IFUCA found similar first-line platinum ORR in altered and WT disease [11]. Differences in site composition, variant definitions, treatment intent, and response ascertainment limit direct comparisons. Within our cohort, lower PV ORR coexisted with frequent SD, an uncertain DCR association, and no consistent adverse survival association.

The absence of a statistically clear OS difference does not necessarily contradict the observed ORR association. Whereas ORR captures tumor shrinkage during first-line platinum therapy, OS reflects the subsequent disease course and the effects of later treatment. Maintenance and subsequent therapies, including ICIs and enfortumab vedotin, have demonstrated survival benefits in advanced UC and may have influenced OS in this cohort [19-21]. Variation in access to these treatments over time could also have affected the relationship between initial response and survival; however, their

contribution to the present findings was not evaluated. These considerations support further investigation of an FGFR-defined response association in UTUC but do not establish UTUC-specific platinum resistance or a predictive biomarker.

In the era of first-line enfortumab vedotin plus pembrolizumab (EV-P), platinum-based chemotherapy remains relevant when EV-P cannot be used and after progression [22, 23]. A retrospective study reported an ORR of 49% (22/45 evaluable patients) and a median PFS of 5.0 months with platinum-based chemotherapy after EV-P [24]. If independently validated, the association between study-defined PV and lower platinum ORR could refine expectations of tumor shrinkage. A potential application would be to inform the choice between platinum and erdafitinib after EV-P in patients with study-defined PV who are eligible for both treatments. This would require validation in that setting and comparative evidence of clinical benefit, as our cohort did not evaluate treatment after EV-P. Timely FGFR results would also be needed when subsequent therapy is selected. These findings do not justify withholding platinum.

Evidence regarding ICI outcomes is also mixed. Wang et al. and Komura et al. reported no significant response difference by *FGFR3* mutation status in ICI trial cohorts [25, 26], and THOR cohort 2 demonstrated pembrolizumab activity in FGFR-altered disease but included no WT comparator [8]. Other analyses have reported less favorable ICI outcomes in *FGFR3*-mutant disease [27]. A recent meta-analysis found inconclusive ORR differences but lower DCR and shorter survival in *FGFR3*-altered UC [28]; its pooled mixed-site evidence does not directly address our selected UTUC cohort. Our second-line analysis included three PV responses. It cannot establish equivalent ICI activity or an

optimal treatment sequence. In particular, a significant platinum association and a nonsignificant ICI association do not demonstrate differential treatment benefit.

FGFR-positive UTUC cases were identified in tissue and liquid assays, primary and metastatic tissue, and across the evaluated profiling intervals. MONSTAR-SCREEN has described liquid-based FGFR findings [9], and a prospective study of 208 metastatic UC patients directly evaluated paired tissue and circulating tumor DNA (ctDNA), reporting 90% concordance among 125 evaluable pairs [29]. Our unpaired registry analyses add UTUC-specific testing context. Possible patient overlap with other C-CAT reports, including the tissue-based *FGFR3/ERBB2 study* [30], also prevents a claim of independent registry replication.

Limitations include retrospective CGP selection, incomplete response recording, missing pretreatment renal-function and disease-burden data, heterogeneous treatment intent, and residual confounding. Age and PS were recorded at CGP/registration and may not reflect pretreatment functional status. CGP performed after treatment failure and survival until testing can distort associations between later genomic results and earlier outcomes. The primary comparison was informed by preliminary UTUC response findings. Sparse VUS and ICI-response subgroups limit precision, and receipt of second-line pembrolizumab additionally selected patients who survived after platinum. The observational design and differently selected treatment cohorts limit treatment-specific inferences and comparisons of relative treatment benefit.

Survival analyses were particularly susceptible to selection because CGP was generally performed after initial treatment, and patients had to survive until testing to enter the cohort. Conventional OS estimates from first-line treatment that do not account for

delayed entry may therefore overestimate survival relative to an unselected treatment cohort [31]. OS measured from CGP describes prognosis after testing in this selected population and cannot be directly compared with OS from treatment initiation in unselected advanced UTUC cohorts. Selection related to the timing and indication for CGP may also affect comparisons across FGFR categories. Moreover, the survival and response analyses involved different populations. These exploratory OS findings therefore do not establish equivalent prognosis across FGFR categories or independently validate the platinum-response association.

Testing-context comparisons involved different patients rather than paired or serial specimens, precluding assessment of assay equivalence or within-patient temporal stability. Only three UTUC patients underwent pre-first-line CGP, and profiling time does not indicate when archival tissue was obtained. Immune and stromal mechanisms were not assessed. The duration of SD was not evaluated. Associations between FGFR alterations and response to FGFR-targeted therapy were not evaluated. Unreported alterations may reflect assay coverage rather than biological absence. External validation requires harmonized variant definitions, pretreatment sampling, and prospectively specified treatment cohorts.

Conclusions

In this large Japanese CGP registry cohort, UTUC showed a heterogeneous *FGFR2/3* spectrum, and selected *FGFR3* PV was associated with lower observed first-line platinum ORR. FGFR-positive cases were identified across evaluated testing contexts, while the

second-line pembrolizumab association remained uncertain. These findings warrant external validation.

List of abbreviations

C-CAT, Center for Cancer Genomics and Advanced Therapeutics; CDx, Companion diagnostic; CGP, Comprehensive genomic profiling; CI, Confidence interval; CKDB, Cancer Knowledge Database; CR, Complete response; ctDNA, Circulating tumor DNA; DCR, Disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EV-P, Enfortumab vedotin plus pembrolizumab; FDA, US Food and Drug Administration; FDR, False discovery rate; FGFR, Fibroblast growth factor receptor; HR, Hazard ratio; ICI, Immune checkpoint inhibitor; IQR, Interquartile range; OR, Odds ratio; ORR, Objective response rate; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survival; PR, Partial response; PV, Study-defined pathogenic variant; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable disease; UC, Urothelial carcinoma; UCB, Urothelial carcinoma of the bladder; UTUC, Upper tract urothelial carcinoma; VUS, Study-defined variant of uncertain significance; WT, Study-defined wild-type.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board at Keio University (Tokyo, Japan) and the C-CAT Data Utilization Review Board (CDU2023-039).

Consent for publication

Not applicable.

Availability of data and materials

The patient-level genomic and clinical data analyzed in this study were obtained from C-CAT and are not publicly available because access is subject to C-CAT data-use requirements. Access requires approval through the C-CAT data-utilization review process and a data-use agreement. Aggregate results are provided in this article and the Supplementary Materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: T.T., Y.M., F.U., H.A., and Y.S. Data curation: T.T., Y.M., K.I., Y.U., and Y.S. Resources: Y.S. Funding acquisition: Y.S. Investigation: T.T., Y.M., F.U., K.I., K.Y., Y.U., T.I., M.N., J.M. and Y.S. Visualization: Y.M., T.T., and Y.S. Supervision: T.K.,

H.A. and Y.S. Writing – original draft: T.T., Y.M., and Y.S. Writing – review and editing: all authors.

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Figure legends

Figure 1. C-CAT cohort, testing context, and UTUC response cohort selection.

(A) The initial cohort comprised 1,650 patients with bladder or upper tract cancer, including 1,053 bladder and 597 upper tract cancers. Exclusion of non-urothelial tumors (290 bladder and 31 upper tract) yielded 1,329 UC cases: 763 UCB and 566 UTUC. The UTUC cohort was stratified into study-defined FGFR PV, VUS, and WT groups. Treatment-evaluable cohorts were subsequently identified within each FGFR group for treatment-specific analyses.

(B) Nested donut chart showing CGP timing in the outer ring and assay platform in the inner ring.

(C) Nested donut chart showing histology in the outer ring, specimen collection site in the middle ring, and assay platform in the inner ring.

CGP, comprehensive genomic profiling; UC, urothelial carcinoma; UCB, urothelial carcinoma of the bladder; UTUC, upper tract urothelial carcinoma.

Figure 2. Genomic landscape of UTUC and a descriptive comparison with bladder UC.

(A) Oncoprint of the 30 genes with the highest alteration frequency among 566 UTUC patients. Each column represents one patient, grouped by tissue or liquid profiling. Mutations, copy-number losses, amplifications, rearrangements, and variants annotated as germline in the registry are displayed; more than one alteration type may be present for an individual patient and gene.

(B) Gene-level alteration frequencies for the same genes in 763 UCB and 566 UTUC patients. Each patient contributes once per gene. Reported alterations include variants of

uncertain significance and copy-number alterations. These gene-level summaries are distinct from the mutually exclusive study-defined PV, VUS, and WT patient categories used in clinical analyses. The heatmap shows descriptive frequencies without significance testing. The absence of a displayed alteration indicates that none was reported. The bladder oncoprint and the comparison of genomic alterations by tumor site are presented in Fig. S1.

Figure 3. *FGFR2/3* small variants and fusion spectrum in UTUC.

(A) FGFR-focused oncoprints in tissue- and liquid-profiled UTUC cases, showing *FGFR3* and *FGFR2* small variants and *FGFR3* fusions. Each column represents one patient. Colors distinguish PV, VUS, and fusions, and adjacent bars show alteration frequencies within each oncoprint. All non-PV small variants are displayed using the VUS color. Fusions are displayed separately from the patient categories of PV, VUS, and WT. The genomic annotations summarized in these oncoprints differ from the study-defined patient categories used in Table 2. The absence of a displayed alteration indicates that none was reported. The study-defined patient-level VUS group additionally includes amplifications and alterations with CKDB-annotated potential therapeutic relevance in patients without qualifying PV.

(B) Lollipop plots showing patient counts at reported *FGFR3* and *FGFR2* amino-acid positions in UTUC, with a log(1+n) vertical scale. Red indicates the four PV-defining *FGFR3* hotspots, and blue indicates all other small variants grouped as VUS. Each variant is colored according to its own classification, irrespective of other FGFR alterations in the same patient.

(C) Numbers of patients with each reported *FGFR* fusion partner and isoform. Small variants and fusions can coexist, so features are not mutually exclusive.

Figure 4. Platinum and pembrolizumab response by FGFR category in UTUC.

(A–B) Both panels use the same 287 response-evaluable first-line platinum patients: PV, n=49; VUS, n=29; WT, n=209. Panel A shows the distribution of complete response, partial response, stable disease, and progressive disease. Panel B shows pairwise odds ratios for objective response, with conditional exact 95% confidence intervals and nominal two-sided Fisher p values.

(C–D) Both panels use the same 118 response-evaluable patients receiving second-line pembrolizumab monotherapy following first-line platinum: PV, n=26; VUS, n=10; WT, n=82. Panel C shows response distributions. Panel D shows pairwise odds ratios for objective response, with conditional exact 95% confidence intervals and nominal two-sided Fisher p values. Disease control estimates are provided in Table S6.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; ICI, immune checkpoint inhibitor; CI, confidence interval.

Supplementary Materials

Tables S1–S6 and Figs. S1–S3 are provided in the Supplementary Materials.

Fig. 1

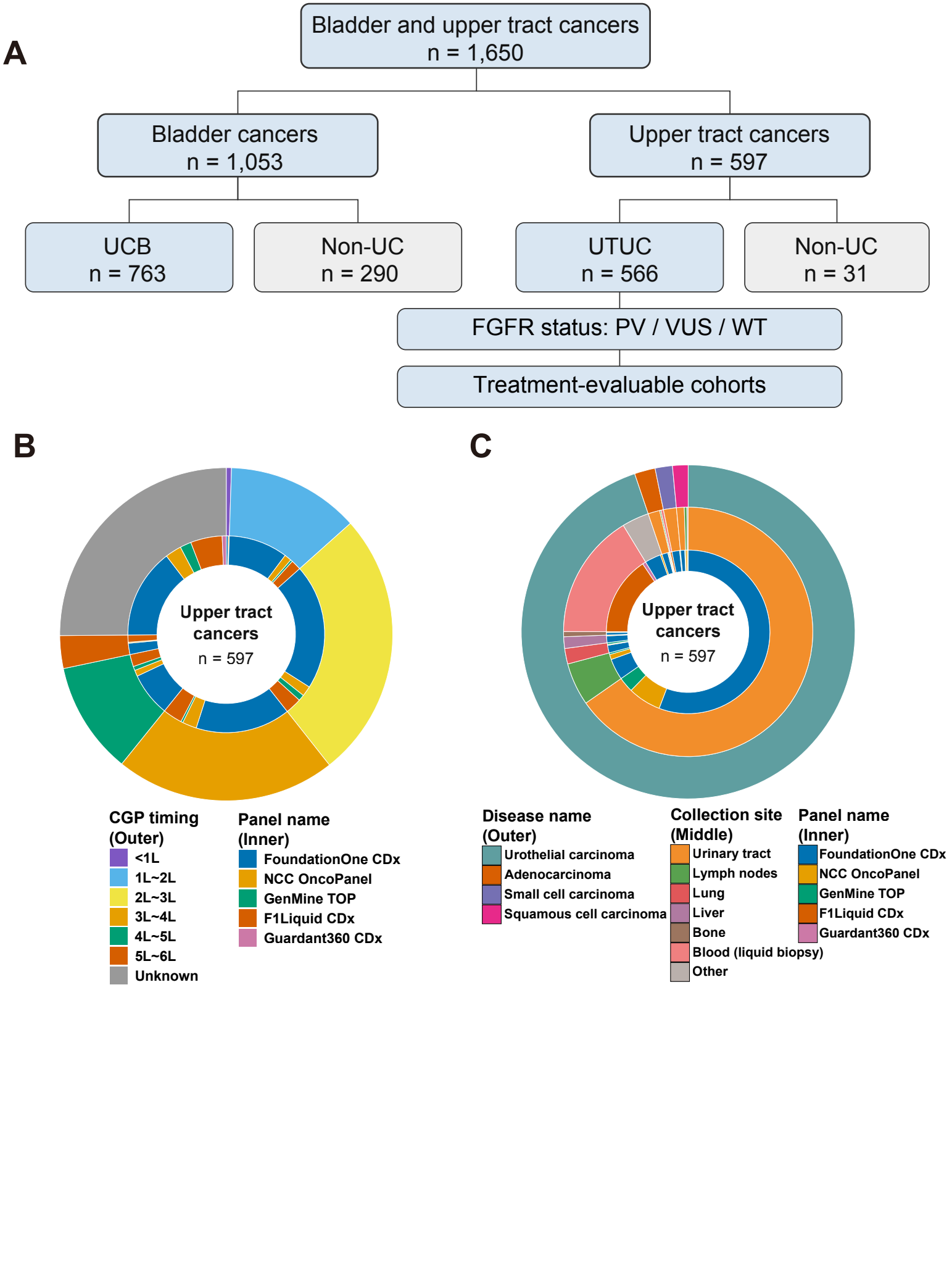
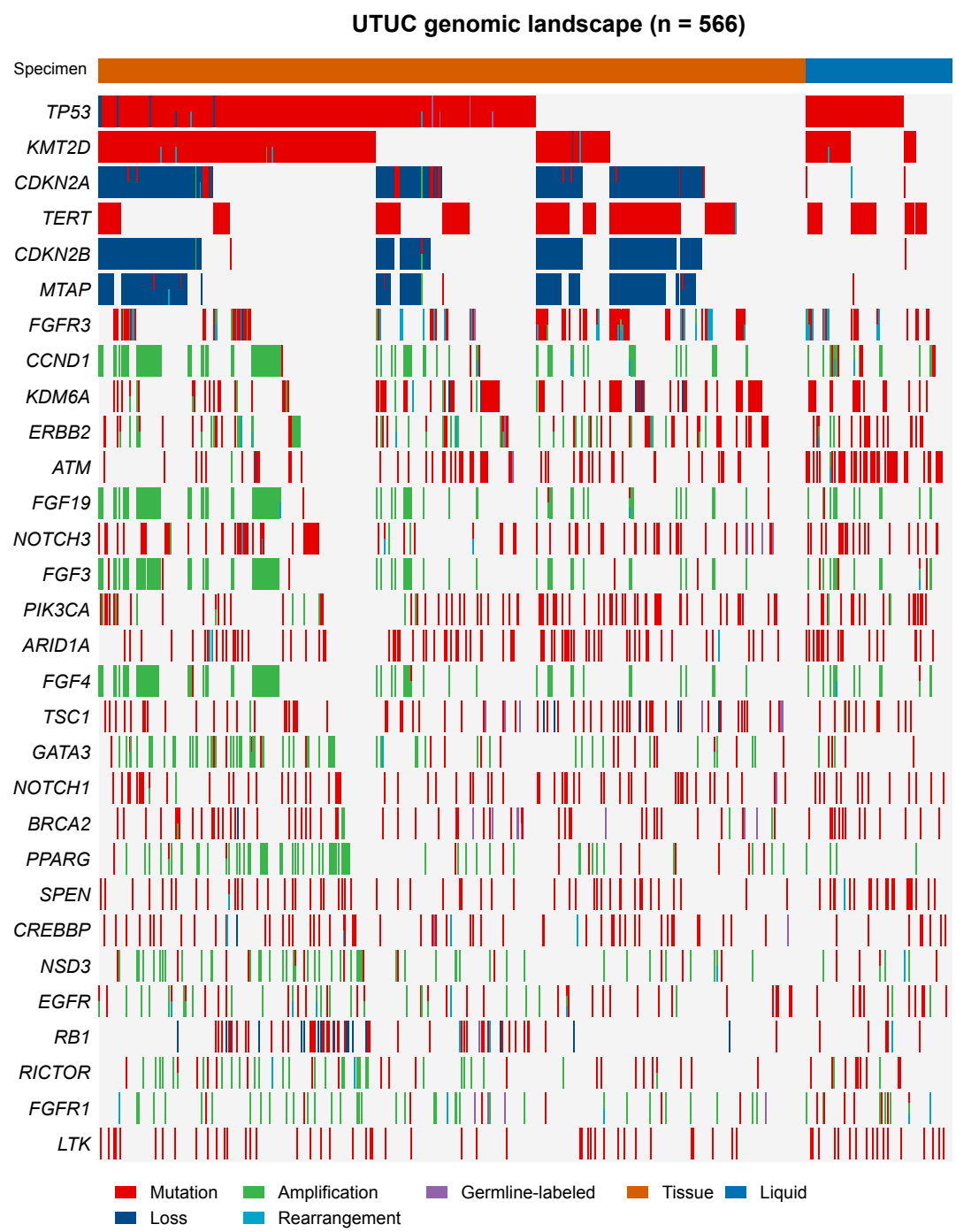

A
Bladder and upper tract cancers
n = 1,650
Bladder cancers
n = 1,053
Upper tract cancers
n = 597
UCB
n = 763
Non-UC
n = 290
UTUC
n = 566
Non-UC
n = 31
FGFR status: PV / VUS / WT
Treatment-evaluable cohorts
B
Upper tract cancers
n = 597
CGP timing (Outer)
<1L
1L~2L
2L~3L
3L~4L
4L~5L
5L~6L
Unknown
Panel name (Inner)
FoundationOne CDx
NCC OncoPanel
GenMine TOP
F1Liquid CDx
Guardant360 CDx
C
Upper tract cancers
n = 597
Disease name (Outer)
Urothelial carcinoma
Adenocarcinoma
Small cell carcinoma
Squamous cell carcinoma
Collection site (Middle)
Urinary tract
Lymph nodes
Lung
Liver
Bone
Blood (liquid biopsy)
Other
Panel name (Inner)
FoundationOne CDx
NCC OncoPanel
GenMine TOP
F1Liquid CDx
Guardant360 CDx

Fig. 2

A



B

Recorded frequency (%)	
UTUC (n=566)	UCB (n=763)
62.7	61.1
47.9	36.7
38.3	35.8
35.2	57.3
33.7	29.8
27.4	25.3
21.0	20.3
20.5	16.6
20.3	28.0
19.1	22.5
18.2	13.8
17.8	13.8
17.5	17.4
17.3	13.4
17.0	18.6
16.6	23.3
16.3	13.1
14.7	13.9
14.3	11.4
13.4	15.5
13.1	16.6
13.1	11.5
12.9	15.2
11.8	12.7
11.8	8.1
11.7	8.1
11.7	17.7
11.0	11.8
10.8	7.1
10.8	14.2

Fig. 3

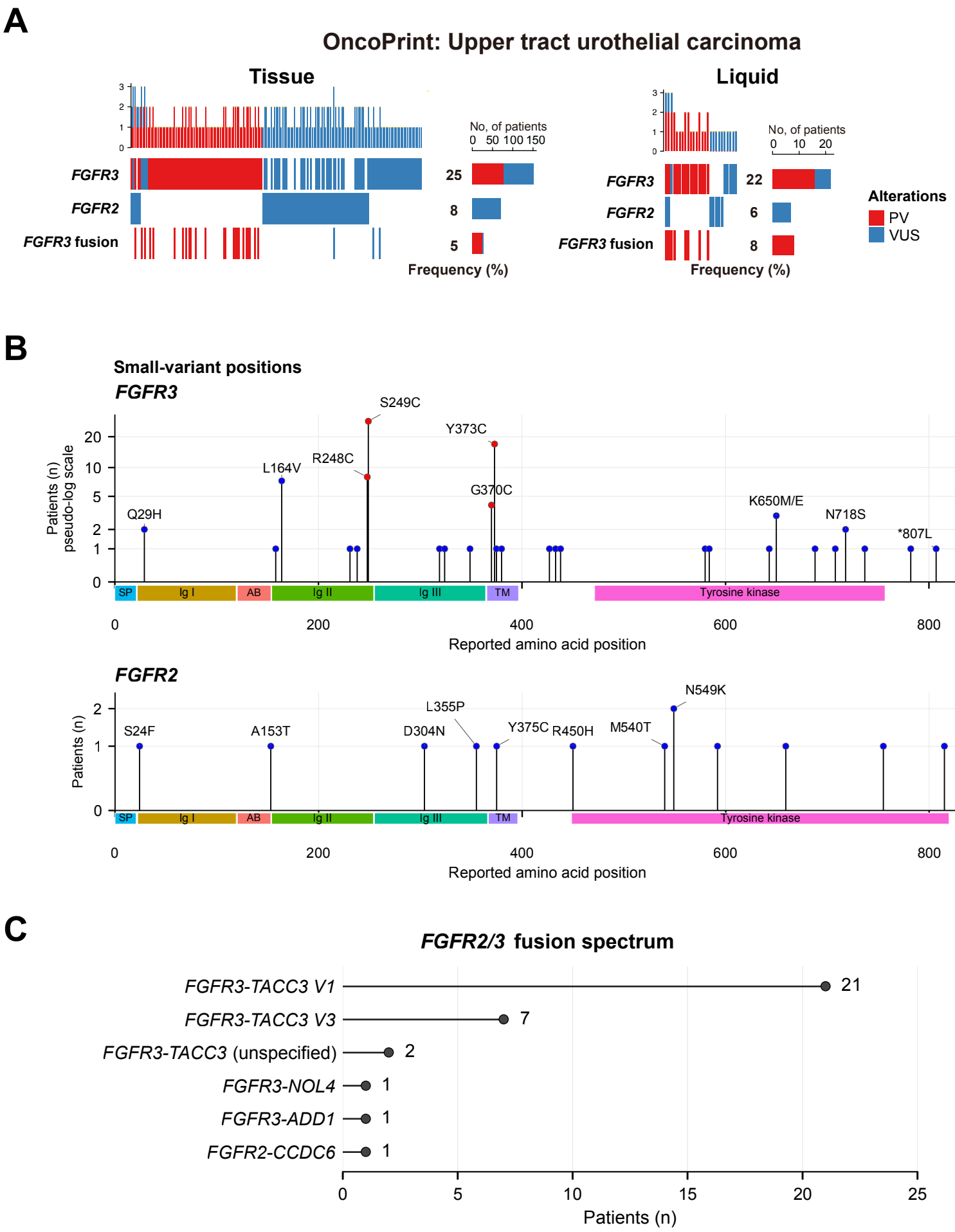
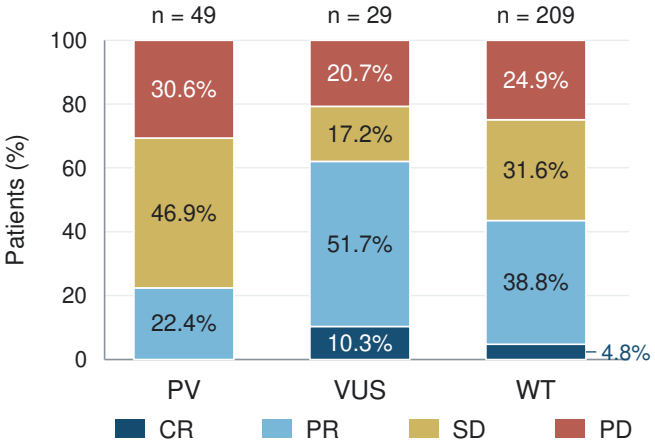

A
OncoPrint: Upper tract urothelial carcinoma
Tissue
Liquid
FGFR3
FGFR2
FGFR3 fusion
No, of patients
25
8
5
22
6
8
Frequency (%)
Alterations
PV
VUS
B
Small-variant positions
FGFR3
Patients (n)
pseudo-log scale
Q29H
L164V
R248C
S249C
Y373C
G370C
K650M/E
N718S
*807L
SP
Ig I
AB
Ig II
Ig III
TM
Tyrosine kinase
Reported amino acid position
FGFR2
S24F
A153T
D304N
L355P
Y375C
R450H
M540T
N549K
C
FGFR2/3 fusion spectrum
FGFR3-TACC3 V1
FGFR3-TACC3 V3
FGFR3-TACC3 (unspecified)
FGFR3-NOL4
FGFR3-ADD1
FGFR2-CCDC6
21
7
2
1
1
1
Patients (n)

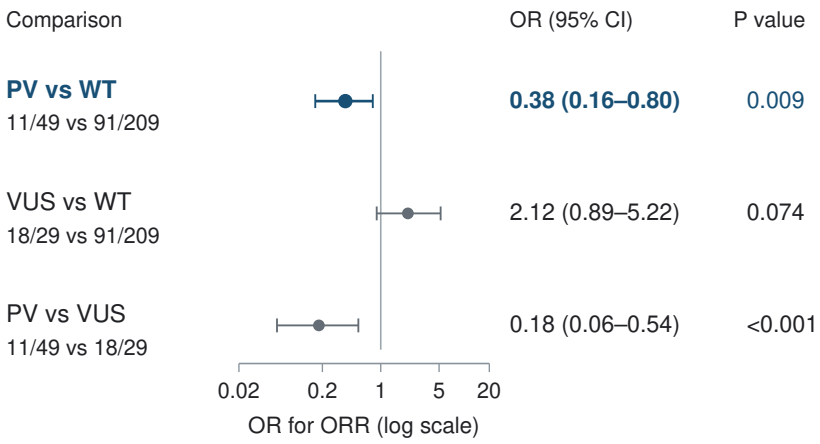
Fig.4

First-line platinum chemotherapy

A Best overall response

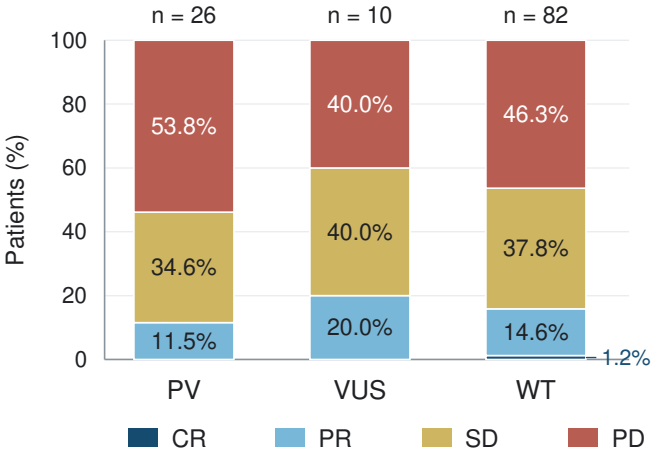


B Objective response

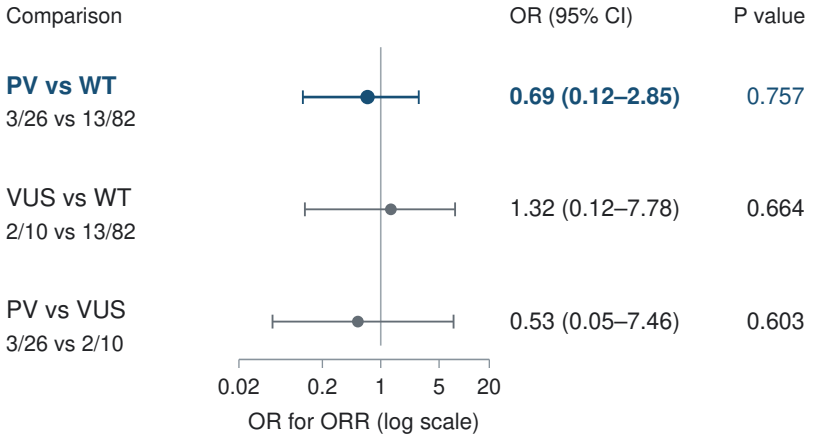


Second-line pembrolizumab

C Best overall response



D Objective response



Conditional exact ORs and 95% CIs; nominal two-sided Fisher P values.

VUS includes amplifications and additional non-CDx alterations in patients without qualifying PV.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1V2UTUCpatientcharacteristics.docx
- Table2FGFRtestingcontextAmplificationnonCDxVUS.docx
- SupplementaryMaterials.docx