Category: Rapid Impact

Title: Molecular profiling of metastatic bladder cancer early-phase clinical trial participants predicts patient outcomes

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Running title: DNA sequencing in Phase 1 mBC trials

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Abstract:

Prognosis for patients with metastatic bladder carcinoma (mBC) remains limited and in need of novel therapies. We retrospectively analyzed medical records of 43 patients with platinum-refractory metastatic bladder cancer (mBC) who participated in one or more phase 1 trials of various investigational therapies. Patients’ tumors or circulating tumor DNA were analyzed by next generation sequencing. Median progression-free survival was 4.2 months, median overall survival was 9.6 months, and the overall response rate was 17.5%. TP53, ERBB2, PI3KCA, FGFR3 and ARID1A alterations were detected in 66%, 29%, 27%, 24%, and 22% of all patients, respectively. Alterations in FGFR3 were almost mutually exclusive of TP53. More than half (64%) of patients with an FGFR alt received an FGFR inhibitor, 67% of which, achieved disease control. Among patients with urothelial carcinoma histology, those harboring a TP53 alteration had a shorter median PFS compared to those whose tumors carry wild-type TP53. The reverse relationship was observed in patients harboring an FGFR alteration.

Implications: Patients with platinum-refractory mBC derive clinical benefit from participating in early phase clinical trials and their survival outcomes correlate with the genetic profile of the tumor.
Main text:

1. Introduction:

Before 2019, patients with metastatic bladder cancer (mBC) had limited treatment options, which included cisplatin-based chemotherapy regimens, immune checkpoint inhibitors (CPIs), and single-agent chemotherapy. Up to 50% of patients with mBC are ineligible for cisplatin-based chemotherapy regimens due to medical co-morbidities (1). Furthermore, in platinum-ineligible or -resistant mBC, CPIs provide low response rates of 15% to 25% despite their substantial clinical benefit (2-8). Molecular profiling (9) suggests that certain subtypes of bladder cancer have distinct prognoses and benefit differently from chemotherapy (10), immunotherapy (3), or targeted therapy (11). Erdafitinib, a pan-FGFR receptor tyrosine kinase inhibitor, was approved for patients with mBC and \textit{FGFR2 or FGFR3} alterations, which are estimated to represent in approximately 15-20% of patients with mBC (11). Erdafitinib had a response rate of 40% and median PFS is 5.5 months (11). The clinical benefit seen with erdafitinib is a beacon of hope for targeting genomic alterations in mBC, a challenging and incurable disease with an unmet need for novel therapies.

Enrolling patients with mBC in early phase clinical trials might be challenging due to their medical co-morbidities, toxicities from prior systemic therapies, and poor performance status at referral (12). However, there are potential benefits to enrolling patients with mBC in an early phase clinical trial. Depending upon the situation, early phase trials may provide access to promising therapies in development for mBC. Furthermore, many early phase clinical trials have two cohorts, a dose-escalation (First-in-human: FIH) and a dose expansion cohort (using the Recommended Phase 2 Dose: RP2D). Dose expansion cohorts are becoming more prevalent and are sometimes used for initial drug registration. In fact, a PD-L1 CPI, avelumab, was granted Food and Drug Administration (FDA) accelerated approval for mBC based upon the results of two dose-expansion early phase trials (13). When considering all of the above factors,
it can be difficult for clinicians to decide when or whether to recommend phase 1 trials for patients with mBC.

The objective of the present study is to evaluate the molecular and clinical characteristics and treatment outcomes of patients with mBC who enroll on early phase clinical trials and to assess how specific and common genomic aberrations influence outcomes in these trials.

2. Methods

2.1. Patients

Baseline characteristics and clinical outcomes were retrospectively collected for patients with mBC who were enrolled on one or more phase 1 clinical trial at the University of Texas MD Anderson Cancer Center (MDACC), Houston, Texas. Patients who received an investigational checkpoint inhibitor CPI combination during their first trial participation were labeled as having received prior CPI for their second trial participation. Given the known biological differences between bladder UC, upper tract UC (UTUC) or urethral UC, the latter two were excluded. Furthermore, the majority of patients with UTUC have borderline renal function, which limited their accrual to phase I trials. Next, we investigated if patients had tumor next-generation sequencing (NGS) performed prior to trial enrollment. Tumor NGS was either performed on tumor tissue, using one of five CLIA certified laboratory tests with a range of 50 to 400 cancer-related genes assessed, or circulating tumor DNA (ctDNA), using Guardant360. This study was approved by the Institutional Review Board (IRB) of MDACC. All phase 1 clinical trials were also approved by the MDACC IRB, and patients provided informed written consent to prior to receiving treatment.

2.2. Endpoints

Endpoints of interest included response rate (RR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). RR was defined as complete response (CR) plus partial response (PR). DCR was defined as RR plus stable disease (SD).
Best response was defined by individual trial protocol most commonly based upon the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) or immune-related RECIST (irRECIST). PFS and OS for each patient were calculated based on their individual trial participation. PFS was measured from time of trial enrollment until time of progression, death or last follow-up. OS was measured from time of trial enrollment until death or date of last follow-up. For the 12 patients with >1 trial participation, OS was calculated from the time of enrollment to the first trial, ORR was based on each individual trial response evaluation, and PFS was calculated from C1D1 of each trial.

2.3. **Statistical analysis**

Survival curves were generated using the Kaplan-Meier approach. Median follow-up time was calculated using the reverse Kaplan-Meier method (14). Hazard ratios (HR) were calculated using the Cox proportional hazard model. A p value < 0.05 was considered statistically significant.

2.4. **Somatic alteration identification and annotation**

Somatic alterations were identified in tumor tissues by either hybrid capture–based targeted DNA sequencing in using FoundationOne CDx (15) or PCR-amplicon–based target capture using Oncomine (16). Somatic alterations in cell-free DNA (cfDNA) were detected by Oncomine (17) and Guardant360 (18). Lollipop figures were created using the visualize data feature by cBioPortal (19, 20) and annotation of the biologic and oncogenic effects and prognostic and predictive significance of somatic molecular alterations were extracted from the OncoKB knowledge base (21). For clinical outcomes correlation, we focused on the most common mutations (>20%) in our cohort with a focus on those with available targeted therapies i.e. **FGFR3** and **ERBB2**.

3. **Results:**

3.1. **Baseline characteristics of patients**
Between June 2015 and September 2019, 43 patients with mBC were enrolled in an early phase trial (fig. 1). Table 1 summarizes the baseline characteristics of the patients. Consistent with the 3:1 male-dominant pattern of bladder cancer (22), 72% of patients were male, and 16% (7/43) had non-urothelial carcinoma histology (non-UC), specifically neuroendocrine carcinoma (n=2) and urachal carcinoma (n=5). Additionally, 13% (5/43) had UC with variant histology, specifically squamous cell (n=3) and micropapillary (n=2). 28% (12/43) of patients were enrolled in more than one trial leading to a total of 57 trial participations (TP) who initiated therapy (fig. 1). At time of therapy initiation, 97% (55/57) of TPs had received prior platinum therapy and 60% (34/57) had received prior CPI therapy. 65% (37/57) of patients had a glomerular filtration rate less than 60 mL/min.

3.2. Efficacy and survival analysis

Among the 57 TPs, median follow-up time was 17.9 months (95% CI 16.3 – NA), median PFS was 4.2 (95% CI 2.8 – 9.3) months, and median OS was 9.6 (95% CI 7.5 – 16.5) months (supplemental fig 1a, b). The mechanism of action for each individual trial is detailed in supplemental table 1 and 2. The overall response rate (ORR) was 17.5% in all TPs, 12% in dose escalation cohorts and 26% in dose expansion cohorts at the RP2D (p=0.11) (supplemental fig 1c, supplemental table 3). Survival was similar between both these cohorts (supplemental fig 1d, e). Across the UC cohort (n=48), median PFS was 4.3 months, median OS was 10.1 months, and the ORR was 19% compared to median PFS of 3.1, median OS of 9.6 months and ORR of 11% among the non-UC cohort (n=9).

3.3. Landscape of genomic alterations and the impact on efficacy and survival

Clinical NGS analysis was done in 95% (41/43) patients, which included cell-free DNA (cfDNA)-based NGS in 6 patients and tumor-based NGS in 35 patients (Fig 2a). 98% of sequenced patients (40/41) harbored at least one somatic alteration (Fig 2a); TP53, ERBB2,
PI3KCA, FGFR3 and ARID1A alterations (alt) were detected in 66%, 29%, 27%, 24%, and 22% of all patients, respectively (Fig 2f, Supplemental fig 3a, c). Variant and non-UC histologies clustered among the TP53 alt (Fig 2f, Supplemental fig 3b). Among the 12 patients harboring an ERBB2 alter, 34% (4/12) received an ERBB2-targeting therapy with 50% (2/4) achieving partial response (Fig 2b, e). Among the 14 patients who harbored FGFR alterations, 64% (9/14) received an FGFR-targeting therapy with 1 PR, 5 SD, 2 PD, and 1 non-evaluable for response due to withdrawal of consent (Fig 2c, d). The patients included in our analysis received a variety of investigational FGFR inhibitors other than the FDA approved agent, erdafitinib.

Patients with UC histology had 48 different TPs, which included 25 TPs in immunotherapy (IO) combinations and 21 in targeted therapy combinations (Fig 3a). Baseline clinical risk factors were fairly balanced between patients with UC who harbored a TP53 alt and those who did not (Supplemental Table 6); nonetheless, those who with TP53 alt had a shorter median PFS of 3.2 months compared to 9.6 months in TP53 no alt patients (HR=2.738 [1.247 - 6.011], p= 0.0121) (Fig 3b). Median OS was shorter in patients with TP53 alt at 5.9 months compared to TP53 no alt at 16.5 months (HR=1.518 [0.732 – 3.147], p=0.3) (Fig 3c). Lower ORR and disease control were noted among patients with TP53 alt in all trials (Fig 3d).

Conversely, median PFS was longer in patients harboring an FGFR alt, compared to those with no alt, 6.3 months vs 3.2 months (HR= 0.4662 [0.224 - 0.971], p= 0.0415) (Fig 3e). Median OS was longer in patients with FGFR alt at 16.5 months compared to FGFR no alt at 5.3 months (HR=0.54 [0.25 – 1.16], p=0.1) (Fig 3f). Disease control was higher among patients with FGR alt as compared to patients with FGFR no alt (Fig 3g). Among patients with FGFR alt (n=14), there was 20 total TPs due to 6 patients participating in more than 1 trial. PFS (HR=0.73 [0.23 – 2.29], p=0.6) and OS (HR=0.78 [0.25 – 2.42], p=0.7) were not precise enough to demonstrate a difference between TPs targeting FGFR (n=8) and those not targeting FGFR (n=12) (Supplemental fig 4a, b, supplemental table 4). Median PFS was 4.2 months in patients...
harboring an *ERBB2* alt, compared to those with *ERBB2* no alt at 3 months (HR = 1.308 [0.66 – 2.59], p = 0.4) (Fig 3h). No statistical difference was noted between OS of patients with an *ERBB2* alt, compared to those without, 16.1 and 9.36 months, respectively (Fig 3i).

### 3.4. Exploratory analyses

We observed that the response to early phase trials in non-UC histology, which constituted 16% of our TPs, was 11% (1/9) compared to 19% (9/48) in UC histology (Supplemental fig 2a, b). Median PFS (HR = 0.55 [0.26 – 1.17], p = 0.1) and OS (HR = 0.71 [0.31 – 1.64], p = 0.4) had a positive trend among UC as compared to non-UC histology; however, no statistically significant difference was found (Supplemental fig 2c, d). Among IO trials, there were no responses among patients with non-UC histology (Supplemental fig 2e). Furthermore, we analyzed the effect of prior IO therapy on response to IO trials and found that response rate was 28% (5/18) among IO-naïve patients as compared to 7% (1/15) among patient who had prior IO therapy, p = 0.11 (Supplemental fig 3a, supplemental table 5). Drug classes that achieved disease control in patients who had received prior IO include agents targeting CTLA4, CCR4, LXR, STAT3 and IDO1 (Supplemental fig 5a). Patients who had received prior IO tended to have worse PFS (HR = 1.55 [0.70 – 3.41], p = 0.3) and OS (HR = 1.47 [0.64 – 3.36], p = 0.4) on IO-based trials as compared to IO-naïve patients (Supplemental fig 5b, c).

We analyzed patients response to early phase trials based on their ethnicity and observed that patients with Hispanic ethnicity (N = 8) had no responses compared to 22% (10/46) among patients with non-Hispanic ethnicity (Supplemental fig 6a). Potential confounding factors were compared between the patients with Hispanic and non-Hispanic ethnicities (Supplemental fig 6b) and no significant differences were found. PFS was longer among non-Hispanic patients at 4.5 months as compared to 1.9 months in Hispanic patients (HR = 0.29, 95 CI 0.1252 - 0.7073, p = 0.006) (Supplemental fig 6c). OS had a favorable trend among patients of non-Hispanic ethnicity (HR = 0.51 [0.20 – 1.27], p = 0.2) (Supplemental fig 6d).
4. Discussion:

To our knowledge, this is the first study to specifically characterize the clinical and molecular features and outcomes of mBC patients who are referred to early phase clinical trials. We found potential benefits to enrolling in an early phase clinical trial with an ORR of 19%, PFS of 4.2 months, and median OS of 9.6 months in heavily pretreated patients whether in a dose escalation cohort or a dose expansion cohort. Furthermore, we noted that the baseline genomic profile of enrolled patients drove treatment choices and was associated with disease control rate and survival.

According to The Cancer Genome Atlas (TCGA), 48%, 14% and 12% of previously untreated muscle invasive BC harbor a TP53 alt, FGFR3 alt and ERBB2 alt, respectively (9). Of note, sequencing in our study was mostly performed on FFPE tissue from metastatic sites, which may explain the differences in alterations seen in our cohort (enriched for metastatic sites) as compared to the TCGA (enriched for primary tumor sites). Furthermore, we observed a higher rate of ERBB2 alt (29%) and FGFR3 alt (24%) as compared to TCGA, which could be explained by the referral bias of patients with potential targetable alterations to early phase targeted therapy trials.

In our study, we included 7 patients with rare histology variants i.e. neuroendocrine and urachal adenocarcinoma that did not have urothelial carcinoma in their tumor. Furthermore, the genomic/survival analyses were restricted to urothelial histology to avoid the heterogeneity of including other histologies. The first pivotal report to show that TP53 protein change (surrogate for TP53 alt) was predictive of worse outcome in patients with localized UC undergoing cystectomy was published by Esrig et al in 1994 (23). A meta-analysis performed 10 years later was inconclusive due to the lack of sufficient evidence (24). Our results support the association between TP53 alt and worse outcomes in metastatic UC (mUC). Conversely, FGFR alt (FGFR3 alt, in particular) has been correlated with a better survival in patients with invasive UC (25) and this is supported by our analysis in mUC. The improved PFS among FGFR alt patients could be
due to distinct disease biology (10) versus the availability of agents to target this alteration. Of note, majority of patients with mUC and FGFR alt (n=14) have received an FGFR-targeting agent in an early phase trial (n=9). On the other hand, only a minority of patients harboring an ERBB2 alt received an ERBB2-targeting agent (34%), perhaps explaining the lack of improved PFS among this cohort as compared to those with ERBB2 no alt.

Patients with mBC frequently present with multiple comorbidities including obstructive renal insufficiency (12) and this frequently results in their exclusion from early phase trials. We observed that 38% (26/69) of consented patients with mBC were not able to proceed with treatment due to a variety of reasons (Fig 1), which highlights the challenges in enrolling patients with mBC in early phase trials. The American Society of Clinical Oncology (ASCO) has recently recommended the ASCO-Friends eligibility criteria in clinical trials (26), which could enable nearly twice as many patients to participate in a trial (27). ASCO-Friends criteria could be considered for patients with mBC participating in early phase trials.

Next, we report patients’ clinical response to early phase trials in rare non-UC histology that do not currently have an approved agent by the Food and Drug Administration (FDA) after progression on frontline platinum-based chemotherapy. Our analysis showed that variant histologies enrich for TP53 alt, which could explain the trend toward worse outcomes in this cohort. Nonetheless, agents targeting ERK, CCR4, and PARP achieved disease control in few patients.

We did observe that patients with prior IO exposure had low responses to IO-based trials compared to patients who were IO-naïve. However, we did note, in a small sample, that agents targeting CTLA4, CCR4, LXR, STAT3, and IDO1 showed some early signs of clinical activity in the post-IO setting.

Additionally, we did observe that patients of Hispanic ethnicity had lower response rates and shorter PFS with a trend toward shorter OS. The clinical significance of this disparity finding is unclear given the small sample size and will need to be validated using larger cohorts.
Our study is limited by the small sample size, which reflects difficulties in referring patients with mBC to early phase trials. Furthermore, our patients were treated with agents utilizing diverse mechanisms of action i.e. immunotherapy vs targeted therapy; therefore, our findings need to be validated in a more expanded cohort of patients. In addition, among patients with FGFR-alt, treatment agents targeting FGFR had different molecular structure and spectrum of FGFR1-4 inhibition making the evaluated group heterogeneous. Nonetheless, the evaluated FGFR-targeting agents were consistently effective in providing disease control.

5. Conclusions:

Our study specifically characterized the outcomes of patients with mBC treated on early phase trials. We observed promising clinical activity with several novel immunotherapeutic and targeted therapy strategies. In particular, the responses noted with agents inhibiting FGFR and ERBB2 support the value of targeting these pathways in mBC. Furthermore, we observed that harboring a somatic TP53 alt after receiving standard of care platinum-based therapy is associated with low response and survival in early phase trials and remains an area of need for novel therapy strategies.

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Hahn ea. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma (UC). *ASCO Annual Meeting* 2017;Abstract #4525.


Table legend:
Table 1: Baseline Characteristics of patients. Key: C1D1: Cycle 1 Day 1, UC: urothelial carcinoma.

Figure legend:
Figure 1 Title: Study consort diagram
Figure 1 Legend: Abbreviations: C1D1 = cycle 1 day 1, FGFRi = FGFR inhibitor, MAPK = MAP kinase pathway, ERKi = ERK inhibitor, DDR = DNA damage repair pathway, PARPi = PARP inhibitor, HER2i = HER2 inhibitor, VEGFi = VEGF inhibitor, ERKi = ERK inhibitor, NOTCHi = NOTCH inhibitor, cMETi = cMET inhibitor, JAKi + PI3Ki = JAK inhibitor plus PI3K pathway inhibitor, XPO1i = XPO1 inhibitor, TORC1/2i = TORC1/2 inhibitor.

Figure 2 Title: Molecular profiling of urothelial carcinoma tumors based on clinical next-generation sequencing (NGS)
Figure 2 Legend: Panel A depicts a Consort diagram for type of NGS patients had performed and number of alterations detected. Panel B depicts the specific ERBB2 alteration by patient and their best response to treatment. Panel C depicts the specific FGFR alteration by patient and their best response to treatment. Panel D is a Lollipop plot depicting the location and frequency of genomic alterations along the FGFR3 gene. Panel E is a Lollipop plot depicting the location and frequency of genomic alterations along the ERBB2 gene. Panel F is an “Oncoplot” depicting the most common genomic alterations in our cohort, the type of alterations within that gene, and the associated histology.

Figure 3 Title: Impact of molecular profile on survival and response
Figure 3 Legend: Panel A is a flow diagram depicting the type of early phase trial patients received (immunotherapy or targeted therapy) and number of patients who had somatic next-
generation sequencing (NGS) performed. Panel B is a Kaplan-Meier curve depicting progression-free survival (PFS) by presence of a *TP53* alteration. Panel C is a Kaplan-Meier curve depicting overall survival (OS) by presence of a *TP53* alteration. Panel D depicts best objective response to treatment by whether that patient had a *TP53* alteration. Panel E is a Kaplan-Meier curve depicting PFS by presence of a *FGFR* alteration. Panel F is a Kaplan-Meier curve depicting overall survival OS by presence of a *FGFR* alteration. Panel G depicts best objective response to treatment by whether that patient had a *FGFR* alteration. Panel H is a Kaplan-Meier curve depicting progression-free survival (PFS) by presence of an *ERBB2* alteration. Panel I is a Kaplan-Meier curve depicting overall survival (OS) by presence of an *ERBB2* alteration.
Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(N=43)</th>
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<tr>
<td>Age at C1D1</td>
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<td>Interquartile range</td>
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<tr>
<td>Sex - no. (%)</td>
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</tr>
<tr>
<td>Male</td>
<td>31 (72%)</td>
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<tr>
<td>Female</td>
<td>12 (28%)</td>
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<tr>
<td>Histology (%)</td>
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<tr>
<td>UC with squamous cell carcinoma component</td>
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<tr>
<td>UC with micropapillary features</td>
<td>2 (4.5%)</td>
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<tr>
<td>Pure UC</td>
<td>31 (72%)</td>
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<tr>
<td>Urachal carcinoma</td>
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<td>Ethnicity (%)</td>
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<tr>
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<tr>
<td>White</td>
<td>36 (84.5%)</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Black</td>
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<td>Number of trial participations per patient</td>
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<td>1 trial</td>
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<td>3 trials</td>
<td>2 (4.5%)</td>
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Key: C1D1: Cycle 1 Day 1, UC: urothelial carcinoma.
69 patients with metastatic bladder carcinoma consented for phase I trial at MD Anderson Cancer Center June 1 2015 - September 30 2019

26 patients did not proceed to C1D1
- Didn’t meet inclusion criteria (n=23)
- Withdrew consent (n=2)
- Dropped out due to insurance issues (n=1)

43 patients with 57 trial participations (N=57)

Urothelial carcinoma - n=48 (84%)

- Immunotherapy* n=6 (66%)
- Targeted therapy* n=3 (34%)

- Non-urothelial carcinoma n=9 (16%)

Immunotherapy†* n=27 (56%)

Targeted therapy* n=21 (44%)

Genomically unmatched (n=6)
- NOTCHi (n=1)
- cMETi (n=1)
- JAKi + PI3K (n=2)
- XPO1i (n=1)
- TORC1/2 (n=1)

Genomically matched (n=15)
- FGFR (n=7)
- ERBB2 (n=5)
- DDR (n=1)
- VHL (n=1)
- BRAF (n=1)

FGFRi (n=1)

MAPK (n=1)

FGFRi (n=1)

ERKi (n=1)

PARPi (n=1)

DDR (n=1)

† including adoptive cellular therapy and immuno-targeted therapy combination trials
* Either alone or in combination with other strategies

Figure 1. Study consort diagram
Figure 2. Molecular profiling of urothelial carcinoma tumors based on clinical NGS

a Enrolled on early phase trial (n=43)

NGS not done (N=2)

Available NGS data (N=41)

Tumor-based (N=35) cfDNA-based-based (N=6)

98% harbored at least 1 somatic alteration

b ERBB2 alterations (n=12)

- ERBB2 gain
- ERBB2 amplification
- ERBB2 S310Y: Oncogenic
- ERBB2 S310F: Oncogenic. F864I: Unknown
- ERBB2 S310F: Oncogenic
- ERBB2 R678Q: Oncogenic
- ERBB2 G1201R and H843Y: Unknown
- ERBB2 I767M: Oncogenic
- ERBB2 S250C: Oncogenic

b FGFR alterations (n=14)

- FGFR1 ampl
- FGFR2 N549K: Oncogenic
- FGFR2 P477S: Unknown
- FGFR3 S249C: Oncogenic
- FGFR3 R248C: Oncogenic
- FGFR3 Y373C: Oncogenic
- FGFR3 G197S: Unknown + FGFR3 R750H: Unknown
- FGFR3 Q48*: Unknown + FGFR1 H164Y: Unknown
- FGFR4 R525Q: Unknown

E 5

Missense

- Missense Mutation
- Gain
- Intron
- Amplification

Histology
- Pure UC
- UC + micropapillary
- UC + squamous
- Urachal
- Neuroendocrine

Alteration Type
- Nonsense Mutation
- Frame Shift Ins
- Frame Shift Del
- In Frame Ins
- In Frame Del
- Nonstop Mutation
- Translation Start Site
- Splice Site
- Missense Mutation
- Introns
- Gain
- Amplification

# FGFR3 Mutations

- S249C
- L608V R750H
- R248C
- G197SQ48*

# ERBB2 Mutations

- Q48*
Figure 3. Impact of molecular profile on survival and response

a) mUC MDA trial participant

Phase I trial therapy
- Immunotherapy combination (n=25)
- Targeted therapy (n=21)

Survival and response evaluation (RECIST 1.1)

Analysis (n=46)

Clinical next-generation sequencing

(b) TP53
- TP53-alt=no
- TP53-alt=yes

(c) FGFR
- FGFR-alt=no
- FGFR-alt=yes

(d) TP53
- TP53 no alt
- TP53 alt

(e) FGFR
- FGFR no alt
- FGFR alt

(f) ERBB2
- ERBB2 no alt
- ERBB2 alt

Response rate to all trials

N=26
N=20

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### Trial participations based on histology (n=57)

- **70% Pure UC**
- **7% UC with micropapillary features**
- **7% UC with squamous features**
- **11% Urachal**
- **5% Neuroendocrine**

### mUC MDA trial participant

- **Phase I trial therapy**
  - Immunotherapy combination (n = 25)
  - Targeted therapy (n = 21)

### Survival and response evaluation (Recist 1.1)

- Analysis (n = 46)

### FGFR alterations (n = 14)

- **FGFR2**
  - ampl
  - N549K: Oncogenic
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  - Y373C: Oncogenic
  - G197S: Unknown
  - R750H: Unknown
  - Q48*: Unknown
  - H164Y: Unknown
  - R525Q: Unknown

### Clinical next-generation sequencing

- Tissue-based
- cfDNA-based

### Progression-free survival rate

- FGFR-alt=no
- FGFR-alt=yes
- TP53-alt=no
- TP53-alt=yes

- P = 0.037
- P = 0.0091
Molecular cancer research

Molecular profiling of metastatic bladder cancer early-phase clinical trial participants predicts patient outcomes

Omar Alhalabi, Andrew W Hahn, Pavlos Msaouel, et al.


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