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Molecular Profiling of Metastatic Bladder Cancer Early-Phase Clinical Trial Participants Predicts Patient Outcomes

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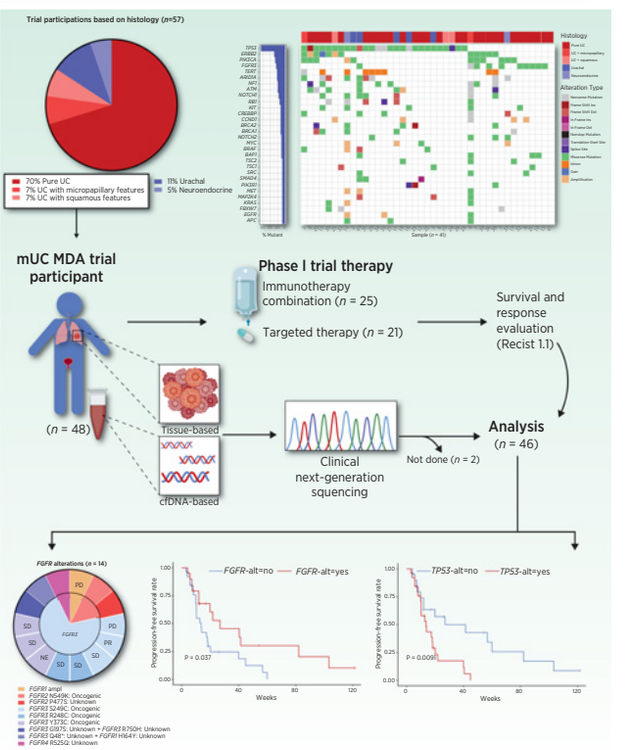
ABSTRACT

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 I trials of various investigational therapies. Patients' tumors or circulating tumor DNA were analyzed by next-generation sequencing. The median progression-free survival was 4.2 months, the 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 progression-free survival (PFS) compared with 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.

Visual Overview: http://mcr.aacrjournals.org/content/molcanres/19/3/395/F1.large.jpg.



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Introduction

Before 2019, patients with metastatic bladder cancer (mBC) had limited treatment options, which included cisplatin-based chemotherapy regimens, immune-checkpoint inhibitors (CPI), and single-agent chemotherapy. Up to 50% of patients with mBC are ineligible for cisplatin-based chemotherapy regimens due to medical comorbidities (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 *FGFR2 or FGFR3* alterations, which are estimated to represent in approximately 15% to 20% of patients with mBC (11). Erdafitinib had a response rate of 40%, and the median progression-free survival (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 comorbidities, 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 II 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 I 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.

Materials and Methods

Patients

Baseline characteristics and clinical outcomes were retrospectively collected for patients with mBC who were enrolled on one or more phase I 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 50–400 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 I clinical trials were also approved by the MDACC IRB, and patients provided informed written consent to prior to receiving treatment.

Endpoints

Endpoints of interest included response rate (RR), disease control rate (DCR), 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, overall response rate (ORR) was based on each individual trial response evaluation, and PFS was calculated from C1D1 of each trial.

Statistical analysis

Survival curves were generated using the Kaplan–Meier approach. The 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.

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 biological 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*.

Results

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 nonurothelial 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 ($n = 2$). Twenty-eight percent (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. Sixty-five percent (37/57) of patients had a glomerular filtration rate less than 60 mL/min.

Efficacy and survival analysis

Among the 57 TPs, the 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,

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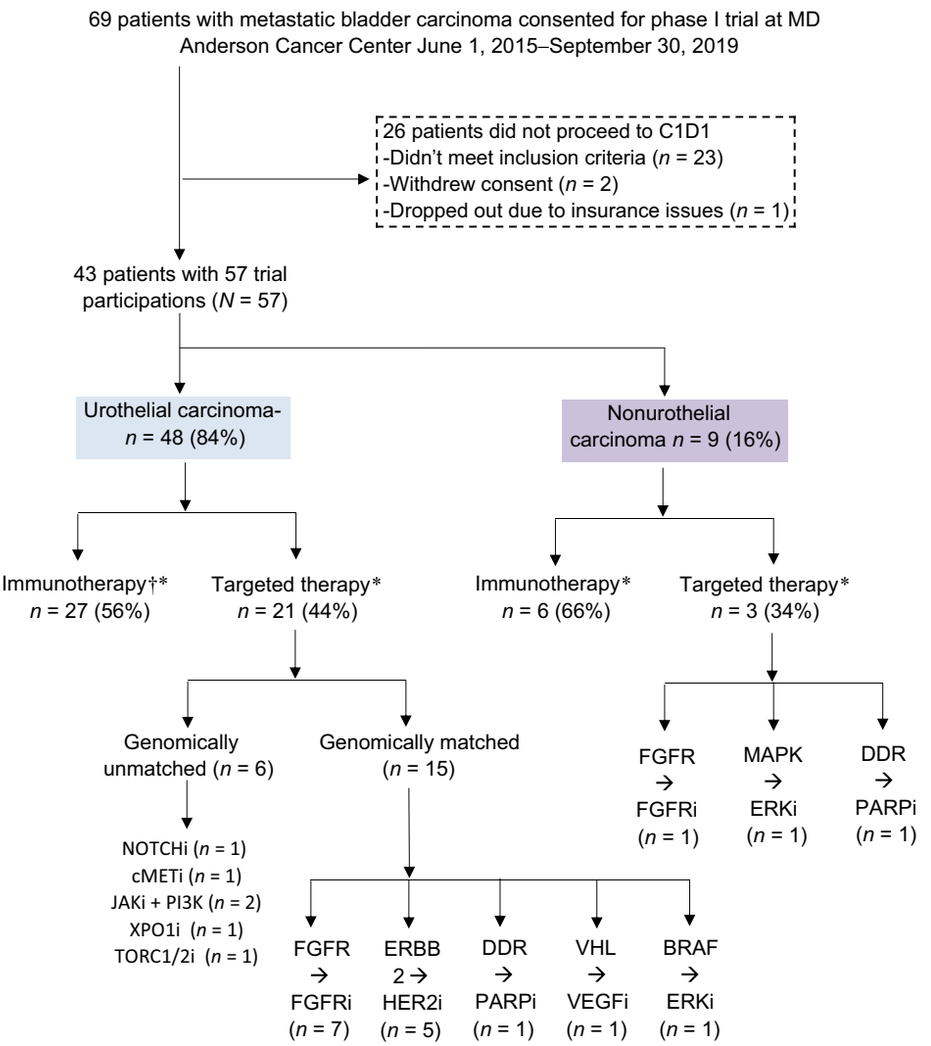

Figure 1.

Study consort diagram. 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 + PI3K = JAK inhibitor plus PI3K pathway inhibitor, XPO1i = XPO1 inhibitor, TORC1/2i = TORC1/2 inhibitor.

and median OS was 9.6 (95% CI, 7.5–16.5) months (Supplementary Fig. S1A and S1B). The mechanism of action for each individual trial is detailed in Supplementary Tables S1 and S2. The ORR was 17.5% in all TPs, 12% in dose-escalation cohorts and 26% in dose-expansion cohorts at the RP2D ($P = 0.11$; Supplementary Fig. S1C; Supplementary Table S3). Survival was similar between both these cohorts (Supplementary Fig. S1D and S1E). Across the UC cohort ($n = 48$), the median PFS was 4.3 months, median OS was 10.1 months, and the ORR was 19% compared with median PFS of 3.1, median OS of 9.6 months and ORR of 11% among the non-UC cohort ($n = 9$).

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**). Ninety-eight percent 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**; Supplementary Fig. S3A and S3C). Variant and non-UC histologies clustered among the *TP53* alt (**Fig. 2F**; Supplementary Fig. S3B). Among the 12 patients harboring an *ERBB2* alteration, 34% (4/12) received an *ERBB2*-targeting therapy with 50% (2/4) achieving PR (**Fig. 2B** and **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 nonevaluable for response due to withdrawal of consent (**Fig. 2C** and **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 (Supplementary Table S6); nonetheless, those who

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Table 1. Baseline characteristics of patients.

Characteristics	(*N* = 43)
Age at C1D1	
Median	64
Range	25–82
Interquartile range	56–71
Sex, *n* (%)	
Male	31 (72%)
Female	12 (28%)
Histology (%)	
UC with squamous cell carcinoma component	3 (7%)
UC with micropapillary features	2 (4.5%)
Pure UC	31 (72%)
Urachal carcinoma	5 (12%)
Neuroendocrine carcinoma	2 (4.5%)
Ethnicity (%)	
Hispanic	5 (12%)
Non-Hispanic	37 (86%)
Unknown	1 (2%)
Race (%)	
White	36 (84.5%)
Asian	2 (4.5%)
Black	1 (2%)
Other	2 (4.5%)
Unknown	2 (4.5%)
Number of trial participations per patient	
1 trial	31 (72%)
2 trials	10 (23.5%)
3 trials	2 (4.5%)

Abbreviations: C1D1: cycle 1 day 1; UC: urothelial carcinoma.

with *TP53* alt had a shorter median PFS of 3.2 months compared with 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 with *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 with those with no alt, 6.3 months versus 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 with *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 with 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 ($n = 12$; Supplementary Fig. S4A and S4B; Supplementary Table S4). The median PFS was 4.2 months in patients harboring an *ERBB2* alt, compared with 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 with those without, 16.1, and 9.36 months, respectively (**Fig. 3I**).

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 with 19% (9/48) in UC histology (Supplementary Fig. S2A and S2B). The 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 with non-UC histology; however, no statistically significant difference was found (Supplementary Fig. S2C and S2D). Among IO trials, there were no responses among patients with non-UC histology (Supplementary Fig. S2E). Furthermore, we analyzed the effect of prior IO therapy on response to IO trials and found that RR was 28% (5/18) among IO-naïve patients as compared with 7% (1/15) among patient who had prior IO therapy, $P = 0.11$ (Supplementary Fig. S3A; Supplementary Table S5). Drug classes that achieved disease control in patients who had received prior IO include agents targeting CTLA4, CCR4, LXR, STAT3, and IDO1 (Supplementary Fig. S5A). 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 with IO-naïve patients (Supplementary Fig. S5B and S5C).

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 with 22% (10/46) among patients with non-Hispanic ethnicity (Supplementary Fig. S6A). Potential confounding factors were compared between the patients with Hispanic and non-Hispanic ethnicities (Supplementary Fig. S6B) and no significant differences were found. PFS was longer among non-Hispanic patients at 4.5 months as compared with 1.9 months in Hispanic patients (HR = 0.29, 95 CI, 0.1252–0.7073, $P = 0.006$; Supplementary Fig. S6C). OS had a favorable trend among patients of non-Hispanic ethnicity [HR = 0.51 (0.20–1.27), $P = 0.2$; Supplementary Fig. S6D).

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 DCR and survival.

According to The Cancer Genome Atlas (TCGA), 48%, 14%, and 12% of previously untreated muscle-invasive bladder cancer 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 with the TCGA (enriched for primary tumor sites). Furthermore, we observed a higher rate of *ERBB2* alt (29%) and *FGFR3* alt (24%) as compared with 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 and colleagues 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

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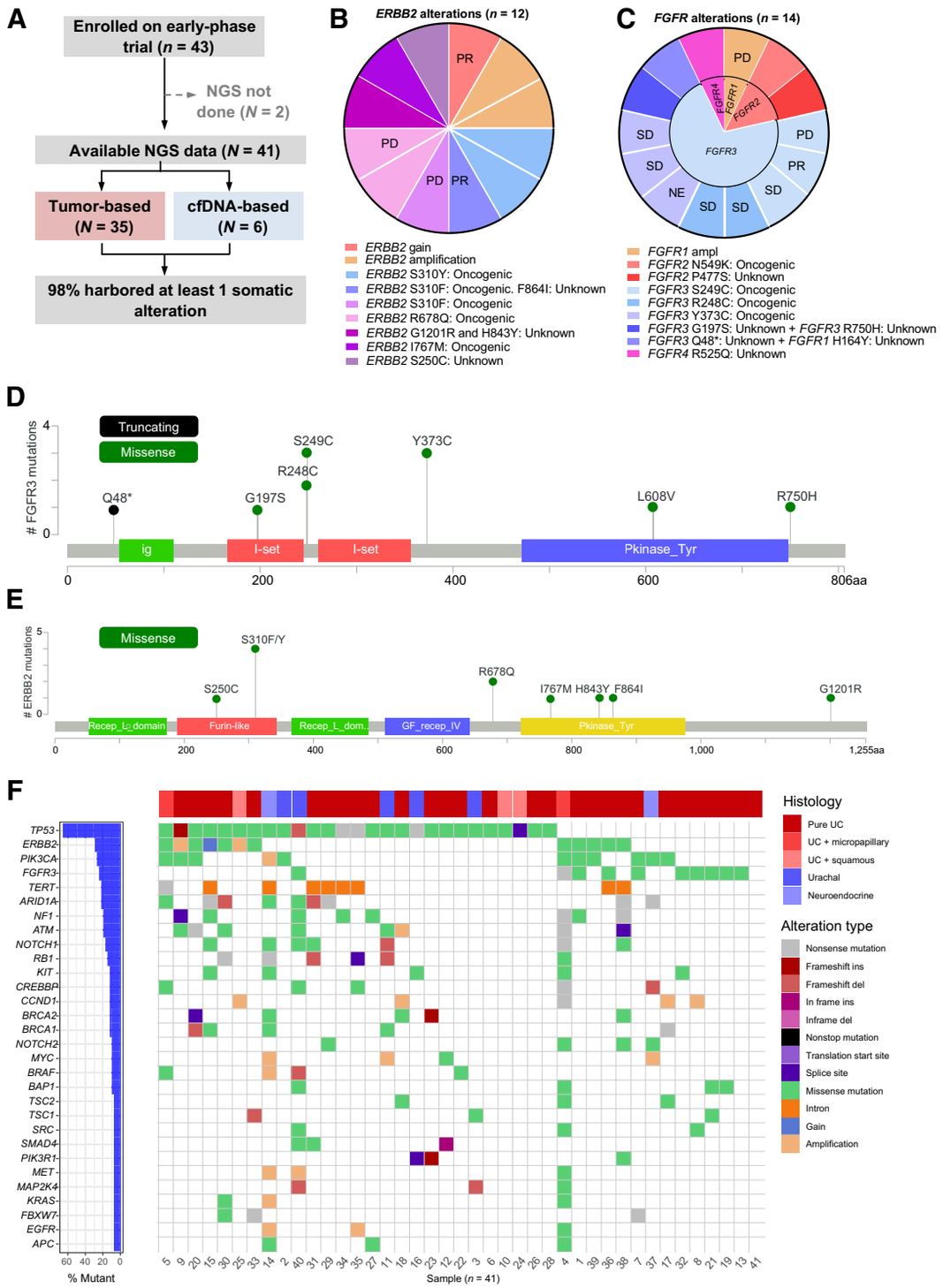

Figure 2.

Molecular profiling of urothelial carcinoma tumors based on clinical NGS. **A,** A consort diagram for type of NGS patients had performed and number of alterations detected. **B,** Specific *ERBB2* alteration by patient and their best response to treatment. **C,** Specific *FGFR* alteration by patient and their best response to treatment. **D,** Lollipop plot depicting the location and frequency of genomic alterations along the *FGFR3* gene. **E,** Lollipop plot depicting the location and frequency of genomic alterations along the *ERBB2* gene. **F,** An "Oncoplot" depicting the most common genomic alterations in our cohort, the type of alterations within that gene, and the associated histology.

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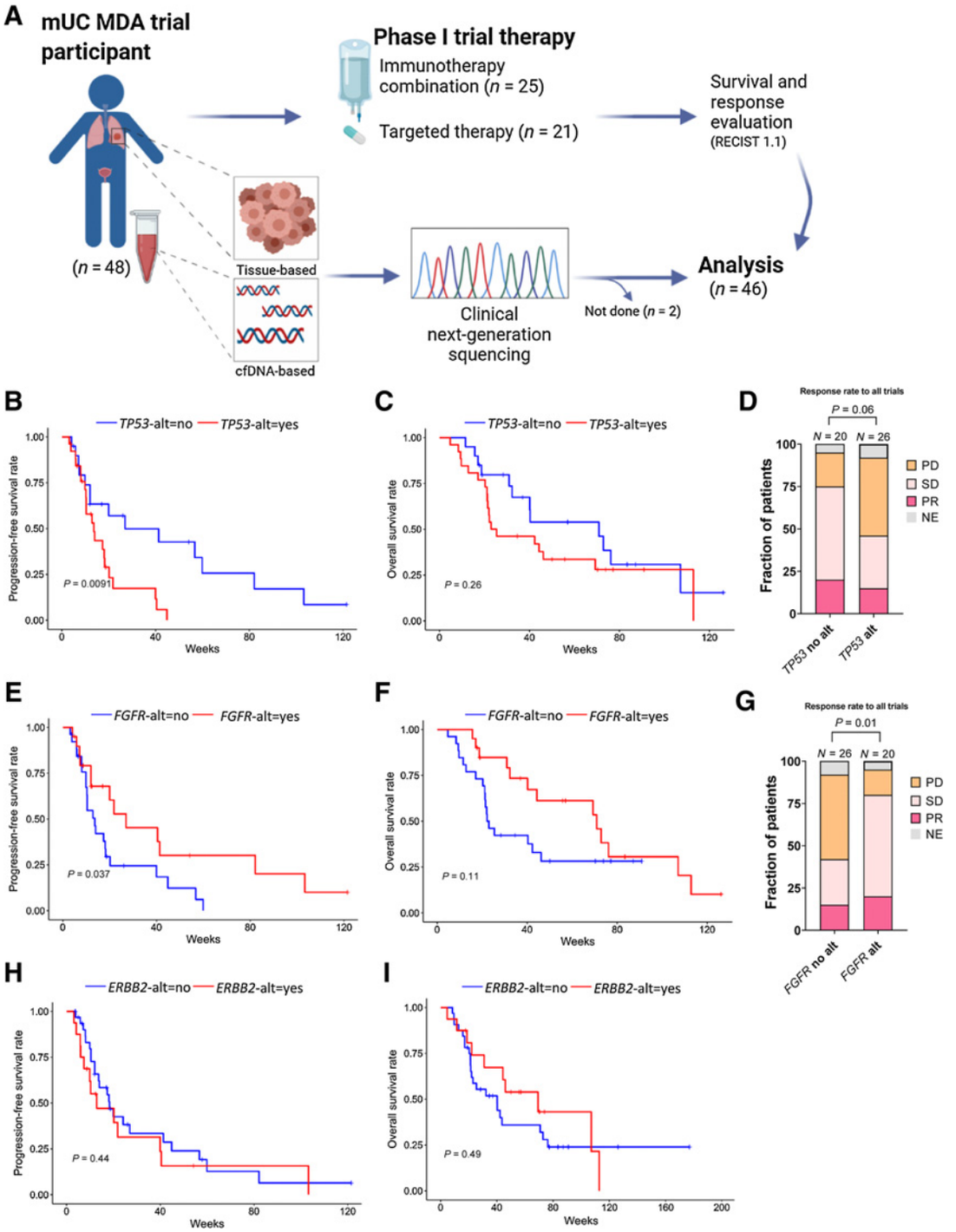

Figure 3.

Impact of molecular profile on survival and response. **A,** Flow diagram depicting the type of early-phase trial patients received (immunotherapy or targeted therapy) and number of patients who had somatic NGS performed. **B,** Kaplan–Meier curve depicting PFS by presence of a *TP53* alteration. **C,** Kaplan–Meier curve depicting OS by presence of a *TP53* alteration. **D,** Best objective response to treatment by whether that patient had a *TP53* alteration. **E,** Kaplan–Meier curve depicting PFS by presence of an *FGFR* alteration. **F,** Kaplan–Meier curve depicting OS by presence of an *FGFR* alteration. **G,** Best objective response to treatment by whether that patient had an *FGFR* alteration. **H,** Kaplan–Meier curve depicting PFS by presence of an *ERBB2* alteration. **I,** Kaplan–Meier curve depicting OS by presence of an *ERBB2* alteration.

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due to distinct disease biology (10) versus the availability of agents to target this alteration. Of note, a 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 with 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 FDA after progression on first-line 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 observed that patients with prior IO exposure had low responses to IO-based trials compared with patients who were IO naïve. However, we noted, 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 observed 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 versus 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.

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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