Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and Other DNA Damage Response Pathway-Deficient Neoplasms

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ABSTRACT

PURPOSE BRCA1-associated protein 1 (BAP1) is a critical cell cycle and DNA damage response (DDR) regulator with mutations (mBAP1) causing a functional protein loss. PARP inhibitors (PARPis) demonstrate synthetic lethality in mBAP1 preclinical models, independent of underlying BRCA status. This study aimed to explore the clinical activity of niraparib in patients with advanced tumors likely to harbor mBAP1.

METHODS This was a phase II multicenter trial in which refractory solid tumor patients were assigned to cohort A (histology-specific tumors likely to harbor mBAP1) or cohort B (histology-agnostic tumors with other known non–BRCA-confirmed DDR mutations). All patients received niraparib 300 mg orally once daily on a 28-day cycle. The primary end point was objective response rate, and secondary end points included progression-free survival (PFS) and overall survival.

RESULTS From August 2018 through December 2021, 37 patients were enrolled with 31 evaluable for response (cohort A, n = 18; cohort B, n = 13). In cohort A, the best response was one partial response (PR; 6%), eight stable disease (SD; 44%), and nine progressive disease (PD; 50%). This cohort stopped at the first stage following the prespecified Simon's design. mBAP1 was confirmed in 7/9 patients (78%) with PR or SD but in only 3/9 (33%) in those with PD. The median PFS in patients with mBAP1 (n = 10) was 6.7 months (95% CI, 1.0 to 9.2) versus 1.8 months (95% CI, 0.9 to 4.5) for wild-type (n = 8; $P = .020$). In cohort B, the best response was six SD (46%) and seven PD (54%), with SD in those with *ATM*, *CHEK2*, *PTEN*, *RAD50*, and *ARID1A* mutations.

CONCLUSION Niraparib failed to meet the prespecified efficacy end point for response. However, clinical benefit was suggested in a proportion of patients who had a confirmed mBAP1, supporting further investigation.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

BRCA1-associated protein 1 (BAP1) exerts tumor suppressor effects through regulation of cell cycle, cellular differentiation, cell death, and DNA damage responses (DDRs).[1-4] *BAP1* is located on chromosome 3p21.1, a genomic region frequently deleted in human malignancies such as mesotheliomas, uveal melanoma, lung cancers (small cell and non–small cell), and renal cell carcinomas.[5-10] In addition to this loss of heterozygosity, there are several inactivating mutations affecting the BAP1 protein deubiquitinating catalytic site or, in some cases, epigenetic silencing of the BAP1 gene. Thus, mutated BAP1 (mBAP1) leads to a loss of functional protein in several solid tumors, including uveal melanoma (47%), intrahepatic cholangiocarcinoma (26%), mesothelioma (23%), and clear cell renal carcinoma (15%).[5,10]

Poly (ADP-ribose) polymerases (PARP-1 and PARP-2) are nuclear proteins that are essential for DNA repair processes. The inhibition of PARP prevents single-strand DNA break repair and, in the presence of homologous repair deficiency (HRD), enhances cell death. The development of PARP inhibitors (PARPis) in clinical practice has demonstrated positive clinical efficacy, particularly in those who harbor BRCA1/BRCA2 mutations or HRD.[11,12] PARPis demonstrate synthetic lethality in mBAP1 preclinical models, independent of underlying BRCA status.[13] We postulated that PARP

CONTEXT

Key Objective
Do advanced tumors that are enriched with somatic BAP1 loss-of-function mutations derive clinical benefit from inhibition with the PARP inhibitor (PARPi) niraparib?

Knowledge Generated
Niraparib monotherapy did not demonstrate significant radiographic responses in the cohort of all patients, but in those who had a confirmed BAP1 mutation, there appeared to be some evidence of temporary disease stabilization. There were no new toxicity concerns with use.

Relevance
This study adds to the general body of knowledge about the role of BAP1 mutations as a potential biomarker for PARPi sensitivity. However, PARPi monotherapy should not be used for such patients at this time.

inhibition would result in significant cytoreduction in tumors that lack functional BAP1, as well as other DDR pathway mutations.

Niraparib, a potent inhibitor of PARP-1 and PARP-2, is US Food and Drug Administration (FDA)–approved for the maintenance treatment of adult patients with advanced epithelial, ovarian, fallopian tube, or primary peritoneal cancer.[14] Here, we report the results of the signal-seeking phase II UF-ETI-001 study (ClinicalTrials.gov identifier: NCT03207347) evaluating clinical response and toxicity of niraparib in two specific biologic populations: (1) malignancies known to potentially harbor mBAP1 (ie, cholangiocarcinoma, uveal melanoma, mesothelioma, or clear cell renal cell carcinoma) and (2) malignancies with known somatic gene mutations involved in DDR.

METHODS

Study Design

The UF-ETI-001 trial was an open-label, phase II, prospective, investigator-initiated, multicenter institution trial that included two biologically distinct cohorts. Eligible patients were age 18 years and older with measurable (as defined by RECIST v.1.1) incurable and histologically confirmed cancer.[15] Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1, acceptable organ function, and formalin-fixed paraffin-embedded tissue available for research purposes. Selected exclusion criteria included previous treatment with a PARPi, known BRCA1 or BRCA2 mutation, prostate cancer diagnosis, and history of myelodysplastic syndrome or AML. The study was conducted in accordance with general ethical principles outlined in the declaration of Helsinki and was approved by the University of Florida institutional review board. All patients participated voluntarily and provided written informed consent.

Cohorts

Eligible patients for study participation were enrolled in either cohort A or cohort B. Patients in cohort A must have had a confirmed diagnosis of one of the following: uveal melanoma, mesothelioma, renal cell carcinoma (clear cell subtype), or cholangiocarcinoma. Cohort B enrollment was histology-agnostic, but tumors must have had a prespecified DNA DDR repair somatic mutation including any one of the following: *ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK) PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN*, or *XRCC*. Only Clinical Laboratory Improvement Amendments–certified next-generation sequencing (NGS) assays were acceptable. Variants of unknown significance were allowed to enroll on study after discussion with the study PI.

End Points and Assessments

The primary end point was objective response rate (ORR) for patients in cohort A defined as the proportion of patients with a confirmed partial response (PR) or complete response (CR) per RECIST version 1.1 as their best radiographic response. Secondary end points included clinical benefit rate (CR + PR + stable disease [SD]), progression-free survival (PFS) at 3 and 6 months, and overall survival (OS). Exploratory end points included outcomes relative to confirmation/mechanism of BAP1 loss, other DDR pathway dysfunction (cohort B), and other biomarkers that might predict response to PARPi.

Radiologic assessment was performed at baseline and every 8 weeks after treatment initiation by either computed tomography or MRI. Toxicity assessments occurred at baseline, days 1 and 15 of the first cycle, and day 1 of each subsequent 28-day cycle. All serious and unexpected adverse events (AEs) were collected, including those thought to be associated with protocol-specified procedures. Collection of

all AEs was continued for 90 days after the last administration of niraparib (or to a minimum of 30 days after treatment if patient initiated alternate anticancer therapy).

Statistical Considerations

For cohort A, a Simon's optimal two-stage design was used. The null hypothesis was an ORR of 10%. The null hypothesis was tested against a one-sided alternative. In the first stage, 18 patients were planned for accrual. If ≤two responses were identified in these 18 patients, the study was stopped. Otherwise, 17 additional patients were planned for a total sample size of 35 for cohort A. The null hypothesis was rejected if ≥seven responses were observed in these 35 patients. This design yields a type I error rate of 0.05 and power of 90% when the true ORR is 30%.

The sample size for cohort B was based on an estimated increase in the ORR from 10% (the null) to 50% (alternative) in this molecularly selected/enriched patient population. Power and one-sided α were set at 90% and 5%, respectively. Considering a 20% dropout rate, a total of 12 patients were planned for accrual to cohort B. Thus, a total sample size of 47 patients was planned inclusive of both cohorts A and B.

All patients enrolled who received at least one dose of study drug were evaluable for toxicity. Patients were considered evaluable for the primary efficacy end point if they successfully enrolled, received at least one dose of study drug, were followed for at least 28 days, and had radiographic determination via RECIST at the end of treatment. The binary primary and secondary end points and their 95% CIs were estimated on the basis of the exact binomial distribution for each cohort. The secondary time-to-event data were estimated using the Kaplan-Meier method along with the log-rank test.

RESULTS

Patient Population

Between August 2018 and December 2021, 37 patients were enrolled and received at least one dose of study drug (cohort A, n = 23; cohort B, n = 14), with 31 patients evaluable for the primary response end point (cohort A, n = 18; cohort B, n = 13; Fig 1). Demographics for all enrolled patients are listed in Table 1. The median age was 67 years for cohort A and 65 years for cohort B. Most patients identified their race as White, while two patients (5%) identified as Black or African American and one patient (3%) identified as Asian. Ten patients (37%) had an ECOG PS of 0, and 27 (73%) had an ECOG PS of 1. In total, 70% of patients had received two or more previous regimens, while 24% had received three or more previous regimens. Fifty-eight percent (18/31) of evaluable patients had previous platinum exposure. A complete list of all patient histologies and available NGS (tissue) results are listed in Appendix Tables A1 and A2.

Efficacy and Molecular Profiling

In cohort A, the confirmed ORR was 6% (95% CI, 0.1 to 27.3) in those evaluable for the primary response end point. Specifically, one PR (6%) and eight SD (44%) were observed. The one PR was a patient with mesothelioma harboring a mBAP1. All 18 evaluable patients in this cohort had adequate archival tissue for analysis and 10 (56%) had a confirmed mBAP1. mBAP1 was present in 7/9 patients (78%) with PR or SD but in only 3/9 (33%) in those with PD. The ORR efficacy analysis of individual patients in cohort A is shown in Figure 2. Ten patients had received a previous platinum in cohort A, with responses for those who had received previous platinum being one PR, two SD, and seven PD. Of note, several patients in cohort A with PD (67%) had progression defined only by the development of new nontarget lesions despite documented stability in their baseline measurable tumor burden. Regardless, further enrollment to this cohort was stopped at the first stage following the prespecified Simon's design because of an insufficient response signal to continue to full enrollment.

In cohort B, there was no CR or PR observed. The best confirmed response was SD in six of 13 patients (46%). Somatic mutations in those patients with SD included ATM, CHEK2, PTEN, RAD50, and ARID1A. In cohort B, responses for those who had received previous platinum were four SD and four PD.

Survival

In the evaluable cohort A patients, the median PFS was 2 months (95% CI, 1.7 to 5.6) and OS was 11.2 months (95% CI, 3.5 to 17.2; Figs 3 and 4). The PFS rate at 3 months was 44% (95% CI, 22 to 65) and at 6 months was 28% (95% CI, 10 to 49; Fig 3A). The OS rate at 6 months was 76% (95% CI, 49 to 90) and at 12 months was 41% (95% CI, 19 to 63; Fig 4A). Notably, the median PFS of patients with mBAP1 (n = 10) in cohort A was 6.7 months (95% CI, 1.0 to 9.2) versus 1.8 months (95% CI, 0.9 to 4.5) for wild-type (n = 8; $P = .02$; Fig 3B). A nonsignificant trend in OS was noted between mBAP1 and WT-BAP1 patients in cohort A (Fig 4B).

In cohort B, the median PFS was 3.3 months (95% CI, 1.8 to 7.3) and OS was 8.2 months (95% CI, 3.6 to 15.5). The PFS rate at 3 and 6 months was 54% (95% CI, 25 to 76) and 31% (95% CI, 9.5 to 55), respectively. The OS rate at 6 and 12 months was 69% (95% CI, 37 to 87) and 46% (95% CI, 19 to 70), respectively (Figs 3 and 4).

Safety

All 37 enrolled patients received at least one dose of niraparib and were evaluable for toxicity. The relative dose intensity for all patients was >90%. No new safety concerns were identified with the use of this previously FDA-approved therapy in these investigational patient populations. A summary of the most common treatment-related AE with

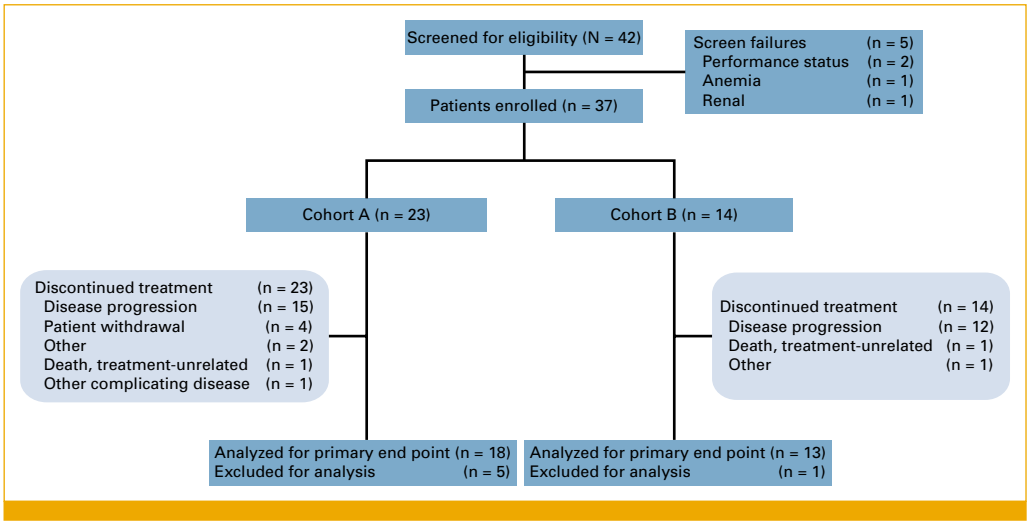

FIG 1. CONSORT diagram. Cohort A included patients with histologic diagnosis of mesothelioma, uveal melanoma, renal cell carcinoma, or cholangiocarcinoma. Cohort B included patients with confirmed histologic diagnosis of malignancy and known somatic mutation of component of DNA damage repair pathway. Both cohorts received niraparib 300 mg orally once daily on each day of the 28-day cycle. If patients' baseline body weight <77 kg or baseline platelet count <150,000 μL, niraparib 200 mg/d orally once daily was administered.

both cohorts combined is presented in Table 2. There were no unexpected or grade 5 toxicities. These adverse events were managed with treatment interruptions and other supportive interventions. Eight patients required dose reductions of niraparib because of toxicities (cohort A n = 5; cohort B n = 3). These dose reductions occurred for hematologic (n = 5) and nonhematologic (n = 3) AEs. One patient (cohort B) was withdrawn from treatment because of inability to comply with protocol requirements. There was no concern for enhanced AE rates in patients who harbored a mBAP.

TABLE 1. Baseline Demographic Characteristics

Characteristic	Cohort A (n = 23)	Cohort B (n = 14)
Age, years, median (range)	67 (39-86)	65 (33-73)
Sex, No. (%)		
Male	13 (57)	1 (7)
Female	10 (43)	13 (93)
Race, No. (%)		
White	21 (92)	13 (93)
Black or African American	1 (4)	1 (7)
Asian	1 (4)	0
Ethnicity, No. (%)		
Non-Hispanic	23 (100)	14 (100)
ECOG PS, No. (%)		
0	7 (30)	3 (21)
1	16 (70)	11 (79)
Previous therapies, No. (%)		
0-1	6 (26)	5 (36)
2	13 (57)	4 (28)
≥3	4 (17)	5 (36)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

DISCUSSION

In this study, we report the antitumor activity of niraparib in two distinct patient cohorts with advanced cancers: (1) cancer types known to be enriched with mBAP1 and (2) histology-agnostic malignancies with prespecified DNA DDR repair somatic mutations. Treatment with niraparib at the FDA-approved doses was manageable with adverse events consistent with previous studies and no new safety signals identified.[16-18] A synopsis of published reports suggesting PARPi activity in mBAP populations of patients is provided in Table 3. These mutations are typically associated with more aggressive disease and in some reports are considered a negative prognostic factor. In uveal melanoma, BAP1 mutations are associated with spread beyond the eye and a worse prognosis.[24] Similarly, published data in cholangiocarcinoma and renal cell carcinoma suggest BAP1 mutations are associated with aggressive disease and short survival.[25,26] However, BAP1 germline mutations in malignant mesothelioma (MM) may be associated with a more favorable prognosis and higher sensitivity to chemotherapy.[27,28]

Niraparib failed to meet a prespecified efficacy end point with limited objective radiographic antitumor activity observed in either cohort (ORR: 6% cohort A; 0% cohort B). The only radiographic responder was a patient with peritoneal mesothelioma harboring a BAP1p.R150fs variant. This patient was platinum-sensitive and had progressed through

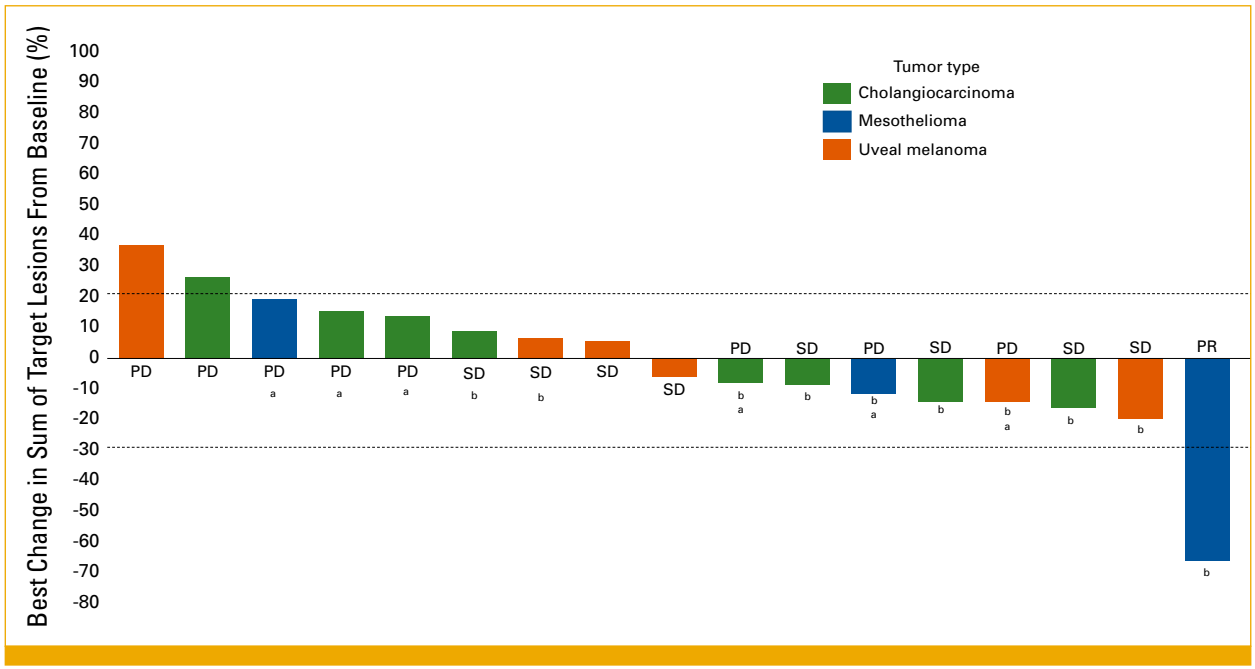

FIG 2. Waterfall plot of cohort A patients showing best tumor responses (n = 17). One patient with cholangiocarcinoma (BAP-negative) with multiple new progressive lesions not shown above. [a]Patients had overall PD with <20% increase in target lesions but had new nontarget lesions. [b]BAP1 mutation. PD, progressive disease; PR, partial response; SD, stable disease.

two lines of therapy before entering this trial. After four cycles of niraparib, the patient withdrew from the trial due to adverse events (G2 confusion, G3 tremor). Two months later, the patient received carboplatin and pemetrexed for one cycle, but it was discontinued shortly thereafter because of worsening peritoneal disease.

A phase II study that evaluated olaparib in MM reported results on eight patients with somatic mBAP1. Best responses also included PR (n = 1, peritoneal), SD (n = 5, pleural and peritoneal), and PD (n = 2, peritoneal).[19] The patient who achieved a PR in that study also had a MRE11A germline mutation, which is notable, given synthetic lethality reported between MRE11 and PARPi.[29] Dudnick et al[21] reported no responses on four other patients who received PARPi in mBAP1 malignant pleural mesothelioma. In our patient who achieved a PR, they also harbored a SETD2 somatic mutation. SETD2 mutations are present in approximately 5%-15% of mesotheliomas.[30-32] Given the role of SETD2 in homologous recombination DNA repair,[33] this could provide some rationale in the favorable radiographic response of niraparib in this particular patient with peritoneal mesothelioma.

Our attempt to explore whether other DNA DDR pathway deficiencies could also benefit from PARPi was conducted in cohort B, which demonstrated no objective responses. It should be noted that this was a very heterogeneous population of both tumor types and molecular subsets. Additionally, since the time that this study activated, additional scientific knowledge suggests that the list of mutations that are suggested to confer PARPi sensitivity should likely be refined.[34] That said, there continues to be robust evaluation of PARPi activity in phase II basket trials targeting specific genomic alterations beyond BRCA and PALB2. A cohort in the ASCO TAPUR trial investigated olaparib in solid tumor patients with ATM mutations or deletions met its primary end point of disease control (DC). DC and objective response were observed in 27% and 8% of patients, respectively. One patient with prostate cancer achieved a CR with an ATM mutation and BRCA1 M1775R comutation.[35] Promising data with PARPi in patients with metastatic castration-resistant prostate cancer (mCRPC) containing specific HRD alterations continue to emerge.[16,36-38] In the GALAHAD study, niraparib was evaluated in mCRPC with BRCA1/2, ATM, FANCA, PALB2, CHEK2, BRIP1, and HDAC2 mutations. The ORR in the BRCA cohort was 34.2%, compared with 10.6% in the non-BRCA cohort.[16] In our study, somatic mutations in cohort B patients achieving SD included ATM, CHEK2, PTEN, RAD50, and ARID1A. Given our modest antitumor activity identified in this cohort, combination strategies with other targeted therapies, immune checkpoint inhibitors, chemotherapy, or radiotherapy might prove more effective. Indeed, numerous combination studies are ongoing with opportunities to better understand molecular mechanisms and biomarkers of PARPi response.

Several of our patients demonstrated SD with a clinical benefit rate of 78% in patients whose tumors harbored mBAP1, suggesting that synthetic lethality per se may not be

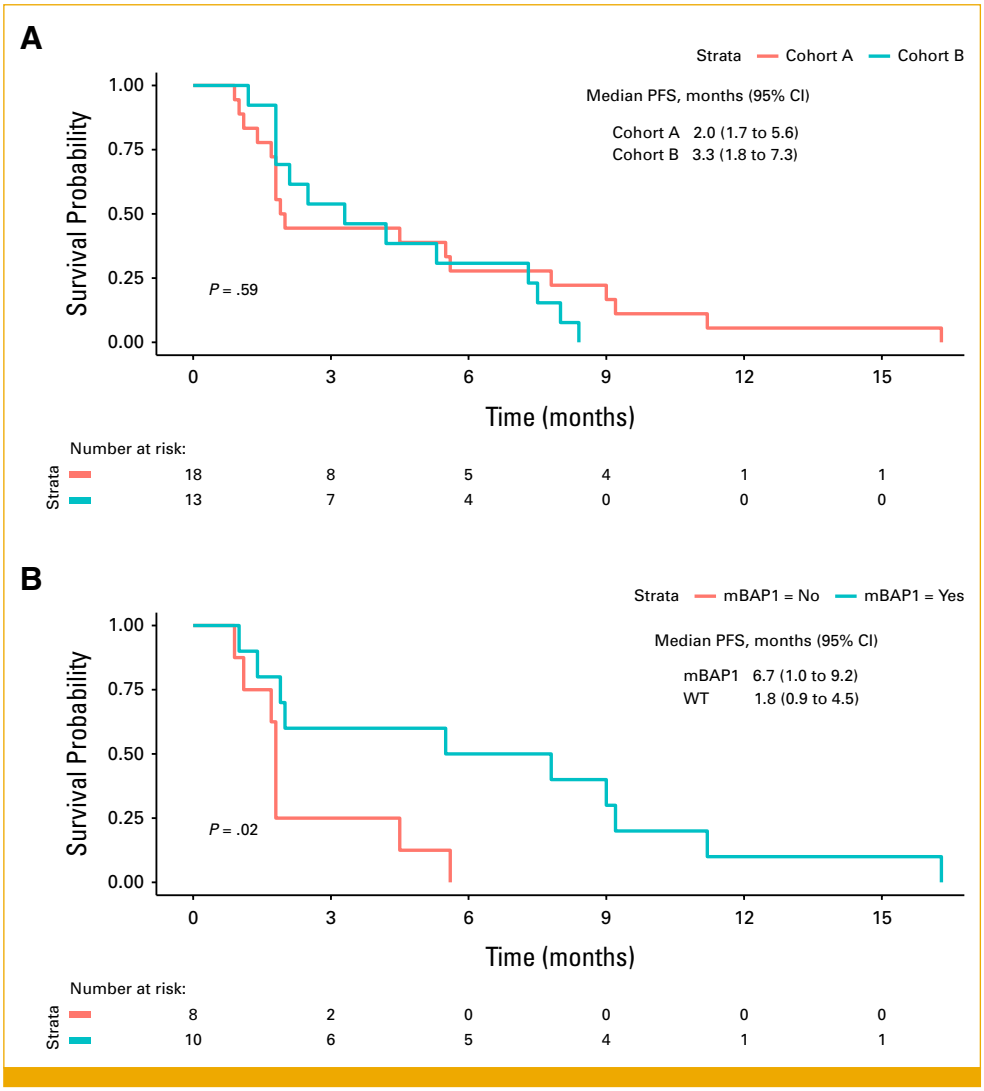

FIG 3. (A) Kaplan-Meier PFS curves for cohorts A and B. (B) PFS by BAP1 status for cohort A. 95% CIs are indicated in parentheses. PFS, progression-free survival; WT, wild-type.

demonstrated, but biologic activity is present. Even in several of our patients with documented PD, it was the development of new metastases in the setting of stable radiographic target lesions that suggests the potential for clonal evolution. In another single-center, open-label, phase II trial, rucaparib 600 mg orally twice daily provided a 12-week DC rate of 58% (95% CI, 37 to 77) in metastatic mesothelioma.[39] Our median and landmark OS results suggest there might be a subset of patients who are deriving some clinical benefit in this late-line study of advanced disease. However, it is unclear whether this association is a result of the intervention, the underlying biology of the cancer, or other variables that we cannot account for in this study design. That said, an ongoing study in heavily pretreated patients with mBAP1 metastatic renal cell carcinoma suggests that the incorporation of DC into the primary end point could augment the demonstration of promising clinical activity.[40]

Despite our study being a prospective multicenter study that enrolled rapidly, our study is not without limitations or weaknesses. Cohort A enrolled histologies enriched for mBAP1 rather than just restricting enrollment to just those with confirmed mBAP1, thus potentially diluting the impact of the effect size. At the time this study activated, NGS for several of the histologies eligible was not routinely performed and testing was thus completed after study closure. However, given that we saw a higher proportion of patients with clinical benefit (PR and SD) harboring a mBAP1 tumor, a larger sample size restricted to just confirmed mBAP1 tumors might have demonstrated a better signal. Published reports of patients who harbor mBAP achieving a PR are limited.[20,22,23] However, other studies cited above call that assumption into question. In other malignancies that are PARPi-sensitive, biomarkers that extend beyond the binary presence or absence of single somatic DNA alterations are proving to be predictive (eg, HRD), thus genomic composite

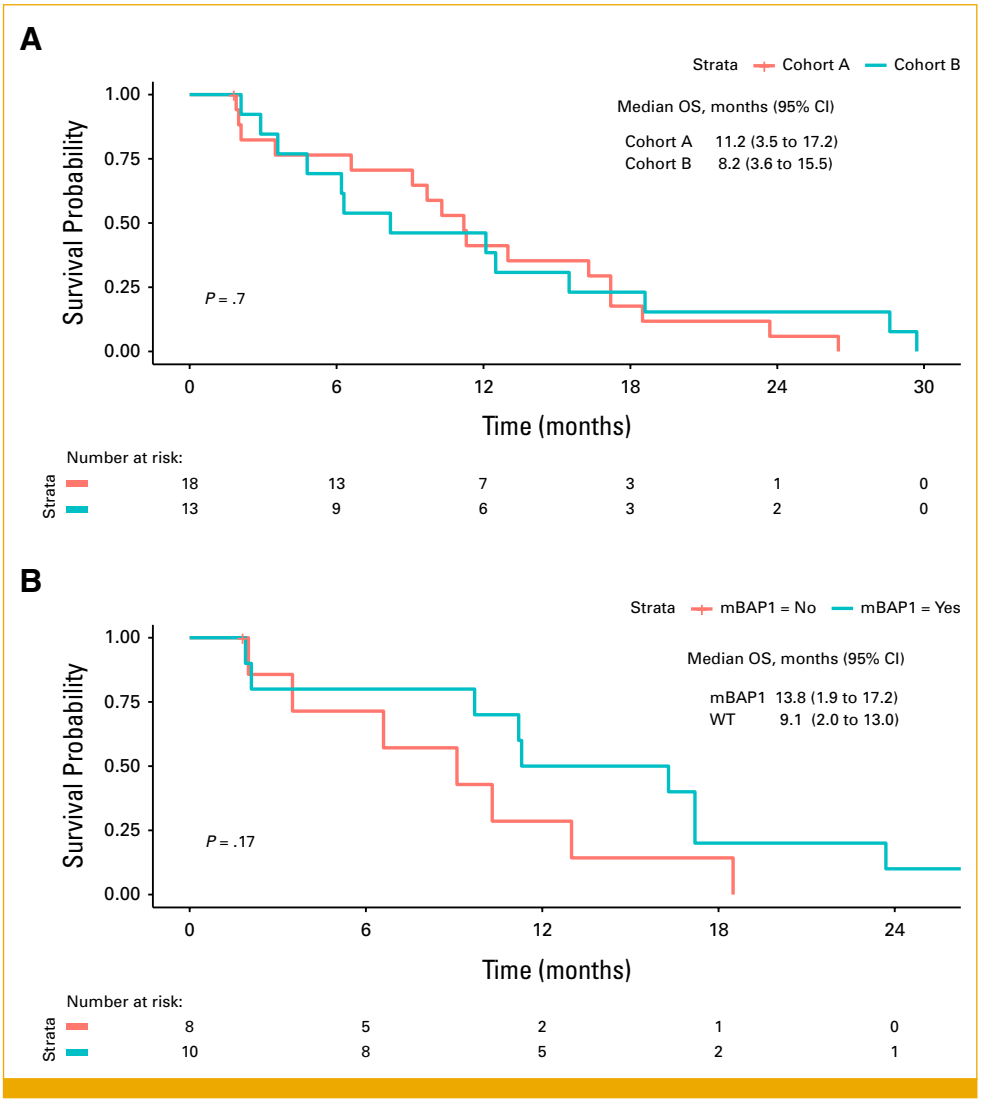

FIG 4. (A) Kaplan-Meier OS curves for cohorts A and B. (B) OS by BAP1 status for cohort A. 95% CIs are indicated in parentheses. OS, overall survival; WT, wild-type.

TABLE 2. Summary of Study-Associated Adverse Events (n = 37)

Toxicity	Grades 1-2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Nonhematologic (most common)			
Fatigue	25 (68)	3 (8)	0
Nausea	22 (59)	3 (8)	0
Anorexia	16 (43)	0	0
Constipation	14 (38)	1 (3)	0
ALP increase	6 (16)	1 (3)	0
ALT increase	3 (8)	1 (3)	0
Hematologic			
Anemia	6 (16)	6 (16)	0
Thrombocytopenia	5 (14)	3 (8)	4 (11)
Neutropenia[a]	2 (5)	1 (3)	0

NOTE. There were no grade 5 toxicities in this study.
[a]No reported cases of febrile neutropenia were observed.

TABLE 3. Clinical Investigations of PARPis in mBAP1 Tumors

Study	Study Population	Participants (No.)	Treatment Regimen	Efficacy	Reference
Phase II	MM	23	Olaparib 300 mg orally twice a day, every 21 days	ORR: 4% (one PR, 18 SD, four PD) Median PFS 3.6 months (95% CI, 2.7 to 4.2) median OS 8.7 months (95% CI, 4.7 to NE) Median OS 4.6 months *v* 9.6 months (germline mBAP1 *v* no germline mutation); *P* = .0040	Ghafoor et al[19]
Phase II (UNITO-001)	PM and NSCLC	17 (mBAP1 n = 13)	Niraparib 300 mg orally once daily + dostarlimab 500 mg intravenously once every 21 days × four doses, 1,000 mg intravenously once every 42 days	ORR, 6% (95% CI, 0.1 to 28.7) in all study patients. One PR in an NSCLC patient with BRCA2 somatic mutation Median PFS in the cohort of somatic mBAP1: 2.9 months (95% CI, 2.7 to NA) One patient with a germline mBAP1 had SD for 14.1 months	Passiglia et al[20]
Case series	MM	45 (n = 4 mBAP treated with PARPi)	Olaparib 300 mg orally twice a day or carboplatin AUC 2 intravenously once per week + olaparib 300 mg or veliparib 200 mg orally twice a day	OR: 0% One patient achieved SD for 3.4+ months mPFS was 1.8 months (95% CI, 1.8 to NR)	Dudnik et al[21]
Case report	ccRCC	1 (BAP1 frameshift mutation)	Niraparib 200 mg orally once daily	Patient experienced PR in both lungs after 2 months of therapy New metastatic lesions emerged after 5 months of therapy	Lian et al[22]
Case report	ICC	1 (mBAP1 and RAD21 amp)	Olaparib 800 mg orally once daily	Patient continued olaparib for 11 cycles with positive response OS from time of ICC diagnosis was 37.2 months	Sabbatino et al[23]

Abbreviations: ccRCC, clear cell renal cell carcinoma; ICC, intrahepatic cholangiocarcinoma; mBAP1, BAP1 mutation; MM, malignant mesothelioma; mPFS, median progression-free survival; NA, not available; NE, not evaluable; NR, not reported; NSCLC, non–small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PARPi, PARP inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PM, pleural mesothelioma; SD, stable disease.

or functional biomarker assays may outperform our approach to look at single mutations. Our study enrolled a relatively heavily pretreated patient population, which may have masked the ability for monotherapy PARPi to induce synthetic lethality or led to the development of additional mechanisms of resistance unaccounted for in the archival NGS. Finally, our study has not yet analyzed germline DDR mutations, or biallelic versus monoallelic loss of somatic mBAP1 that may be associated with clinical benefit or resistance synonymous to what we now know about some BRCA mutations.[41,42]

In conclusion, our results suggest that niraparib monotherapy may provide some disease stability in a proportion of tumors that harbor mBAP1 or other select mutations involving DNA DDR pathways, but there is otherwise limited antitumor activity as measured by radiographic response. These findings suggest that ongoing studies evaluating PARPis in combination with immune checkpoint inhibitors, chemotherapy, or other novel targeted therapies to enhance tumor response are reasonable, with results are eagerly awaited.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Molecular Profiles of Cohort A

Patient ID	Malignancy	BAP1 Mutation (Yes/No)	Other Variants	TMB (mut/Mb)	MSI Status
1-001	Cholangiocarcinoma	Yes BAP E198fs*45	PBRM1 E991	4	MSS
1-007	Mesothelioma	Yes BAP1 (splice site 1729 + 1G > C, Y418)	PTEN Q171 mutation, TP53 mutation (R249S)	4	MSS
1-009	Melanoma	Yes BAP1 W202	GNA11 Q209L	1	MSS
1-010	Cholangiocarcinoma	No	IDH1 R132S, PIK3CA E545K, ARID1A F1738fs*3	7	MSS
1-011	Cholangiocarcinoma	No	CDKN2A loss, CDKN2B loss, CHEK2 T367fs*15; CTNNB1 545P; SMAD4 P470fs*6; STK11 R333fs*28	3	MSS
1-014	Mesothelioma	Yes BAP1, variant of unknown significance. Alteration: Exon 2: c.67+4_67+65del62	GNA11 (mutated, pathogenic. Exon 5: p.Q209L)	4	MSS
1-015	Mesothelioma	Yes BAP1 frameshift insertion—S325Afs*75, BAP1 splicing mutation X13_splice (c.38-1G>A)	CDKN2Ap14ARF loss, CDKN2B loss	3	MSS
1-016	Cholangiocarcinoma	Yes BAP1 (exon 13, p.S455fs)	IDH1 exon 4, p.R132C, ARID1A, CHEK2 and RAD50	7	MSS
1-026	Cholangiocarcinoma	Insufficient tissue	Insufficient tissue	NA	NA
1-029	Cholangiocarcinoma	No	ATM S2394L; FGFR2 GRSF1, FGFR2 fusion (G1;F18); PBRM1 splice site 3432_3458+85del112	0	MSS
1-030	Cholangiocarcinoma	No	ATM G2891D-subclonal, BRAF V600E PIK3CA E542K-subclonal, PIK3CA H1047R, TET2 Y620-subclonal, U2AF1 S34F-subclonal VUS: MAF A105_E111del, MYC rearrangement	1	MSS
1-031	Melanoma	Yes BAP1 p.P302fs Frameshift-LOF	GNA11 p.Q209L missense variant-GOF VUS: MLH1 c.2162A>G p.Y721C missense variant, EPHB1 c.1480G>T p.D494Y missense variant, BARD1 c.1360C>G p.P454A missense variant, KIF1B c.3026G>T p.G1009V variant, ARIDIB c.1041_1043dup p.A348dup inframe insertion	4.2	MSS
1-032	Melanoma	Yes BAP1 K26_G26del	GNAQ Q209P, IDH1 R132H subclonal, ASXL1 E635fs*15 subclonal, PBRM1 Y558fs*12 VUS: NTRK1 P494T, ROS1 V979A	1	MSS
1-033	Cholangiocarcinoma	No	ARID1A p.P867fs frameshift-LOF, ERBB3 p.V104L missense variant-GOF, TP53-p.T125M splice region variant-LOF, ATM c.5497-2A>C splice region variant-LOF, MSH2 p.D91fs Frameshift-LOF VUS: NFE2L2 c.1300C>T p.P434S missense variant NM_006164	2.1	MSS

(continued on following page)

TABLE A1. Molecular Profiles of Cohort A (continued)

Patient ID	Malignancy	BAP1 Mutation (Yes/No)	Other Variants	TMB (mut/Mb)	MSI Status
1-034	Melanoma	Yes BAP1 p.Q267Hfs*4	GNA11 p.Q209L, MYC amplification (chr8: g.128748839_128753204(4)) copies: 4 (low level) VUS: APC p.S2242G c.6724A>G chr5: g112178015A>G, ERBB2 p.S281A c.841T>G chr17:g.37866674T>G	NA	NA
1-035	Cholangiocarcinoma	Yes BAP1 Q322	CCND1 amplification, FGF19 amplification, PBRM1 1873fs*2 VUS: BCORL1 K1123E, CARD11 L769P, KDM5A R1467W, NTRK1 R6W, RAF1 S228C	1	MSS
2-001	Cholangiocarcinoma	No	KRAS G12D (c.35G>A), TP53 splicing mutation X126_splice (c.378-10_384del), KDM6A splicing mutation Q443R (c.132BA>G), KMT2C missense mutation E4532K (c.13591G>A), TGFBR1 missense mutation D104Y (c.31CG>T) VUS: FBXW7 T15_G16insP, FGFR1 R507C, PARP2 R15K, SPEN G2022S	4.4	MSS
2-002	Melanoma	No	None	NA	NA
2-003	Melanoma	No	VUS: POLE: c.691C>T (p.Arg231Cys), WT1: c.600C>G (silent)	NA	NA
2-004	Peritoneal Mesothelioma	Yes BAP1 p.R150fs	SETD2 p.P211fs	4	MSS
2-005	Cholangiocarcinoma	Yes—BAP1 splice site deletion	TET2 S1107Ter (c. 3320C>G)	NA	NA
2-006	Cholangiocarcinoma	No	NF2 and TERT promoter, PDGFRA	8	MSS
2-007	Cholangiocarcinoma	No	NRAS G12C, IDH1 R132C	1	MSS

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable; mut/MB, mutations per megabase; NA, not available; TMB, tumor mutational burden; VUS, variants of unknown significance.

TABLE A2. Molecular Profiles of Cohort B

Patient ID	Malignancy	Somatic Mutation(s) for Study Enrollment	Other Variants	TMB (mut/Mb)	MSI Status
1-002	Ovarian	PTEN R130G, T319fs*24 ARID1A K327fs*33	KRAS G12D BCORL1 F376fs*44—subclonal CHD4 Y1144fs*1 CTCF E179* VUS-TRX H493R, CHD4 Y988_1989>F, ERBB4 E973K, KDM6A D530V, MLL3 S1724I, PIK3R1 G376V	8	MSS
1-004	Ampullary carcinoma	RAD50 M1I	ERBB2 D769Y CTNNB1 S45P ACVR1B M1I ARID2 S417 TP53 Y220D VUS: ABL1 E197K, AKT1 E441L, ARID1B E1743K, BCL6 R459C, CDK12, V463M, CSF1R V32G, EP300 S106G, KDM5A H857R, MPL Q219E, MSH6, R1068Q, SLIT2 G715R, TSC1 H732Y, ZNF703 S583L	7	NA
1-005	Breast	PTEN C136fs*44, T319fs*1 VUS-BAP1 M687I	CDKN2A/B loss FUS FUS-DDIT3 fusion (variant 1) PIK3CA E545A VUS: FLCN P298L, MLL2 R2847H, NTRK2 S167Y, ZNF703 P203F	2	MSS
1-008	Pancreatic	BAP1 splice site 256-9_272del26 VUS-BAP1 N89Y, ATM I2606V	CDKN2A/B loss NRAS Q61R VUS: ABL2 amp, AKT3 amp, CDC73 amp, DDR2 amp, FH amp, H3F3A amp, IKBKE amp, MDM4 amp MYCN P237L, PIK3C2B amp, SDHC amp, SPTA1 R1081L, TSC2 A415V	1	MSS
1-017	Malignant peripheral nerve sheath	BLM V826L VUS	CDKN2A/B loss VUS: FANCA T306M, GATA2 P161A MDM4 rearrangement, MTOR Q2499R NF1 R1325K, SDHA R352Q	0	MSS
1-018	Uterine	ARID1A A821fs*43, F2141fs*59 PTEN Q298*	GNA13 R334C KRAS K117N MSH3 splice site 2253 + 2T>G PIK3RT N564D VUS: BRD4 P903R, CREBBP S237N,DAXX K637Q, MED12 K1610_N1615del PIK3C2B C340fs*3	5	MSS
1-019	Breast	CHEK2 K235fs*3	CCNE1 amp CD274 (PD-L1) amp CDK12 S582* CUL4A amp FANCC E539K IRS2 amp JAK2 amp KRAS amp LYN amp MCL1 amp NOTCH1 S2467fs*10 PDCD1LG2 (PD-L2) amp RAD21 amp SETD2 S2199fs*49 TP53 L308fs*35; R337C VUS: ABL1 W405C, ALK R1530S BCORL1 G1170E, CEBPA amp, CTCF S276C, DDR2 amp, ERBB2 P523S ERBB4 D948N, FANCA D944A, GATA6 M4721, HRAS R169W, HSD3B1 R279H, IKZF1 R515C, JAK2 A440V, KDM6A S878T, MLL2 S1346T, MSH6 A25S MST1R P392A, NOTCH3 C360F PIK3C2B A1182T; amp, PTPRO amp ROS1 S300F, SDHC amp	18	MSS
1-020	Appendiceal	RAD51C loss	CDKN2A/B p16INK4a R58* and p14ARF P72L NF1 Q2531* TP53 R175H VUS: APC L2039F, CARD11 R1104W, CTNNA1 V386L, KEAP1 R536C MED12 Q2119_Q2120insHQQQ, NOTCH3 P359S, RICTOR W548C TGFBR2 V387M	4	MSS
1-021	Gallbladder	BAP1 E9*, BAP1 T613fs*30	CDKN2A/B loss ERBB3 A232V FANCA R764fs*29 MTAP loss VUS: BRD4 amp, CBL H42_L43insH, ERG M219I, FANCC Q465R MSH3 I507L and R669W TNFRSF14 H200Y	4	MSS
1-023	Pancreatic	ATM P1759fs	None	NA	MSS

(continued on following page)

TABLE A2. Molecular Profiles of Cohort B (continued)

Patient ID	Malignancy	Somatic Mutation(s) for Study Enrollment	Other Variants	TMB (mut/Mb)	MSI Status
1-024	Bladder	ATM H2872Q—subclonal CHEK2 CHEK2(NM_007194)-TTC2B(NM_001145418) fusion (C8; T2)	FGF23 R198W TP53 loss exons 5-6 VUS: BRCA2 K1180R, CASP8 M1 CREBBP S302N, EED T50P, FGFR4 R394G, MAP3K1 L62R MCL1 rearrangement MED12 Q2119_Q2120insHQQQ MSH3 A60_A62del, PDGFRB V316M PIK3C2G A823T, SMARCA4 G1162V	4	MSS
1-025	Chondrosarcoma	IDH2 R172S	CDKN2A/B CDKN2A loss; rearrangement VUS KMT2C (MLL3) Y306* TP53 C135F, H214fs*33—subclonal VUS: EPHA7 N361K, ESR1 H6Y, GATA2 P41A, JAK3 R925S, MYO18A R1372Q, MYST3 R1086C, PCLO D1866E, SDHA V461F, TCF3 A463V	2	MSS
1-027	Non–small cell lung cancer	BRIP1 Y748*	KEAP1 V155F KRAS G12V TP53 R213L VUS: DOT1L S997L, HGF P465H MKNK1 R93Q, MST1R R75S NOTCH3 R1546C, PDGFRB D111E TET2 P174H	NA	NA
1-028	Cervical	PTEN loss exons 6-9, R130Q	PIK3CA R108H AURKA amp ARFRP1 amp BCL2L2 amp—equivocal GNAS amp, R201H ZNF217 amp VUS: AR A403V, ASXL1 amp, BCL2L1 amp, CDKN2C amp, EPHA5, V742A MAP3K1 A671V, MLL E156del PTCH1 H73, TOP1 amp	3	MSS

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable; mut/MB, mutations per megabase; NA, not available; TMB, tumor mutational burden; VUS, variants of unknown significance.