

Pamiparib plus surufatinib with ctDNA monitoring in platinum-resistant ovarian cancer after PARP inhibitor progression: A phase Ib/II trial (POST-PARPi)

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Research Article

Keywords:

Posted Date: March 24th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9056248/v1>

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Additional Declarations: Competing interest reported. Chuqiao Liang, Dongqin Zhu, and Lingling Yang are employees of Nanjing Geneseeq Technology Inc. All other authors declare no competing interests.

Version of Record: A version of this preprint was published at BMC Medicine on August 17th, 2026. See the published version at <https://doi.org/10.1186/s12916-026-05122-1>.

Abstract

Background

PARP inhibitors (PARPi) are standard front-line maintenance therapy for advanced ovarian cancer, but the efficacy of PARPi retreatment in later lines remains unclear. This phase Ib/II study evaluated the combination of pamiparib (a PARPi) and surufatinib (a small-molecule tyrosine kinase inhibitor) in platinum-resistant ovarian cancer patients who have progressed on or after prior PARPi treatment.

Methods

Eligible patients with platinum-resistant ovarian cancer and progression on or after prior PARPi treatment were enrolled. In phase Ib, a 3 + 3 design determined the recommended phase 2 dose (RP2D) of surufatinib in combination with pamiparib (40 mg twice daily). Surufatinib was administered starting at 250 mg once daily, with dose de-escalation if needed. After determining the RP2D, phase II enrollment commenced to assess antitumor activity. The primary endpoints were to establish the RP2D of surufatinib (phase Ib) and the 6-month progression-free survival (PFS) rate (phase II). Tumor tissue sequencing, homologous recombination deficiency (HRD) testing, and dynamic circulating tumor DNA (ctDNA) analysis were also performed.

Results

A total of 29 patients were enrolled. The RP2D of surufatinib was established at 250 mg once daily, with no dose-limiting toxicities (DLTs). As of the data cut-off (June 20, 2024), the median follow-up was 7.3 (range, 1.0–18.1) months. Two patients remained on treatment, while 27 had discontinued. The 6-month PFS rate was 46.7% (95% CI: 24.4–66.2), and the median overall survival was 14.7 (95% CI: 9.9–NE) months. The objective response rate was 8% in the efficacy evaluable set. Grade 3/4 treatment-related adverse events occurred in 37.9%, with thrombocytopenia (20.7%), and anemia (17.2%) being the most common. No significant difference in PFS was found between BRCA-mutant and wild-type patients, or HRD-positive and HRD-negative tumors. At cycle 7, day 1 (C7D1), ctDNA concentrations were significantly higher in patients who progressed within 6 months ($P = 0.05$). Patients with ctDNA partial response (CPR) at C3D1 and C7D1 had significantly longer PFS ($P = 0.05$ and $P = 0.01$, respectively).

Conclusions

The combination of pamiparib and surufatinib demonstrated modest yet clinically meaningful antitumor activity with manageable toxicities in platinum-resistant ovarian cancer patients who had progressed on or after prior PARPi treatment. CtDNA may serve as a valuable biomarker for predicting treatment outcomes, warranting further validation in larger studies.

Introduction

Ovarian cancer ranks as the second leading cause of gynecologic cancer-related death worldwide, with an estimated 207,252 deaths in 2020 [1]. Approximately 70% of patients with ovarian cancer are diagnosed at advanced stages. Front-line treatment typically includes debulking surgery followed by platinum-base chemotherapy. However, most patients experience relapse within the initial three years after diagnosis [2]. In recent years, poly (ADP-Ribose) polymerase inhibitors (PARPi) have significantly transformed the treatment landscape of ovarian cancer. Pivotal phase III trials, including SOLO-1 [3], PRIMA [4], VELIA [5], and ATHENA-MONO [6], have demonstrated that PARPi used as first-line maintenance therapy dramatically improves median progression-free survival (PFS), particularly in patients with BRCA-mutated or homologous recombination-deficiency (HRD)-positive tumors. Notable, long-term data from the SOLO-1 trial confirmed a survival benefit, with 7-year overall survival (OS) reinforcing the efficacy of olaparib in BRCA-mutated ovarian cancer. Additionally, the PAOLA-1 trial showed that the combination of olaparib and bevacizumab as maintenance therapy in newly diagnosed advanced ovarian cancer significantly improved 5-year OS rates in HRD-positive patients compared to bevacizumab plus placebo [7]. As a results, PARPi has now been approved as front-line maintenance therapy for a broad population of patients with advanced ovarian cancer.

Despite the promising outcomes, most patients ultimately develop resistance to PARPi and require treatment for recurrent disease. This raises the question of whether PARPi retreatment could be effective in later lines of therapy, which is a situation that many patients will encounter as PARPi becomes widely used in front-line settings.

For recurrent ovarian cancer, nearly all patients eventually develop resistance to platinum-based therapies. The sequential use of single-agent non-platinum is considered the standard approach for platinum-resistant relapse; however, response rates remain low (10%–20%) and progression-free intervals are typically short (3–4 months) [8–10]. Thus, there is an unmet need for more effective therapies.

Recently, mirvetuximab soravtansine-gynx (MIRV), an antibody-drug conjugate (ADC) targeting folate receptor α (FR α), has altered the treatment landscape for platinum-resistant ovarian cancer. The phase III MIRASOL trial compared the efficacy and safety of MIRV with the investigator's choice of single-agent chemotherapy in patients with platinum-resistant, FR α -positive high-grade serous ovarian cancer [11]. MIRV demonstrated a significant improvement in both PFS (median, 5.62 versus [vs.] 3.98 months, $P < 0.001$) and OS (median, 16.46 vs. 12.75 months; $P = 0.005$) compared with chemotherapy. However, the clinical benefit was restricted to patients with FR α positive, defined as $\geq 75\%$ of cells with $\geq 2+$ staining intensity.

Another promising strategy is anti-angiogenic therapy, which has shown efficacy in platinum-resistant ovarian cancer. Surufatinib (formerly sulfatinib), a small-molecule tyrosine kinase inhibitor (TKI), selectively targets vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, fibroblast growth factor receptor-1 (FGFR-1) and colony-stimulating factor-1 receptor (CSF-1R) [12–14]. Preclinical studies

suggest that anti-angiogenic agents may induce hypoxia, which contributes to genomic instability by inhibiting DNA repair [15]. This provides a strong rationale for combining PARPi with anti-angiogenic agents to achieve synergistic therapeutic effects.

Pamiparib, a potent and selective PARP1/2 inhibitor, exhibits strong PARP-DNA complex trapping, anti-tumor activity, and good brain penetration [16]. In a phase II study, pamiparib demonstrated an objective response rate (ORR) of 64.6% in platinum-sensitive ovarian cancer (n = 90) and 31.6% in platinum-resistant cases (n = 23) harboring germline *BRCA1/2* mutations, with durable responses (median duration of response [DOR] of 14.5 months and 11.1 months, respectively) [17]. These results led to the approval of pamiparib for the treatment of platinum-resistant ovarian cancer patients with BRCA mutations, making it the first PARPi approved for this patient population in China.

Given these findings, we hypothesized that combining pamiparib with surufatinib could provide clinical benefits for patients with platinum-resistant ovarian cancer who have progressed on or after prior PARPi treatment. Circulating tumor DNA (ctDNA) has emerged as a valuable predictor of treatment response, prognosis, and disease progression in various cancers [18, 19]. However, few studies have explored its role in prognostic stratification, efficacy monitoring, and resistance mechanisms in ovarian cancer patients treated with PARPi. In this study, we utilized dynamic ctDNA monitoring to assess the efficacy of pamiparib combined with surufatinib in platinum-resistant ovarian cancer patients who progressed on or after prior PARPi treatment, and to investigate potential resistance mechanisms.

Methods

Study design

This trial was a multi-center, phase Ib/II study investigating pamiparib in combination with surufatinib in patients with platinum-resistant ovarian cancer who had previously received a PARPi (NCT05494580). The study comprised a phase Ib component, which included a safety run-in cohort, followed by a phase II component. The phase Ib portion aimed to establish the recommended phase II dose (RP2D) of surufatinib in combination with pamiparib, while the phase II part was designed to evaluate the efficacy of this combination. The trial protocol was approved by the central and local institutional review boards of all participating centers and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study population

Eligible patients were aged 18–75 years with histologically confirmed epithelial ovarian cancer in women, as documented in medical records, who had platinum-resistant disease. Platinum-resistant was defined as disease progressing within 6 months after the last platinum therapy. We also enrolled patients whose disease progressed within 6 months after the last platinum therapy and who received subsequent non-platinum treatment. Patients were required to have disease progression on or after prior

PARPi treatment. Key eligibility criteria included measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Major exclusion criteria included uncontrolled hypertension; prior treatment with VEGFR TKIs within 6 months, and active brain metastases. All patients provided written informed consent prior to enrollment.

Procedures

In the phase Ib safety run-in cohort, a 3 + 3 design was employed to determine the RP2D of surufatinib in combination with pamiparib. Surufatinib was administered in a dose de-escalation scheme, starting at 250 mg orally once daily (dose level 1), and if necessary, reduced to 200 mg once daily (dose level 2). Based on the reported data [17], pamiparib at 40 mg twice daily may provide comparable efficacy to the recommended 60 mg twice daily dose in the prescribing information, while improving tolerability. Thus, in our study, pamiparib was administered at a fixed dose of 40 mg twice daily. A treatment cycle was defined as three weeks of continuous administration of pamiparib and surufatinib. The dose limiting toxicity (DLT) observation period for each dose level was the first 21 days of treatment. DLT was defined as any grade 3 or higher treatment-related adverse event (TRAE) during the initial treatment cycle, excluding nausea, vomiting, diarrhea (unless adequate supportive treatment was given), and alopecia. In the initial cohort, three patients received surufatinib 250 mg once daily with pamiparib. If one of these patients experienced DLT, three additional patients were enrolled. If no DLT was observed, the dose level was considered safe. However, if DLT occurred in two or more patients, this dose level was declared the maximum tolerated dose (MTD), and testing would proceed with a lower surufatinib dose of 200 mg once daily. After the RP2D was established, additional patients were enrolled in the phase II component to evaluate the antitumor activity of the surufatinib and pamiparib combination. Patients received the RP2D of surufatinib along with 40 mg of pamiparib orally twice daily until disease progression, unacceptable toxicity, or withdrawal of informed consent (see study schema; Fig. 1A).

Assessments

Tumor responses were assessed by investigators according to RECIST 1.1 using computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and then every 6 weeks until disease progression. Adverse events (AEs) were monitored continuously throughout the treatment period and for 30 days after the last dose of the study drug. These events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Outcomes

The primary endpoint was to determine the RP2D of surufatinib in phase Ib and to evaluate the 6-month PFS rate in phase II. The 6-month PFS rate was defined as the percentage of patients who were alive without documented progression 6 months after treatment initiation.

Secondary endpoints were ORR, disease control rate (DCR), OS, and safety. ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR), as assessed by investigators according to RECIST 1.1. Objective responses had to be confirmed by a repeat scan at least 4 weeks later. DCR was defined as the proportion of patients who achieved confirmed CR or PR or stable disease (SD). OS was defined as the time from treatment initiation to death from any cause. Exploratory endpoints reported here included the associations between antitumor activity and ctDNA status, as well as changes in ctDNA concentration during treatment.

Tissue DNA and cell-free DNA extraction and sequencing

For formalin-fixed, paraffin-embedded (FFPE) tumor samples, only those with a tumor cell content greater than 10% were considered eligible for the study. Peripheral blood samples were collected in EDTA-coated tubes for circulating tumor DNA (ctDNA) analysis at screening, cycle 3, day 1 (C3D1, six weeks), cycle 7, day 1 (C7D1, 18 weeks), and at progressive disease (PD) (Fig. 1A). Plasma was extracted within 4 hours of blood collection and shipped to the central testing laboratory in Nanjing Geneseeq Technology Inc. (Nanjing, China) within 48 hours. CtDNA was analyzed using panel sequencing of 437 cancer-related genes. The panel has been previously used in study of gastric cancer immunotherapy [20], nasopharyngeal carcinoma immunotherapy [21], immunotherapy in pan-cancer [22]. Genomic DNA from FFPE sections, biopsy samples, and whole blood cells (WBCs) was extracted using the DNeasy Blood and Tissue kit (Qiagen, USA). Circulating cell-free DNA (cfDNA) from plasma was obtained with the QIAamp Circulating Nucleic Acid kit (Qiagen, USA). Sequencing libraries were prepared using the KAPA Hyper Prep Kit (KAPA Biosystems, Cape Town, South Africa) according to the manufacturer's instructions. Libraries underwent PCR amplification and purification before targeted enrichment using customized xGen Lockdown Probes (Integrated DNA Technologies, Coralville, IA) designed to capture 437 genes. Hybridization reaction were conducted with the NimbleGen SeqCap EZ Hybridization and Wash Kit (Roche, Madison, WI, USA). Target-enriched libraries were then sequenced in Nanjing Geneseeq Technology Inc.(Nanjing ,China).

Sequence data processing and identification of clinically actionable mutations

FASTQ file were subjected to quality control (QC) using Trimmomatic. Local realignment around insertions and deletions (indels) and base quality score recalibration were performed with the Genome Analysis Toolkit (GATK 3.4.0). Somatic mutations were identified using VarScan2 and annotation with ANNOVAR based on the hg19 reference genome (version 2024). Copy number variations (CNVs) were analyzed with ADTEX (<http://adtex.sourceforge.net>), with default parameters. Somatic CNVs were detected by comparing paired normal and tumor samples across each exon. HRD score was calculated using the genome-wide allele-specific copy number result obtained from the NGS analysis of matched tumor tissue and blood samples [23].

CtDNA Concentration and Status

The ctDNA status was determined by detecting mutations in plasma ctDNA. Samples were classified as ctDNA-positive if mutations were identified, and as ctDNA-negative if no mutations were detected. The ctDNA concentration was calculated using the following formula:

$$\text{ctDNA concentration (hGE/ml)} = (\text{mean VAF} \times \text{cfDNA concentration (pg/ml)}) \div 3.3$$

In this equation, the mean variant allele frequency (VAF) represents the average allele frequency of the mutated gene, and hGE denotes haploid genome equivalents per milliliter. CtDNA partial response (CPR) was defined according to the liquid biopsy response assessment criteria for solid tumors (LB-RECIST) as a decrease in ctDNA levels of more than 10% before and after treatment [24].

Statistical analysis

The phase Ib safety run-in utilized a 3 + 3 design. For phase II, the sample size was determined using a single-stage phase II design. Previous studies reported a 6-month PFS rate of approximately 25% for platinum-resistant ovarian cancer patients treated with single-agent non-platinum chemotherapy or targeted therapy [25–28]. We hypothesized that the combination of pamiparib and surufatinib would achieve a 6-month PFS rate of 45%. With 80% power and a one-sided significance level of 0.05, 26 patients were required, including those treated at RP2D in phase Ib. Accounting for a 15% dropout rate, approximately 30 patients were planned for enrollment in phase II.

The 95% confidence intervals (CIs) for ORR and DCR were calculated using the Clopper–Pearson method in the efficacy evaluable set (EES) and the full analysis set (FAS). PFS and OS were assessed in the FAS using the Kaplan–Meier method with the log-rank test. Safety was descriptively summarized by adverse events in the safety set. For biomarker analyses, oncoplots were generated to explore tissue and ctDNA characteristics using the maftools and ComplexHeatmap package (Bioconductor). Post-hoc comparisons between multiple biomarker subgroups were performed using t-tests, Fisher’s exact test, Mann-Whitney U test, Log-rank test, and Cox proportional hazards regression as appropriate. All statistical analyses were conducted using R Statistical software (v.4.3.2). A p-value of < 0.05 was considered statistically significant.

Results

Patient disposition and baseline characteristics

A total of 29 patients were enrolled in the study. Three patients were initially enrolled in the phase Ib portion from September 22 to November 4, 2022. No DLTs were observed with surufatinib (250 mg orally once daily) combined with pamiparib (40 mg twice daily), establishing the RP2D of surufatinib at 250 mg once daily. Recruitment continued until November 4, 2023. Baseline characteristics were shown in

Table 1. The median age of the patients was 54 years (range, 31–69), with 27 (93.1%) patients diagnosed with high grade serous carcinoma (HGSC). The median duration of prior PARPi treatment was 5.1 (range, 1.6–37.7) months.

Table 1
Baseline Patient Characteristics

Characteristic, <i>n</i> (%)	Phase Ib (<i>n</i> = 3) + Phase II (<i>n</i> = 26) N = 29
Age, years	
Median (range)	54 (31–69)
FIGO stage at diagnosis	
IC1	1 (3.4)
IIB	1 (3.4)
IIIA1	1 (3.4)
IIIC	15 (51.7)
IVB	11 (37.9)
Histologic subtype	
High grade serous carcinoma	27 (93.1)
Clear cell	1 (3.4)
Carcinosarcoma	1 (3.4)
ECOG performance status	
0	3 (10.3)
1	26 (89.7)
Number of prior lines of systemic therapies	
Median	3
1–2	10 (34.5)
3–4	19 (65.5)
Treatment-free interval (TFI)	
Median (range)	1.2 (0.6–5.8)
^a These 12 patients received at least one line of single-agent non-platinum therapy after being considered as platinum-resistant (defined as progression within 6 months after the last platinum therapy), resulting in a PFI of ≥ 6 months.	
^b Two patients received treatment with both olaparib and niraparib.	
FIGO, The International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group.	

Characteristic, n (%)	Phase Ib (n = 3) + Phase II (n = 26) N = 29
< 3 months	25 (86.2)
≥ 3 months and < 6 months	4 (13.8)
Platinum-free interval (PFI)	
Median (range)	5.2 (0.9–38.0)
< 3 months	9 (31.0)
≥ 3 months and < 6 months	8 (27.6)
≥ 6 months ^a	12 (41.4)
Prior bevacizumab	
Yes	18 (62.1)
No	11 (37.9)
Prior PARP inhibitor therapy	
Olaparib ^b	14 (48.3)
Niraparib ^b	15 (51.7)
Fluzoparib	1 (3.4)
IMP4297	1 (3.4)
Duration of prior PARP inhibitor treatment	
Median (range)	5.1 (1.6–37.7)
< 6 months	17 (58.6)
≥ 6 months and < 12 months	5 (17.2)
≥ 12 months	7 (24.1)
^a These 12 patients received at least one line of single-agent non-platinum therapy after being considered as platinum-resistant (defined as progression within 6 months after the last platinum therapy), resulting in a PFI of ≥ 6 months.	
^b Two patients received treatment with both olaparib and niraparib.	
FIGO, The International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group.	

All 29 patients received study treatment, constituting both the FAS and the safety analysis set. Four patients discontinued treatment before the first post-baseline tumor assessment and were excluded

from the EES. As of the data cut-off date (June 20, 2024), two patients were still on treatment, and 27 patients had discontinued. The main reasons for discontinuation were disease progression (n = 16), adverse events (n = 3), and patient refusal (n = 3) (Fig. 1. B).

Efficacy

As of the data cutoff (June 30, 2024), with a median follow-up time of 7.3 (range, 1.0–18.1) months, 16 PFS events were recorded. The six-month PFS rate was 46.7% (95% CI: 24.4–66.2) (Fig. 2. A). The median PFS was 5.5 (95% CI: 3.2–9.1) months. Eight OS events occurred, with a median survival time of 14.7 (95% CI: 9.9–not evaluable [NE]) months (Fig. 2. B).

Tumor response as assessed by RECIST 1.1 was shown in Fig. 2. C. Two patients achieved a PR, resulting in an ORR of 6.9% (95% CI: 0.8–22.8) in the FAS and 8% (95%CI: 1–26) in the EES. Twenty patients had SD as their best response, yielding a DCR of 69% (95%CI: 49.2–84.7) in the EES and 80.0% (95%CI: 59.3–93.2) in the FAS. Among the 25 patients evaluable for response, 12 (48%) patients showed a decrease in target lesion size.

Safety

In the safety analysis set, 72.4% of patients experienced at least one TRAE (Table 2). The most common TRAEs were anemia (17 patients, 58.6%), thrombocytopenia (13 patients, 44.8%), and neutropenia (12 patients, 41.4%). Grade 3 or 4 TRAEs occurred in 11 (37.9%) patients; the most common were thrombocytopenia (6 patients, 20.7%), anemia (5 patients, 17.2%), and neutropenia (4 patients, 13.8%).

Table 2
Treatment-related adverse events in the total treated patients (N = 29)

Any treatment-related adverse events	No. (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	2 (6.7)	6 (20.7)	4 (13.8)	0 (0)
Anemia	5 (17.2)	7 (24.1)	5 (17.2)	0 (0)
Thrombocytopenia	4 (13.8)	3 (10.3)	3 (10.3)	3 (10.3)
Increased aspartate aminotransferase	3 (10.3)	0 (0)	0 (0)	0 (0)
Increased alanine aminotransferase	1 (3.5)	0 (0)	0 (0)	0 (0)
Proteinuria	1 (3.0)	2 (6.7)	0 (0)	0 (0)
Diarrhoea	1 (3.0)	2 (6.7)	0 (0)	0 (0)
Hypertension	1 (3.0)	2 (6.7)	0 (0)	0 (0)
Anorexia	1 (3.0)	1 (3.0)	0 (0)	0 (0)
Gamma-Glutamyl transferase	1 (3.0)	0 (0)	0 (0)	0 (0)
Vomit	1 (3.0)	0 (0)	0 (0)	0 (0)
Nausea	0 (0)	1 (3.0)	0 (0)	0 (0)
Insomnia	0 (0)	1 (3.0)	0 (0)	0 (0)
Abdominal pain	0 (0)	1 (3.3)	0 (0)	0 (0)

Dose reductions occurred in four (13.8%) patients for surufatinib, with three requiring one dose reduction and one requiring two. For pamiparib, three (10.3%) patients had a single dose reduction. One (3.4%) patient required one dose reduction for both drugs.

Baseline characteristics for the ctDNA detection cohort

Pre-treatment plasma samples were collected from 25 patients in the ctDNA detection cohort, with clinical characteristics summarized in Fig. 3A. At baseline, 23 (92.0%) of 25 patients were ctDNA-positive. Post-treatment plasma samples were collected at C3D1 (n = 24) and C7D1 (n = 10), with ctDNA turning negative in two patients at each time point. At progression, all 14 patients were ctDNA-positive (Fig. 3B). The median age of patients in the ctDNA-detection cohort was 54 years (range 31–65), with clinical characteristics comparable to the overall population. Among these patients, 2 achieved PR, 20 had SD, and 3 had PD as their best response. Tissue samples were available for 21 patients before treatment, and blood white cells from 13 patients were collected for germline mutation analysis.

BRCA mutation and HRD status

Sequencing of tissue (n = 21) and pre-treatment plasma (n = 25) samples identified germline *BRCA1* mutations in six patients and somatic *BRCA1* mutations in two patients, including one with both germline and somatic *BRCA1* mutation, which might be a reversion mutation. A germline *BRCA2* mutation was detected in one patient, while three somatic *BRCA2* mutations were identified in two patients. Notably, one patient showed different somatic *BRCA2* mutations in the tissue and baseline plasma samples. Based on the mutation locations and the timing of samples collection, we hypothesize that the mutation in plasma may be reversion mutation. Additionally, a somatic *BRCA2* mutation emerged at disease progression in one patient (Fig. 4A and 4B). However, no significant difference in PFS was observed between patients with and without *BRCA* mutations (Fig. 4C). To assess HRD status, we calculated HRD scores following a validated approach [23]. Twelve patients were classified as HRD-positive tumors. Similar to *BRCA1/2* mutation, no significant difference in PFS was found between HRD-positive and HRD-negative patients (Fig. 4D). Further analyses were conducted on *BRCA1/2* pathogenic mutations and HRD scores. Consistent with previous findings, there was no significant difference in PFS regardless of *BRCA1/2* mutation status or pathogenicity (Supplementary Fig. S1A). Additionally, HRD scores showed no significant correlation with PFS in either PD patients ($P = 0.50$) or non-PD patients ($P = 0.71$) (Supplementary Fig. S1B).

Baseline tissue sequencing and plasma ctDNA detection

Baseline mutation profiles for tissue (n = 21) and plasma (n = 25) samples were shown in Fig. 5A. *TP53* mutations were the most prevalent, present in 95.2% of tissue samples, followed by *NF1* mutations at 23.8% of cases. Mutations in *FANCD2* and *PKHD1* were each observed in 14.3% of tissue samples.

We assessed the consistency of mutations detected in tissue and plasma prior to treatment. A total of 76 unique mutations were detected in tissue samples, while 74 unique mutations were detected in plasma, with 35 mutations common to both. When using tissue as a reference, 35% of the plasma mutations matched those in tissue (Fig. 5B). Among the 20 patients with *TP53* mutations in tissue, 18 also exhibited *TP53* mutations in plasma, resulting in a 90% consistency rate (Fig. 5C).

Association of ctDNA dynamic change with treatment efficacy

The correlation between the change in ctDNA concentration relative to the baseline at different time points and disease progression was analyzed. No significant correlation was found between ctDNA concentration change at C3D1 and progression within 4 or 6 months (Fig. 6A, 6B). However, at C7D1, ctDNA concentrations were significantly increased in patients who progressed within 6 months ($P = 0.05$; Fig. 6C). When focusing specifically on patients with SD, whose characteristics were detailed in Table S1, those with increased ctDNA concentration at C7D1 also showed a significantly higher likelihood of progressing within 6 months compared to patients with decreased ctDNA concentration ($P = 0.05$; Fig. S2A, S2B).

Further analysis categorized patients based on CPR status at different time points. The median PFS was 7.82 months in patients with CPR at C3D1, compared to 3.52 months in those without CPR ($P = 0.05$; Fig. 6D). Similarly, patients who achieved CPR at C7D1 had a significantly longer PFS than non-CPR patients (9.46 vs. 3.83 months, $P = 0.01$; Fig. 6E). Among SD patients, no significant differences in PFS were observed, based on CPR status at either C3D1 ($P = 0.20$) or C7D1 ($P = 0.12$; Fig. S2C, S2D).

We assessed the dynamic changes of ctDNA concentration in patients with disease progression vs. those without, and observed a generally consistent directional trend between ctDNA concentration trajectories and disease status (Fig. 6F). Specifically, patients experiencing disease progression exhibited a pronounced increase in ctDNA concentration, whereas those without progression demonstrated a discernible decrease. This finding underscores the correlation between ctDNA dynamics and disease progression. By comparing ctDNA changes with radiographic tumor regression in each patient, we found that they were consistent (Fig. S3). In patients with PR, both ctDNA concentration and tumor size decreased markedly. In contrast, patients with PD showed a significant increase in both ctDNA concentration and tumor size.

Comparative analysis of pre-treatment and PD plasma samples from 14 patients revealed a higher ctDNA concentration at PD ($P = 0.09$) (Fig. S4), suggesting an increased release of tumor ctDNA.

Resistance mutations in ctDNA associated with PARPi rechallenge

Plasma mutations were analyzed both before and after treatment to identify genetic changes associated with PD (Fig. 7A). Notably, mutations emerging at PD included *LRP1B* ($n = 2$), *SETD2* ($n = 2$), a *BRCA2* frameshift mutation, *MAP3K1* frameshift mutation, *MYCL* truncating mutation, and *PRKDC* frameshift insertion (one patient each). These newly emerging mutations may be associated with resistance to PARPi rechallenge. Patient-specific analyses further illustrated these dynamics. For instance, patient Pa02, who achieved SD at C3D1, showed a gradual increase in ctDNA VAF (Fig. 7B), while patient Pa07, who achieved PR, experienced a slow decline in ctDNA VAF (Fig. 7C). Patient Pa11 initially achieved PR with undetectable ctDNA at C3D1, but resistance developed with a subsequent rise in ctDNA levels (Fig. 7D). Patient Pa16 experienced a rapid increase in ctDNA levels consistent with disease progression (Fig. 7E), and patient Pa20 exhibited *BRCA2* truncation mutations at PD, suggesting the possibility of a reverting mutation (Fig. 7F).

Discussion

In this study, we evaluated the combination of pamiparib and surufatinib in patients with platinum-resistant ovarian cancer who progressed on or after prior PARPi treatment. The results demonstrated modest but clinically meaningful antitumor activity in this heavily pretreated population. Although only two patients achieved a PR, 46.7% experienced PFS of at least six months, with a median PFS of 5.5 months, which was comparable to other regimens in this challenging setting. While the QUADRA study reported an ORR of only 3% in platinum-resistant, HRD-negative, and PARPi-naïve patients, a 14% 24-

week clinical benefit rate was considered meaningful given the limited options [29]. The EVOLVE study [30], enrolling patients who progressed on prior PARPi, showed an ORR of 14% and a 16-week PFS of 43%. Similarly, our 6-month PFS rate of 46.7% indicates that a subset of patients achieved durable disease control, which is clinically relevant in this setting.

Many studies have looked at PARPi and anti-angiogenic combinations, but our study is different in patient population and study design. The PAOLA-1 study evaluated olaparib plus bevacizumab in first-line maintenance treatment [7]. The OCTOVA study compared olaparib plus cediranib to other regimens in recurrent patients [31], permitting participants with prior PARPi exposure (> 6 months before enrollment), but including only 22% of such patients. The EVOLVE study [30] assessed olaparib plus cediranib in small cohorts with disease progression on prior PARPi treatment. To our knowledge, our study is the largest prospective cohort with platinum resistance who had prior PARPi exposure and developed resistance. Recently, PARPi was withdrawn as a maintenance therapy for BRCA wildtype, platinum-sensitive recurrent ovarian cancer, which emphasizes the importance of redefining their use in later lines treatment. Our study specifically focuses on patients with acquired PARPi resistance in the platinum-resistant population. Although limited by its single-arm design and modest sample size, our results provide exploratory evidence to inform future treatment strategies for this challenging population.

Per study design, patients were eligible if they experienced disease progression on or after prior PARPi therapy, theoretically including those who progressed during PARPi treatment (PARPi-resistant) and after completing maintenance. In our study, 27 received prior PARPi less than 24 months and progressed during treatment. Two others had longer durations: one had poor adherence to a 28-month maintenance and progressed on treatment, and another received prior PARPi monotherapy (not as maintenance) for 37.7 months without regular imaging, continuing until clinical progression. Thus, although the eligibility criteria allowed for potential heterogeneity, all enrolled patients in this study were PARPi-resistant.

The safety profile of pamiparib and surufatinib in our cohort was consistent with prior studies involving these agents. The TRAEs were mild to moderate, with grade 3 or 4 TRAEs occurring in 37.9% of patients. Notably, three (10.3%) patients discontinued treatment due to toxicity, suggesting that the combination regimen is generally well-tolerated in this setting.

An important aspect of this study was the exploration of genetic biomarkers, particularly *BRCA* mutations and HRD status, which are well-established as predictive markers of PARPi efficacy [7]. Despite having 10 patients with *BRCA1/2* mutations, we did not observe significant differences in PFS between those with *BRCA1/2* mutations and those with wildtype *BRCA1/2*. Similarly, no significant PFS difference was found between HRD-positive and HRD-negative tumors. Given the mechanism of PARP inhibitors, the lack of significant outcome differences by *BRCA* or HRD status in our study may reflect true underlying biology or be attributable to limited statistical power. Similar findings have been reported in other studies. For example, in the QUADRA study evaluating niraparib in heavily pretreated ovarian cancer [29], OS among patients achieving SD $\geq$ 24 weeks was similar regardless of *BRCA* or HRD status.

Likewise, in the TOPACIO study of niraparib plus pembrolizumab, ORRs were similar regardless of BRCA mutation (18% in mutation vs. 19% in wildtype) or HRD status (14% in HRD-positive vs. 19% in HRD-negative) [32]. These results are consistent with our observations, suggesting that BRCA or HRD status alone may not fully predict benefit in later-line settings, particularly in the context of PARPi rechallenge. Functional assays could offer a more direct assessment of HRD status at treatment; however, these were not feasible due to limited fresh tissue and the clinical trial setting.

We also observed a high concordance between *TP53* mutations detected in baseline tissue and plasma samples, which is consistent with the high frequency of *TP53* mutations in HGSC. However, the overall consistency between tissue and plasma mutations was lower than expected, with only 35% of mutations detected in plasma matching those found in tissue. This discrepancy may be due to differences in sample collection timing, as tissue biopsies were obtained at baseline, whereas plasma samples were collected at various points during treatment.

Further, we explored the potential of ctDNA as a predictive marker for treatment efficacy using a commercial gene panel targeted 437 cancer-related genes. Previous studies have shown that dynamic ctDNA monitoring during treatment can predict outcomes. For example, in a prospective cohort study of advanced rectal cancer, dynamic ctDNA monitoring during neoadjuvant chemotherapy predicted pathological complete response (pCR) vs. non-pCR with 73.0% accuracy [33]. Similarly, Yuan et al. demonstrated the utility of ctDNA dynamics in monitoring disease recurrence in stage II-III gastric cancer following adjuvant therapy, with a sensitivity of 77.8% and specificity of 90.6% [34]. In our study, ctDNA concentrations at progression were significantly higher than at baseline, indicating that ctDNA could serve as a sensitive marker of tumor burden. Although ctDNA concentrations at C3D1 did not significantly correlate with progression, concentrations at C7D1 were notably elevated in patients who progressed within six months. We considered that early ctDNA levels alone may not reliably predict progression in this tumor-bearing patient population. However, monitoring ctDNA over a longer treatment period may offer predictive value as therapeutic responses evolve. Similar results were observed in patients with SD, further supporting this findings.

Patients who achieved ctDNA CPR during treatment, whether at C3D1 or C7D1, demonstrated significantly prolonged PFS. This finding supports the potential of ctDNA as a real-time biomarker for monitoring treatment response and suggests that CPR, characterized by a decline in ctDNA, may be a more reliable predictive biomarker than ctDNA concentrations in late-stage patients. Notably, ctDNA dynamic were strongly correlated with imaging-based efficacy assessments, and in some cases, changes in ctDNA levels occurred earlier than radiologic imaging, providing valuable early insight into treatment efficacy. However, its clinical utility requires further validation and comparisons with established criteria such as RECIST and CA125. To our knowledge, this is the first and largest prospective cohort to monitor ctDNA at multiple time points in patients treated with PARPi rechallenge. Future study may further validate and establish CPR as a predictive biomarker for treatment outcomes in ovarian cancer.

Previous studies have shown that reversion of truncating mutations in *BRCA1/2*, which restores functional protein expression and enables homologous recombination repair, is a key mechanism of PARPi resistance [35, 36]. In the EVOLVE study [30], *BRCA1/2* reversion mutations were detected in five patients and were associated with poor outcomes; *RAD51C* overexpression was also implicated in PARPi resistance. Consistent with these findings, one patient in our study exhibited a *BRCA2* truncation mutation at progression, suggesting a possible reversion event. Other mutations identified in our cohort, including *LRP1B*, *SETD2*, and *PRKDC*, have been linked to drug resistance in various cancer [37–39], but their roles in PARPi resistance remain unclear. Further in vitro and in vivo functional studies are needed to clarify their potential contributions.

We acknowledge several limitations in this study. One limitation of this study is its single-arm study, which may introduce selection bias. The small sample size and the wide confidence intervals for the 6-month PFS rate warrant cautious interpretation of our results. Additionally, the translational findings lack validation through in vivo and in vitro experiments, which warrants further exploration.

In conclusion, the combination of pamiparib and surufatinib demonstrated modest yet clinically meaningful antitumor activity with manageable toxicities in patients with platinum-resistant ovarian cancer who had progressed on or after prior PARPi treatment. Our findings also highlight the potential of ctDNA as a valuable tool for predicting treatment outcomes in this challenging setting. However, further validation in larger studies is necessary.

Declarations

Ethics approval and consent to participate

The study was approved by the Sun Yat-sen University Cancer Center Ethics Committee (Reference Number, B2022-348-X01) and the ethics committee at each participating site. All patients provided written informed consent prior to enrollment.

Conflict of interest statement

Chuqiao Liang, Dongqin Zhu, and Lingling Yang are employees of Nanjing Geneseeq Technology Inc. All other authors declare no competing interests.

Competing Interests

Chuqiao Liang, Dongqin Zhu, and Lingling Yang are employees of Nanjing Geneseeq Technology Inc. All other authors declare no competing interests.

Funding information

This study was supported by National 2030 Projects of Scientific and Technological innovation (2023ZD0500304 to C.L.), National Natural Science Foundation of China (82573022 to C.L).

Author Contribution

Conception and design: Chunyan Lan, Xin Huang Provision of study materials or patients: Jing Li, Min Zheng, Ruinian Zheng, Miaofang Wu, Xin Huang, Chunyan Lan Collection and assembly of data: Cheng Fang, Haixi Liang, Xiujiao Shen, Jing Li, Chuqiao Liang, Dongqin Zhu, Lingling Yang, Xuehan Wang, Miaofang Wu, Ruinian Zheng, Chunyan Lan Data analysis and interpretation: Cheng Fang, Haixi Liang, Xiujiao Shen, Chuqiao Liang, Dongqin Zhu, Lingling Yang, Xin Huang, Chunyan Lan Manuscript writing: Chunyan Lan Final approval of manuscript: All authors

Acknowledgement

We thank all of the patients and their families who participated in this study.

Data Availability

The patient data from this study have been recorded on the Research Data Deposit public platform (<http://www.researchdata.org.cn>). While these data are not publicly accessible due to licensing restrictions, they can be made available upon reasonable request and with permission from the Research Data Deposit public platform. The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA012536) that are publicly accessible at <https://ngdc.cncb.ac.cn/gsa-human>.

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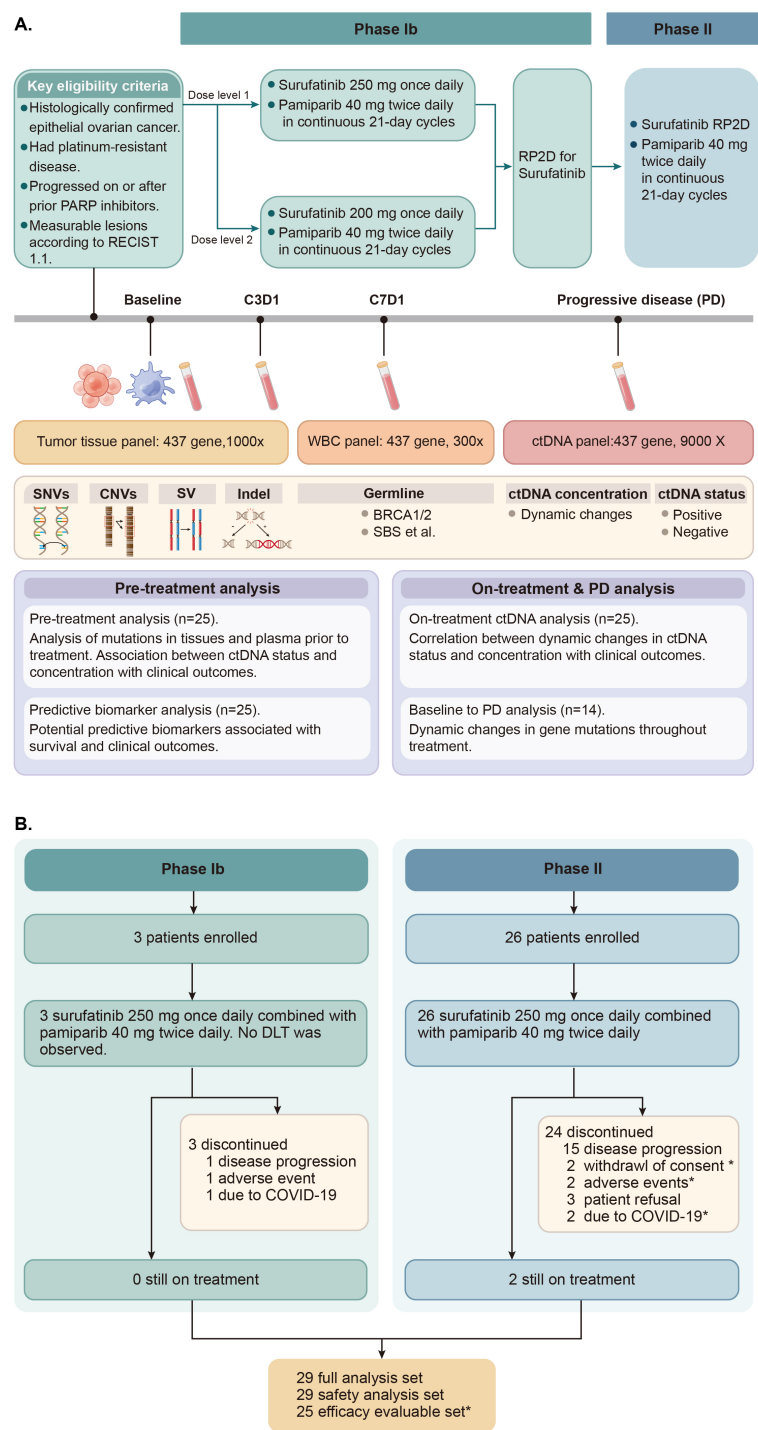
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Figures

Figure 1.



* Four patients discontinued treatment before the first post-baseline tumor assessment and were excluded from the efficacy evaluable set. Among them, two withdrew consent, one discontinued due to an adverse event, and one due to COVID-19.

Figure 1

Study design and profile.

A. Workflow diagram of the study design. The study consisted a phase Ib component, including a safety run-in cohort, followed by a phase II part. Baseline tissue samples were collected for sequencing and homologous recombination deficiency (HRD) testing. Blood samples for circulating tumor DNA (ctDNA) analysis were collected at the following time points: cycle 1, day 1 (C1D1, pre-treatment); cycle 3, day 1 (C3D1); cycle 7, day 1 (C7D1); and at progressive disease.

B. Profile of the study.

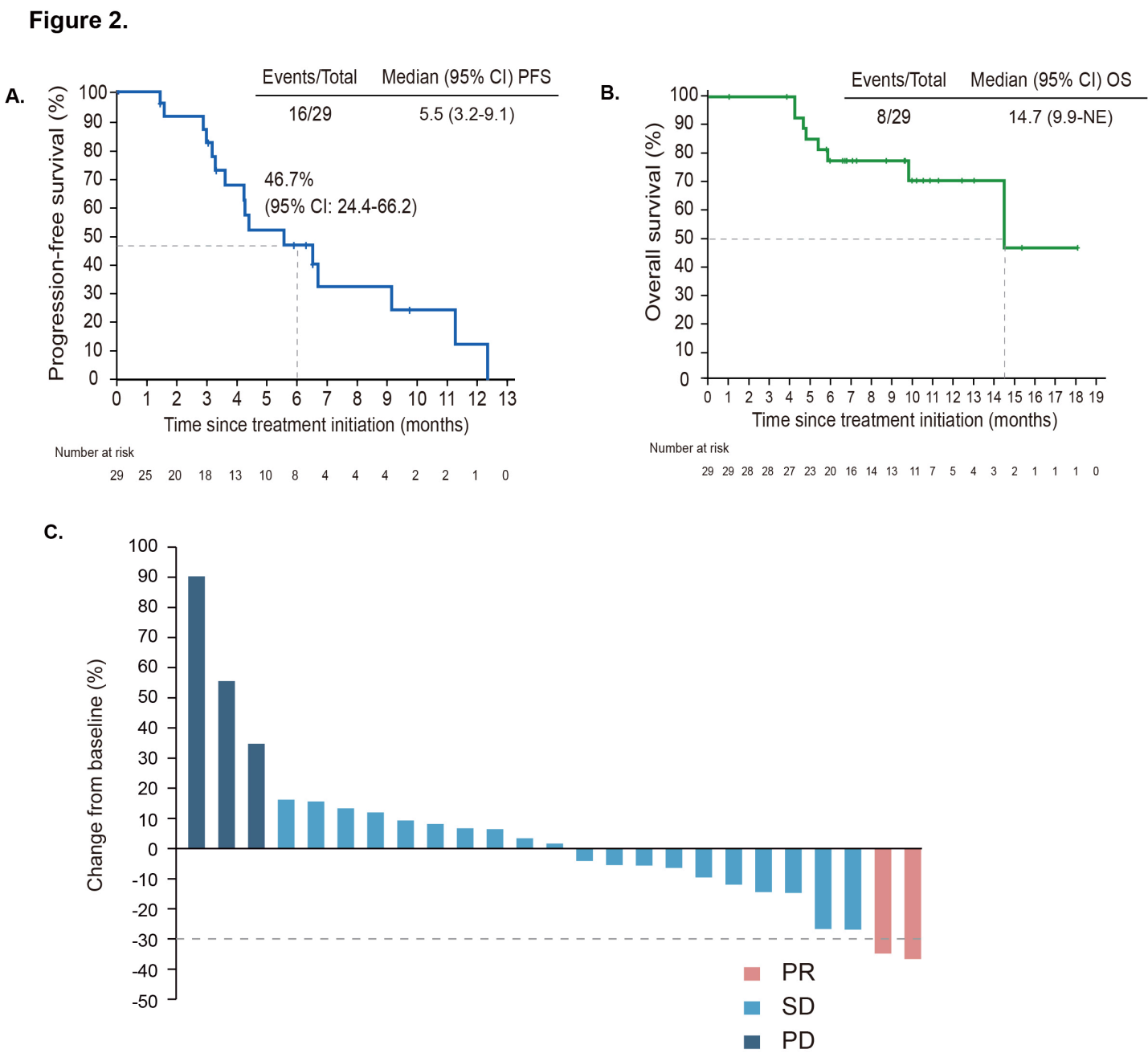


Figure 2

Efficacy profiles of patients treated with pamiparib and surufatinib

- A. Kaplan-Meier curves of progression-free survival (PFS).
- B. Kaplan-Meier curves of overall survival (OS).
- C. Best percentage change from baseline in target lesions. The dashed line at -30% represents the RECIST 1.1 cutoff to define partial response (PR).

Figure 3.

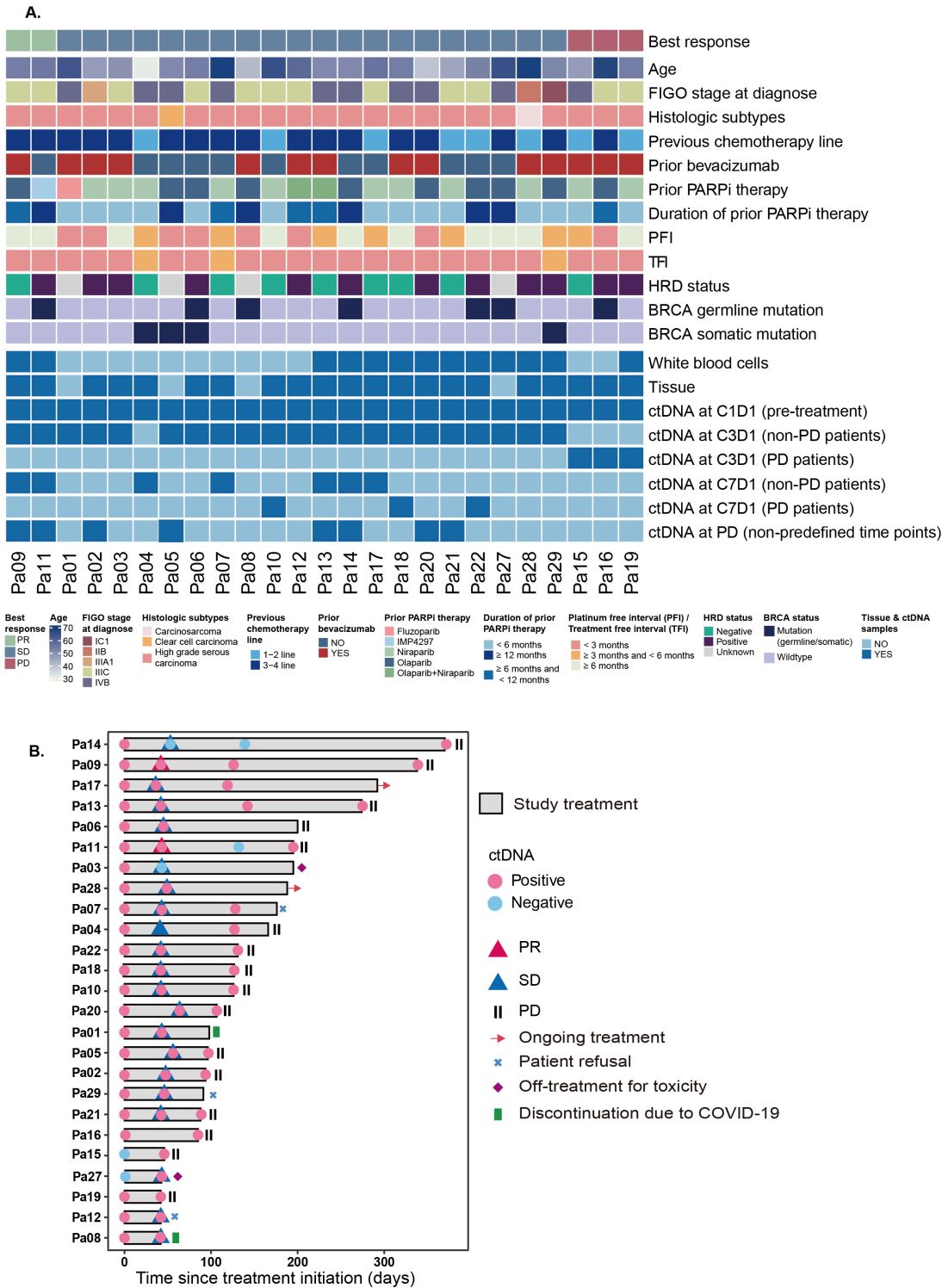


Figure 3

Characteristics of the ctNDA detection cohort

A. Baseline characteristics of patients in the ctDNA detection cohort.

B. CtNDA detection according to treatment duration.

Figure 4.

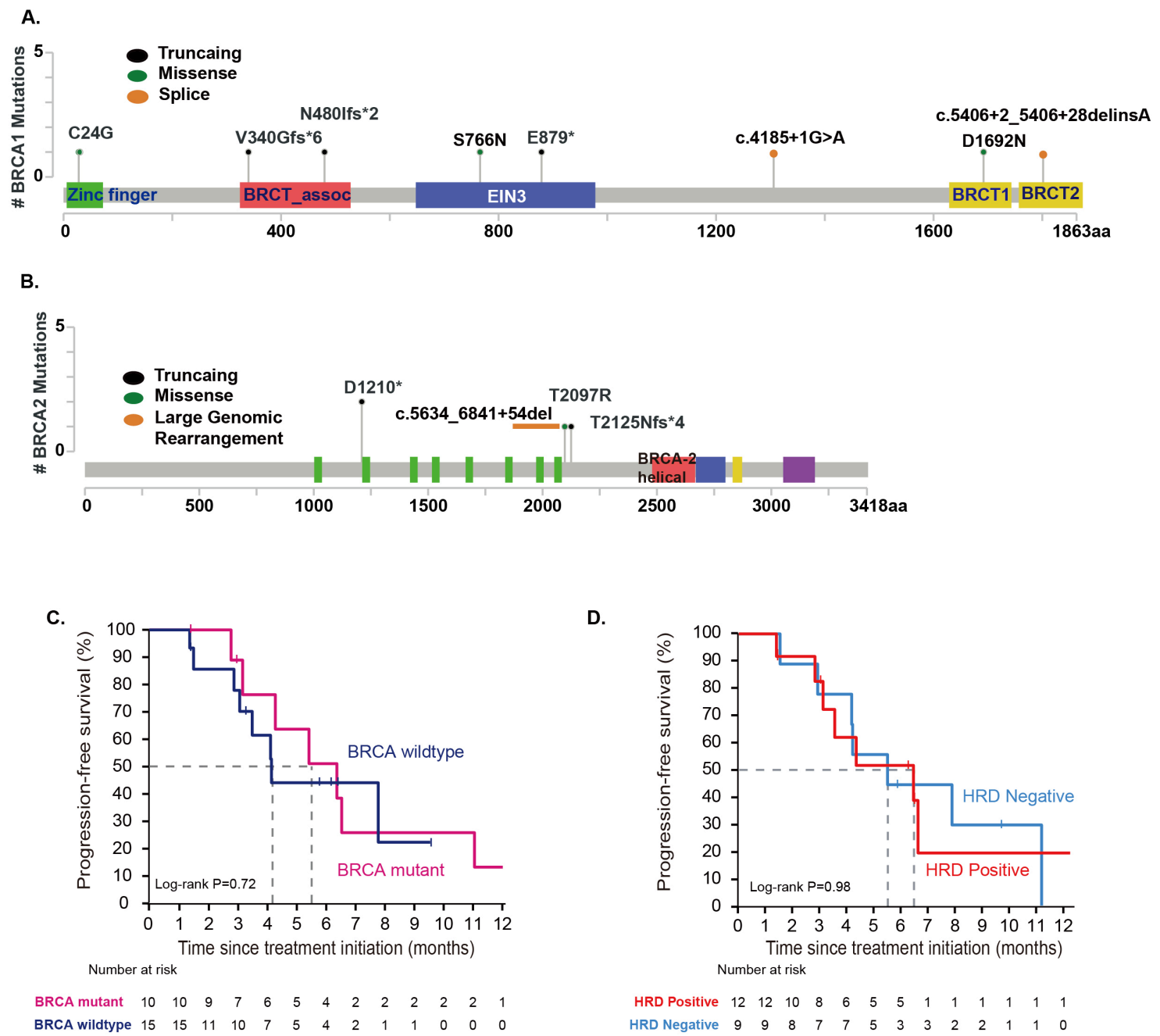


Figure 4

Correlation of BRCA and HRD status with progression-free survival

- A. Lollipop plot depicting the distribution of *BRCA1* variants.
- B. Lollipop plot depicting the distribution of *BRCA2* variants.
- C. Kaplan-Meier curves of progression-free survival according to BRCA mutation.
- D. Kaplan-Meier curves of progression-free survival according to HRD status.

Figure 5.

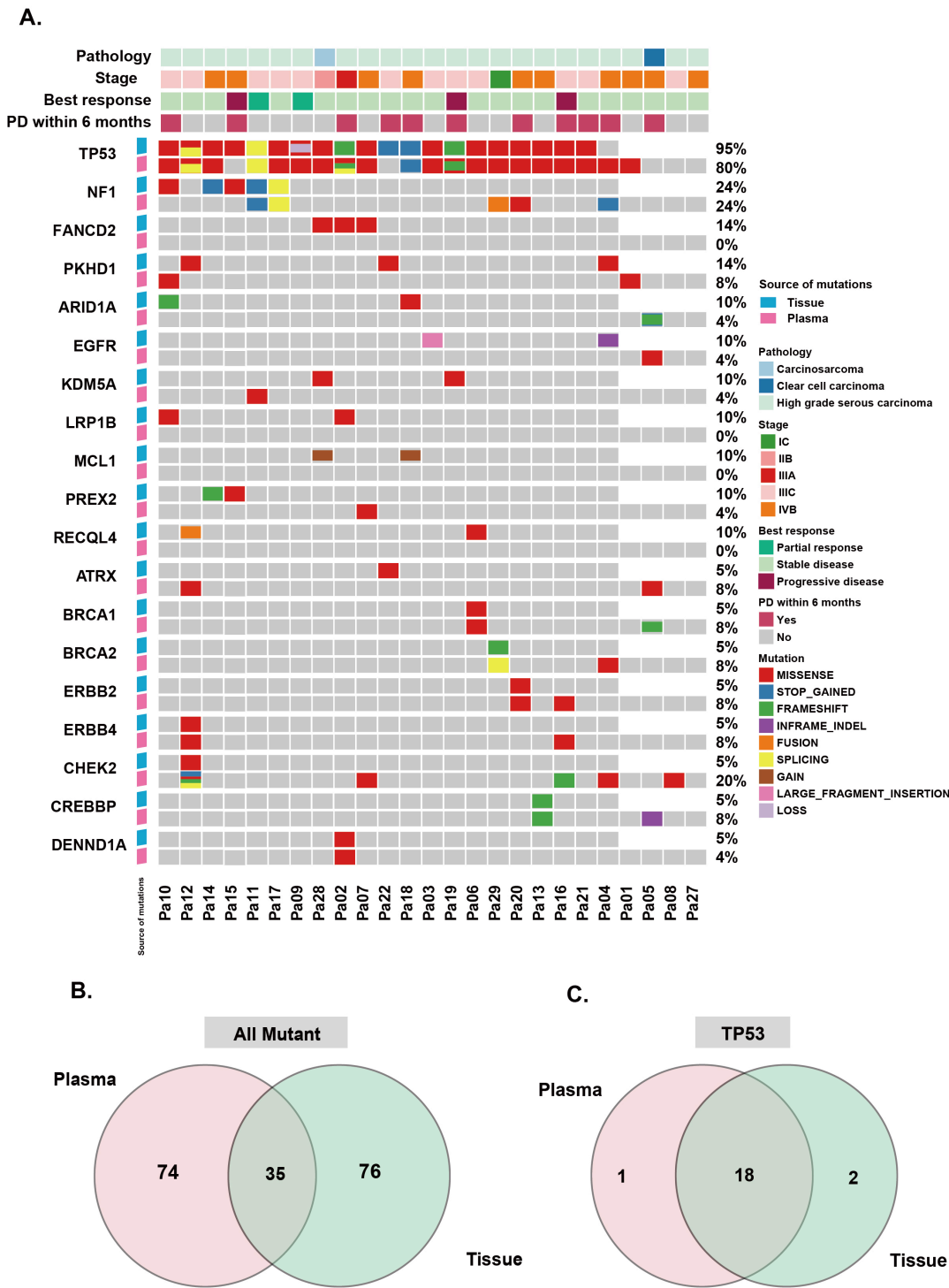


Figure 5

Baseline mutation profiles for tissue and plasma samples

- A. Mutation profiles in tissue (N = 21) and plasma (N = 25) samples, along with corresponding clinical features.
- B. Consistency of all mutations detected in tissue and plasma samples.
- C. Consistency of TP53 mutations detected in tissue and plasma samples.

Figure 6.

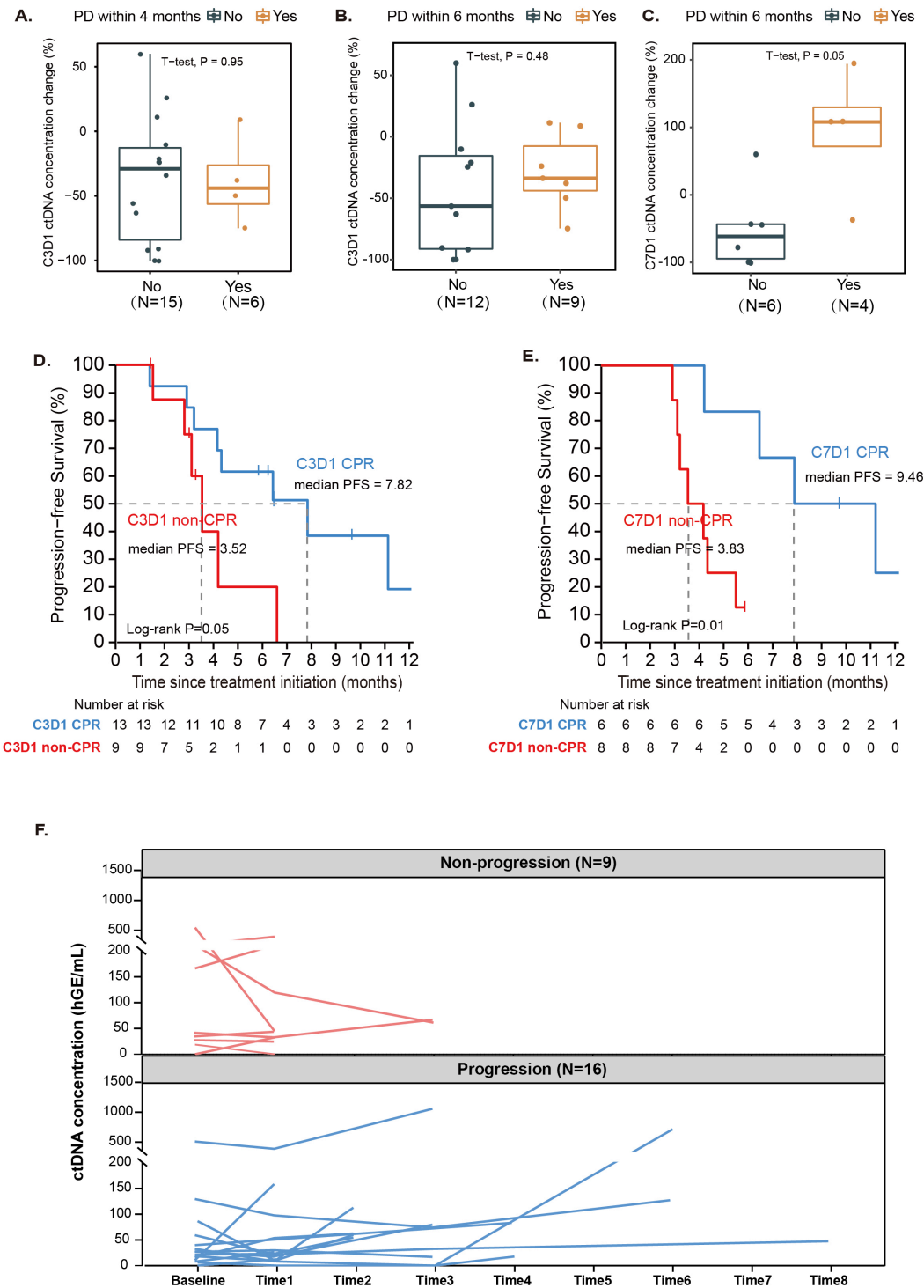


Figure 6

Association of ctDNA dynamic change with treatment efficacy

A. CtDNA concentration at C3D1 in patients with and without progression within 4 months

B. CtDNA concentration at C3D1 in patients with and without progression within 6 months

C. CtDNA concentration at C7D1 in patients with and without progression within 6 months

D. Kaplan-Meier curves of progression-free survival stratified by CPR status at C3D1

E. Kaplan-Meier curves of progression-free survival stratified by CPR status at C7D1

F. Changes in ctDNA concentration in patients with PD and non-PD.

Figure 7.

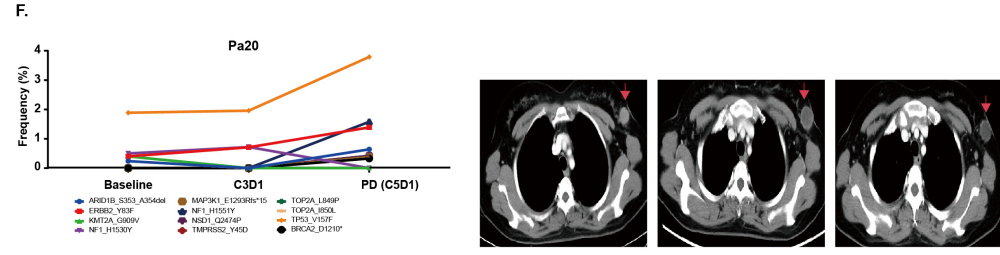
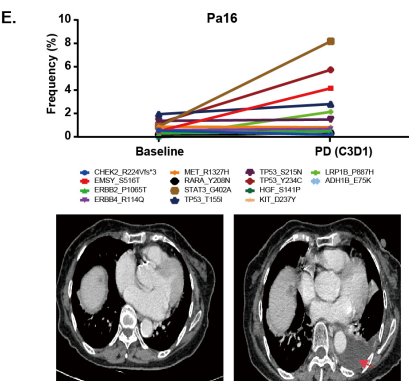
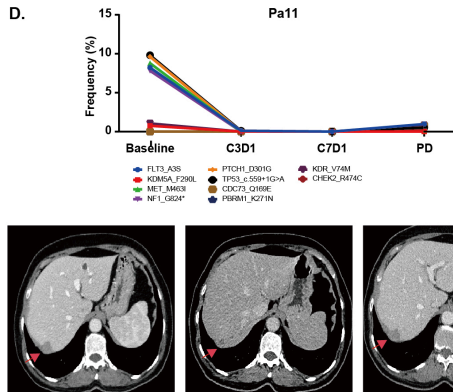
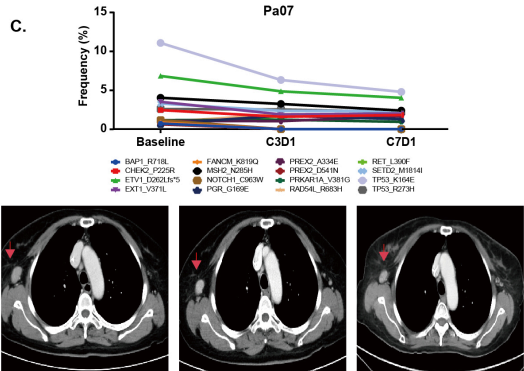
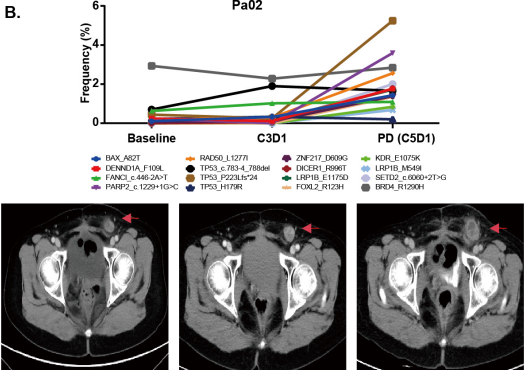
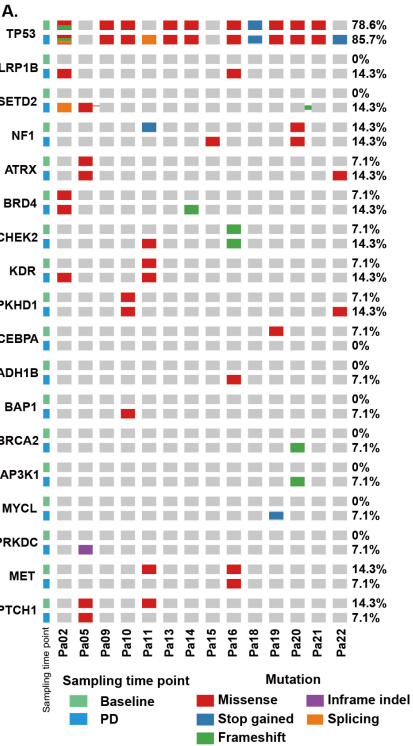


Figure 7

Resistance mutations in ctDNA associated with PARPi rechallenge

- A. Plasma mutation profiles before treatment and at disease progression.
- B. Changes in ctDNA frequency and tumor imaging during treatment in patient Pa02.
- C. Changes in ctDNA frequency and tumor imaging during treatment in patient Pa07.
- D. Changes in ctDNA frequency and tumor imaging during treatment in patient Pa11.
- E. Changes in ctDNA frequency and tumor imaging during treatment in patient Pa16.
- F. Changes in ctDNA frequency and tumor imaging during treatment in patient Pa20.

Supplementary Files

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