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Hematologic complications in patients exposed to poly-ADP ribose polymerase inhibitors

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Author Contributions:
MWD and ASD conceived the study; MWD, ASD, JMC, MRB, SC, and GWR collected and analyzed the data; MWD, JMC, GWR, MT, WS, AAP, OO, RAL, MJT, MTN, GV, ASD cared for the patients; GV, PW, MJT, and JPS performed molecular pathology testing and reporting; JMC and MWD drafted the manuscript; all authors edited the manuscript.

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To the Editor:

Poly ADP-ribose polymerase (PARP) inhibitors are a treatment for solid tumors with mutations in *BRCA1*, *BRCA2,* or other genes conferring homologous repair deficiency.[1] PARP inhibitors are approved for treatment of platinum-sensitive ovarian cancers, and *BRCA1/2* mutated solid tumors, including fallopian tube, breast, prostate, pancreatic, and primary peritoneal cancers.[1,2,3]

PARP inhibitor trial data, retrospective cohort study, and pharmacovigilance analysis demonstrated an increased likelihood of therapy-related myeloid neoplasms (t-MN) among patients exposed to all PARP inhibitors, particularly olaparib.[4-7] Multiple patient cohorts treated with PARP inhibitors describe t-MN incidence in 1.5% to 8.7% of patients.[5,8,9] These t-MN cohorts largely examine patients with primary ovarian cancer, and demonstrate enrichment in adverse cytogenetic findings, and poor risk *TP53* and *PPM1D* mutations.[5,7-11] Outcomes are generally poor even for patients without evidence of their treated solid tumor with median overall survival of 4.3 to 18 months.[9,11,12]

The accumulating evidence for t-MN secondary to PARP inhibitor exposure and expanding indications for PARP inhibitor treatment results in frequent hematology referrals. To inform such referrals, we summarized our institutional experience, including clinical data, available germline data, laboratory findings, age, duration of PARP inhibitor exposure, and outcomes of all patients treated with PARP inhibitors who underwent a bone marrow biopsy.

With approval from our Institutional Review Board (IRB), we reviewed institutional records from January 2014 to November 2023. We identified 265 adult patients prescribed a PARP inhibitor for any solid tumor indication and 17 patients who had a bone marrow biopsy after starting treatment. We also reviewed our leukemia registry and identified five patients with blood cancer and prior exposure to PARP inhibitors. All diagnoses used the 2022 ICC guidelines.[12] We used the Kaplan-Meier method to assess overall survival and Student's T-test to compare peripheral blood counts between patients with and without a t-MN.

We identified 265 patients treated with PARP inhibitors at our institution and five referred for management of t-MN after PARP inhibitor treatment in community practice. 22 patients had a bone marrow biopsy performed for cytopenias after PARP inhibitor treatment (**Figure 1A**). Bone marrow biopsies were prompted by unexplained sustained cytopenias or macrocytosis found in the course of treatment. None of these patients had prior cytopenias suggestive of clonal hematopoiesis (CH) or clonal cytopenias of undetermined potential (CCUS) and no next-generation sequencing (NGS) was available to inform the presence or absence of CH/CCUS prior to cancer-directed therapies. NGS described here were obtained from bone marrow biopsy samples. Among the 22 patients with biopsies, thirteen (59%) were diagnosed with a t-MN, one (5%) had cytomegalovirus-driven hemophagocytic lymphohistiocytosis (HLH), and one (5%) had a myelophthisic process. Excluding patients with an existing t-MN diagnosis, 6.4% (17/265) of institutional cohort patients underwent bone marrow biopsy. T-MN incidence was 3.0% (8/265) among patients with confirmed PARP inhibitor exposure at our institution (**Figure 1B)**. Bone marrow biopsy resulted in a diagnosis in 59% (10/17), with the remainder attributed to therapy toxicity. T-MN was diagnosed in 47% (8/17, **Figure 1C**), including two t-CCUS patients, six t-MDS patients, and one t-AML patient. The clinical and laboratory features of these patients are summarized in **Table 1** (t-MN details in **Supplemental Table 1**) alongside those of patients who underwent a bone marrow biopsy without a t-MN diagnosis.

Compared to the nine patients without t-MN diagnoses, leukocytes were not reduced (p=0.06), but neutrophils (p=0.03) and platelets (p=0.02) were lower in the t-MN group (**Table 1**, **Figure 1C-1F**). Median time to t-MN diagnosis was 4.75 years from initial solid tumor diagnosis (IQR 3.68 to 7.95 years) and 1.93 years from the start of PARP inhibitor therapy (IQR 1.35 to 4.12 years). The median survival for patients with high-risk t-MN was 159 days (n=9) and 148 days for patients receiving treatment (n=8, **Figure 2A and 2B**). These patients were treated with hypomethylating agents in combination with venetoclax or on clinical trials. None received induction with intensive chemotherapy or allogeneic stem cell transplant.

Age at biopsy, number of cytopenias, duration of PARP inhibitor exposure, type of PARP inhibitor, solid tumor diagnosis, and the presence of germline mutations did not differ significantly between patients with and without

t-MNs (**Table 1**). The t-MNs that developed in PARP-exposed patients were enriched for *TP53* mutations (n=9/13, 69%), as has been reported by others (**Figure 2C)**.[5, 7-9] Of these patients, four (44% of *TP53*-mutated and 31% of the total t-MN cohort) had biallelic *TP53* mutations. Similarly, among eleven patients with available data, eight (77%) had a complex or adverse-risk karyotype, consistent with other studies.[7–9] Of the patients who developed a t-MN, five were diagnosed within 60 days of discontinuation of PARP inhibitor (**Figure 2D**). Eight died of their t-MN, three died of their solid tumor, and two remain alive. Patients underwent a diagnostic bone marrow biopsy at time of t-MN diagnosis and subsequent biopsies to assess treatment response.

We hypothesized that germline mutations in *BRCA1*, *BRCA2*, or other DNA damage response genes would increase genomic risk of t-MN development in patients with germline mutations (**Figure 2C**). However, no significant difference in the distribution of germline mutations was observed across patients with t-MN and those without t-MN (**Table 1**). Whether patients with germline mutations are at increased risk will require a larger cohort exposure analysis. Risk of t-MN with PARP inhibitor treatment is present regardless of germline mutational status, which is consistent with other single center reports.[13]

PARP inhibitors increase the risk of CH, including, so we hypothesized that our cohort would be enriched in patients with CH. Except for *TP53*, our institutional NGS panel (**Supplemental Table 2**), found CH-associated mutations in only three patients with bone marrow biopsies (18%). Patient 5, with a germline *BRCA2* (p.K1381fs*) mutation, had a clonal del(7q) (3.5% of cells by FISH) and no mutations on NGS. A classic CH-associated *DNMT3A* mutation (p.Q816* VAF 7%) was detected in a 45-year-old patient with thrombocytopenia and normal bone marrow findings (**Supplemental Table 1**). Patient 10 had a CH-related *TET2* mutation (p.S271fs, VAF 31%) on diagnosis with t-MDS on rucaparib. Mutations in protein phosphatase magnesium-dependent 1 delta (*PPM1D*) following PARP inhibitor maintenance were found in 39% of a separate cohort, but no *PPM1D* mutations were observed in our cohort.[11]

Notably, the t-MNs in our patient cohort had a low peripheral blast burden despite adverse-risk molecular characteristics, making bone marrow evaluation essential for t-MN diagnosis in these patients. For patients on PARP inhibitors at the time of t-MN diagnosis, peripheral blasts ranged from 0 to 5%, with a higher bone marrow blast percentage (0-70%). We noted that Patient 13 presented with overt erythroid lineage atypia and a low frequency del(5q) clone after 6 months of olaparib treatment, yielding a diagnosis of therapy-related myelodysplastic syndrome. The initial bone marrow noted del(5q) and erythroid hyperplasia and atypia with binucleate pronormoblasts and megaloblastoid precursors, both of which resolved on subsequent bone marrow biopsies three and nine months following olaparib discontinuation (**Supplemental Figure 1**). A similar pattern has been reported with PARP inhibitor-associated CH, which can regress with drug discontinuation.[15]

In conclusion, this study reinforces the importance of bone marrow biopsy in PARP inhibitor-exposed patients with persistent leukopenia, neutropenia, or thrombocytopenia, even without the presence of peripheral blasts. We found that 6.4% of patients exposed to PARP inhibitors had bone marrow biopsies performed and 3.0% developed t-MN, including t-AML. These patients were enriched with high-risk molecular features, including *TP53* mutations and complex karyotypes, largely consistent with prior reports except for a lack of mutations in *PPM1D*.[5,9,10,15] None of the patients in our cohort underwent allogeneic transplant, but limited cases on PARP inhibitor t-MN cases and transplant data in *TP53*-mutated AML/MDS indicate a high rate of relapse.[12,13] The median survival for our patients with high-risk t-MNs was 159 days, which is consistent with other reports and reflects a dire need for novel treatments in *TP53*-mutated myeloid disease.[8-11] *TP53* was the only molecular alteration in most patients, which supports the clonal expansion of either an *TP53* existing clone or therapy-related mutation. However, the small sample size of patients with bone marrow biopsies limited our analysis and lack of available NGS data at onset of PARP inhibitor treatment does not rule out clonal expansion of existing *TP53* hematopoietic clones, perhaps under selective pressure of PARP inhibitor treatment. This cohort demonstrates the frequent diagnosis of t-MN despite low or absent peripheral blasts, supporting the use of bone marrow biopsy in patients with PARP inhibitor exposure and unexplained cytopenias. T-MNs occurred in patients with and without germline mutations, so blood cancer risk in PARP-exposed patients is increased regardless of the presence of germline mutations. Our findings suggest that further research is needed into risk factors for these t-MN and the mechanisms driving PARP inhibitor-associated hematologic malignancies and that their clinical use should incorporate evaluation for t-MN if chronic cytopenias develop.

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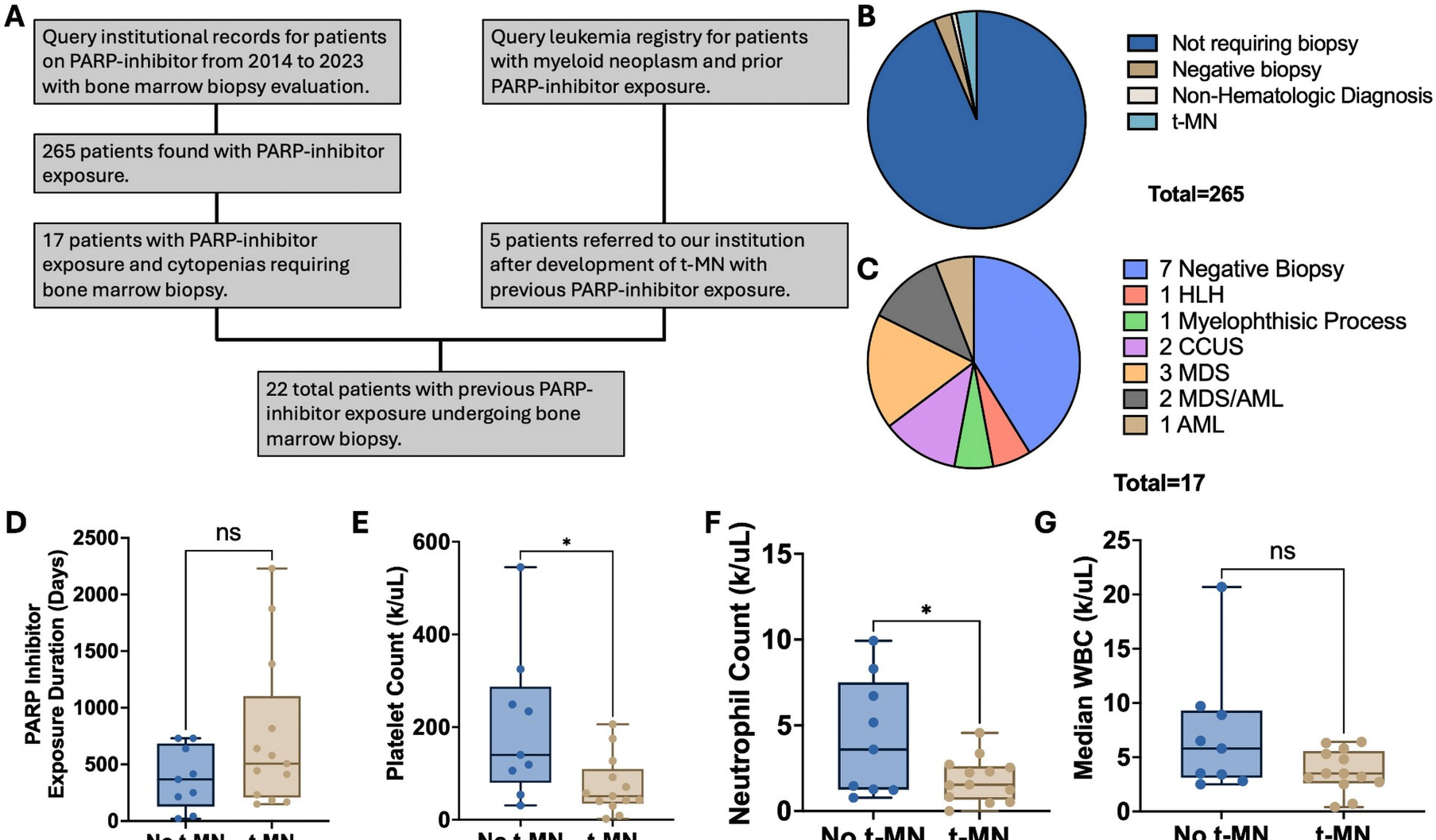
Table 1. Laboratory and clinical features of 22 PARP inhibitor-exposed patients who underwent bone marrow biopsy evaluation for a therapy-related myeloid neoplasm. WBC: white blood cell count; MCV: mean corpuscular volume. Values in parentheses show the interquartile range (IQR). Student's T-test was used to compare the two groups.

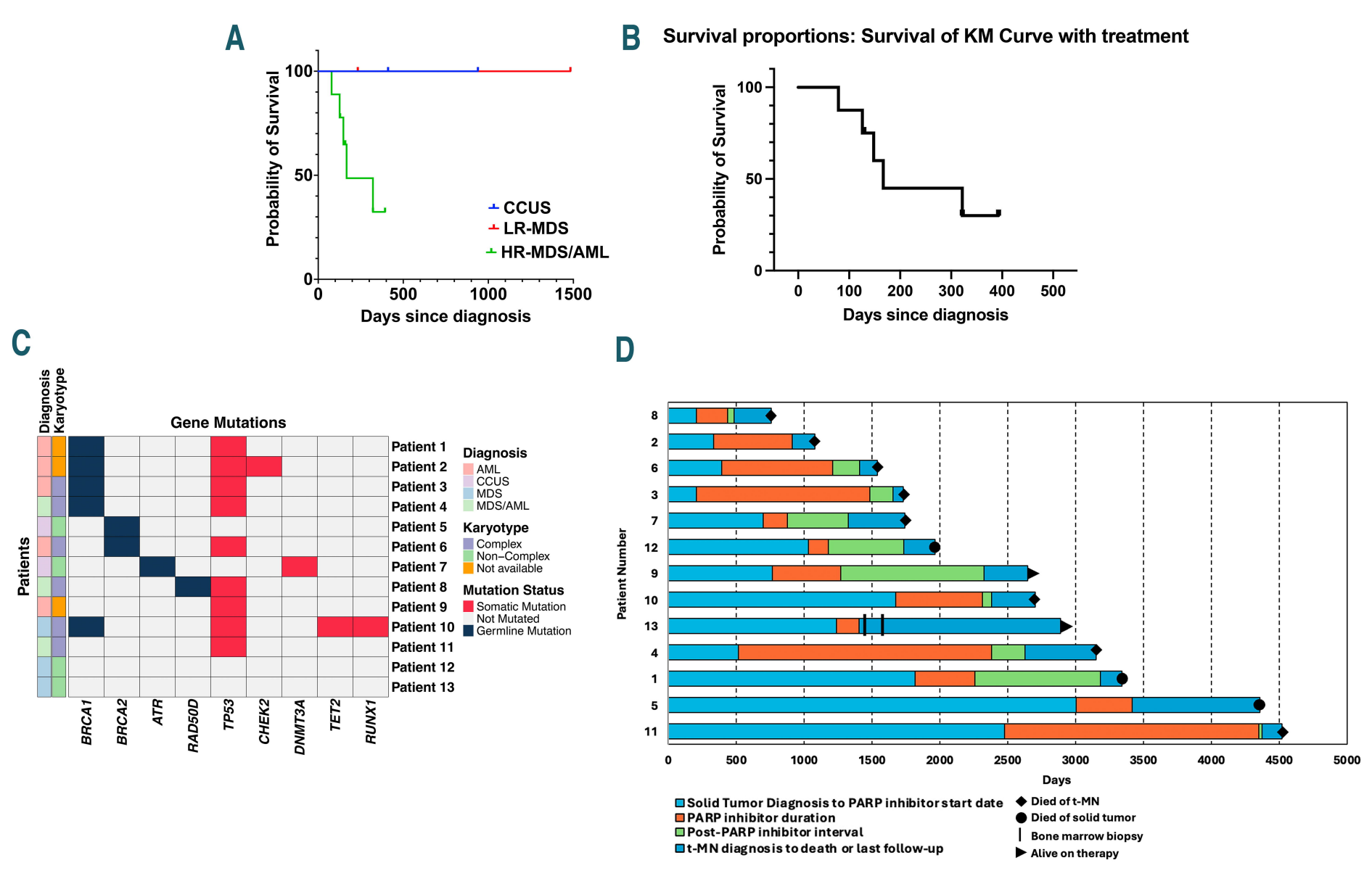
Characteristics at bone marrow biopsy	**Patients diagnosed with blood cancer (n=13)**	**Patients without blood cancer (n=9)**	***p***
Leukocyte count (10^3/μL)	3.5 (2.7 - 5.3)	5.8 (3.4 - 8.9)	0.06
Median Neutrophil Count (10^3/μL)	1.5 (0.8 - 2.5)	3.59 (1.3 - 6.7)	**0.02**
Median Hemoglobin (g/dL)	8.7 (7.5 - 10.6)	10.2 (7.6 - 11.4)	0.7
Median MCV (fL)	91.3 (87.3 – 113.6)	100.6 (99.6 – 108.1)	0.5
Median Platelets (10^3/μL)	51 (40 - 92)	140 (106 – 249)	**0.02**
Median Peripheral Blasts (range, %)	0 (0 - 2%)	0 (0 - 0%)	0.1
Number of Cytopenias	2.3 (2 - 3)	1.7 (1 - 2)	0.17
Median age at first cancer diagnosis (years)	62 (50 - 65)	56 (50 - 68)	0.6
Primary Tumor Type (*n*)			0.5
Ovarian Cancer (*n*, %)	9 (69%)	8 (89%)	
Breast Cancer (n, %)	1 (8%)	1 (11%)	

Prostate Cancer (n, %)	2 (15%)	0 (0%)	
Pancreatic Cancer (n, %)	1 (8%)	0 (0%)	
Median age at bone marrow biopsy	66 (59 - 72.5)	58 (56 - 68)	0.65
Known Germline Mutation (n, %)	8 (61.5%)	4 (44.4%)	0.4
PARP inhibitor			0.4
Olaparib (n, %)	10 (83%)	6 (60%)	
Rucaparib (n, %)	1 (8%)	3 (30%)	
Niraparib (n, %)	1 (8%)	1 (10%)	
Median duration of PARP inhibitor exposure (Days, IQR)	506 (231 - 817)	250 (213 - 639)	0.15

Figure 1. Comparison of clinical features of patients undergoing bone marrow biopsy after PARP inhibitor exposure. A. CONSORT Plot of patients included in this study. **B.** Pie plot showing the proportion of patients who did not undergo bone marrow biopsies (n=248) and patients who underwent bone marrow biopsies (n=17), those with non-hematologic findings (n=2), negative biopsy (n=7), and t-MN (n=8) **C.** Pie plot showing diagnoses from bone marrow biopsies: no diagnosis (n=7), HLH (n=1), myelophthisic process (n=1), t-CCUS (n=2), t-MDS (n=3), t-MDS/AML (n=2), and t-AML (n=1)**. D.** Duration of PARP inhibitor exposure in patients with (gold) and without (blue) diagnoses of therapy-related myeloid neoplasms (t-MN). **E.** Platelet count in patients with (gold) and without (blue) diagnoses of t-MN. **F.** Neutrophil count in patients with (gold) and without (blue) diagnoses of t-MN. **G.** White blood cell count in patients with (gold) and without (blue) diagnoses of t-MN. * denotes $p<0.05$

Figure 2. Disease features and outcomes among patients diagnosed with t-MN. A. Survival curve of patients diagnosed with CCUS (mOS NR, n=2), low-risk myelodysplastic MDS (n=2 mOS NR), and high-risk MDS or AML (mOS 148 days, n=9). Deaths are censored if unrelated to t-MN diagnosis. **B.** Survival curve of patients with HR-MDS/AML who received treatment (mOS 159 days, n=8). **C.** Co-mutation plot for patients who developed therapy-related blood disorders. **D.** Swimmer plot for patients with t-MN. Patients were divided into CCUS: clonal cytopenia of uncertain clinical significance; LR-MDS: low risk myelodysplastic syndrome; HR-MDS: high-risk MDS; and AML: acute myeloid leukemia; mOS: median overall survival. Censored data on Kaplan-Meier plots reflect surviving patients.


A
Query institutional records for patients on PARP-inhibitor from 2014 to 2023 with bone marrow biopsy evaluation.
265 patients found with PARP-inhibitor exposure.
17 patients with PARP-inhibitor exposure and cytopenias requiring bone marrow biopsy.
Query leukemia registry for patients with myeloid neoplasm and prior PARP-inhibitor exposure.
5 patients referred to our institution after development of t-MN with previous PARP-inhibitor exposure.
22 total patients with previous PARP-inhibitor exposure undergoing bone marrow biopsy.
B
Not requiring biopsy
Negative biopsy
Non-Hematologic Diagnosis
t-MN
Total=265
C
7 Negative Biopsy
1 HLH
1 Myelophthisic Process
2 CCUS
3 MDS
2 MDS/AML
1 AML
Total=17
D
PARP Inhibitor Exposure Duration (Days)
2500
2000
1500
1000
500
0
ns
No t-MN
t-MN
E
Platelet Count (k/uL)
600
400
200
0
*
No t-MN
t-MN
F
Neutrophil Count (k/uL)
15
10
5
0
*
No t-MN
t-MN
G
Median WBC (k/uL)
25
20
15
10
5
0
ns
No t-MN
t-MN

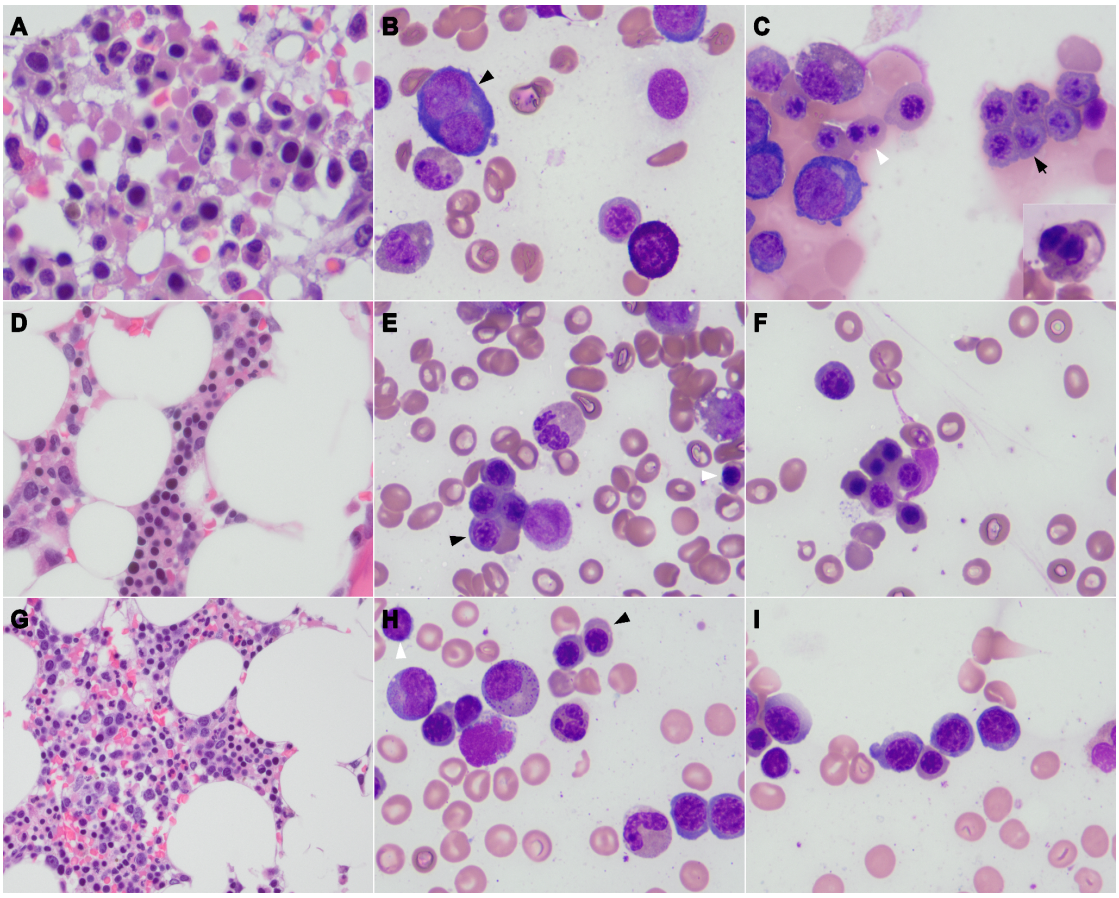

A
Probability of Survival
100
50
0
0
500
1000
1500
Days since diagnosis
CCUS
LR-MDS
HR-MDS/AML
B
Survival proportions: Survival of KM Curve with treatment
Probability of Survival
100
50
0
0
100
200
300
400
500
Days since diagnosis
C
Diagnosis
Karyotype
Gene Mutations
Patients
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
BRCA1
BRCA2
ATR
RAD50D
TP53
CHEK2
DNMT3A
TET2
RUNX1
Diagnosis
AML
CCUS
MDS
MDS/AML
Karyotype
Complex
Non–Complex
Not available
Mutation Status
Somatic Mutation
Not Mutated
Germline Mutation
D
Patient Number
8
2
6
3
7
12
9
10
13
4
1
5
11
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
Days
Solid Tumor Diagnosis to PARP inhibitor start date
PARP inhibitor duration
Post-PARP inhibitor interval
t-MN diagnosis to death or last follow-up
Died of t-MN
Died of solid tumor
Bone marrow biopsy
Alive on therapy

Supplemental Table 1. Patient diagnosis, myeloid molecular features, cytogenetics, and family history.

Patient ID	Hematologic Diagnosis	Karyotype Findings	Gene with Germline Mutation	Variant on Bone Marrow NGS	VAF, %	Genes with Somatic Mutation	Somatic Mutations	VAF,	History of other cancers	Lines of Prior Chemo-therapy	First-degree family history of cancer
1	t-MDS	Not available	BRCA1	p.Q1777Pfs*74	48	TP53	p.H193Y	29	Breast	9	Breast, non-melanoma skin cancer
2	t-AML	Not available	BRCA1	p.Q1777Pfs*74	48	TP53 CHEK2	p.M237I c.1260-1G>A, p.?	18 8	Breast (two primaries), ovarian	4	None
3	t-AML	Complex	BRCA1	p.V1734*	43	TP53 TP53	p.P177R p.H179P	41 20	Pancreatic	2	None
4	t-MDS, progressed to t-AML	Complex	BRCA1	p.S1217Ifs*2	45 (blood)	TP53	p.H193L	84	Ovarian	3	None
5	t-CCUS	del(7q) on FISH	BRCA2	p.K1381Lfs*8	50	None			Pancreatic, prostate	4	Gastric, ovarian
6	t-AML	Complex	BRCA2	p.R3128*	47	TP53	c.672+2T>G, p.?	22	Breast, ovarian	3	None
7	t-CCUS	46XX	ATR	p.D1324Vfs*4	46	DNMT3A	p. Q816*	8	Ovarian	5	Bladder, prostate
8	t-MDS/AML	Complex	RAD51D	p.L164P	Not on NGS panel. Heterozygous on germline report	TP53	p.H193R	69	Ovarian	2	None
9	t-AML	Not available	None			TP53	p.V157G	13	Prostate	2	Breast, prostate
10	t-MDS, progressed to t-MDS/AML	Monosomy 7 and 18, then complex on later marrow	BRCA1	Not documented, separate BRCA assay and only myeloid panel sent at OSH		TP53 RUNX1 TET2	p.R175H p.T148fs p.S271fs	55 20 27	Breast, ovarian	4	Breast, lung, pancreatic, ovarian
11	t-MDS, progressed to t-AML	Complex	None			TP53	p.V218dup	42	Ovarian	2	Bladder, lymphoma
12	t-MDS	46XX,der(1;7)(q10;p10) 46XX,del(20)(q11.2q13.3)	None			Not done			Ovarian	7	Melanoma, prostate, skin cancer
13	t-MDS	46XX, del(5)(q13q21)	None			None			Ovarian	4	None

Supplemental Table 2 – Genes Assayed on Next-Generation Sequencing Oncoplus Panel					
ABL1	NM_005157.6	*ERCC3*	NM_000122.2	*NFE2L2*	NM_006164.5
AKT1	NM_001382430.1	*ESR1*	NM_018010.4	*NOTCH1*	NM_017617.5
ALK	NM_004304.5	*ETV6*	NM_001987.5	*NOTCH2*	NM_024408.4
APC	NM_000038.5	*EZH2*	NM_004456.5	*NPM1*	NM_002520.7
ARID1A	NM_006015.6	*FANCA*	NM_000135.3	*NRAS*	NM_002524.5
ARID2	NM_152641.4	*FAT3*	NM_001367949.2	*PALB2*	NM_024675.3
ASXL1	NM_015338.6	*FBXW7*	NM_001349798.2	*PBRM1*	-
ATM	NM_000051.3	*FGFR1*	NM_023110.3	*PDGFRA*	NM_006206.6
ATR	NM_001184.4	*FGFR2*	NM_000141.5	*PDGFRB*	NM_002609.4
AXL	NM_021913.5	*FGFR3*	NM_000142.5	*PIK3CA*	NM_006218.4
B2M	NM_004048.4	*FH*	NM_000143.3	*PIK3CB*	NM_006219.3
BAP1	NM_004656.3	*FLT3*	NM_004119.3	*PIK3R1*	NM_181523.3
BARD1	NM_004656.3	*FOXL2*	NM_023067.4	*PLCG2*	NM_002661.5
BIRC3	NM_001165.5	*GATA2*	NM_032638.4	*POLE*	NM_006231.3
BRAF	NM_001374258.1	*GNA11*	NM_002067.5	POT1	NM_006231.3
BRCA1	NM_007294.4	*GNAQ*	NM_002072.5	PPP2R1A	NM_014225.6
BRCA2	NM_000059.3	*GNAS*	NM_000516.7	PTCH1	NM_000264.5
CALR	NM_004343.4	*GRIN2A*	NM_001134407.3	PTEN	NM_000314.7
CBL	NM_005188.3	*IKZF1*	NM_006060.6	PTPN11	NM_002834.4
CBLB	NM_170662.5	*H3F3A*	NM_002107.7	RAD21	NM_006265.3
CCND1	NM_053056.3	*HIST1H3B*	NM_003537.4	RAD51	NM_002875.4
CCND2	NM_001759.4	*HIST1H3C*	NM_003531.3	RAD51C	NM_058216.3
CCND3	NM_001760.5	*HNF1A*	NM_000545.8	RAD51D	NM_002878.3
CDH1	NM_004360.4	*HRAS*	NM_005343.4	RB1	NM_000321.3
CDK4	NM_000075.3	*IDH1*	NM_005896.4	RET	NM_020975.5
CDK6	NM_001145306.2	*IDH2*	NM_002168.4	RUNX1	NM_001754.4
CDKN2A	NM_000077.4	*ITPKB*	NM_002221.4	SAMD9	NM_017654.3
CEBPA	NM_004364.4	*JAK2*	NM_004972.4	SDHA	NM_004168.4
CHEK1	NM_00111412.2	*KDR*	NM_002253.4	SDHAF2	NM_017841.2
CHEK2	NM_007194.4	*KIT*	NM_000222.3	SDHB	NM_003000.2
CSF1R	NM_001288705.3	*KMNT2A*	NM_001197104.2	SDHC	NM_003001.3
CSF3R	NM_000760.4	*KRAS*	NM_004985.5	SDHD	NM_003002.4
CTCF	NM_006565.4	*MAP2K1*	NM_002755.4	SETBP1	NM_015559.3
CTNNA1	NM_001903.5	*MAPK1*	NM_002745.5	SF3B1	NM_006842.3
CTNNB1	NM_001904.4	*MDM2*	NM_002392.6	SMAD4	NM_005359.5
CUX1	NM_181552.4	*MET*	NM_000245.4	SMARCB1	NM_003073.5
CXCR4	NM_003467.3	*MLH1*	NM_000249.3	SMC3	NM_005445.4
DAXX	NM_001141969.2	*MLH3*	NM_001040108.2	SMO	NM_005631.5
DDR2	NM_006182.4	*MPL*	NM_005373.3	SRSF2	NM_001195427.2
DDX41	NM_016222.3	*MRE11A*	NM_005591.3	STAT3	NM_139276.3
DICER	NM_177438.2	*MSH2*	NM_000251.3	STAT5B	NM_012448.4
DNMT3A	NM_022552.5	*MSH6*	NM_000179.3	STK11	NM_000455.4
EGFR	NM_005228.5	*MTOR*	NM_004958.4	TERT	NM_198253.2
EP300	NM_001429.4	*MYC*	NM_002467.6	TET2	NM_001146069.2
EPHA3	NM_005233.6	*MYCN*	NM_005378.6	TP53	NM_000546.6
EPHA5	NM_001281766.3	*MYD88*	NM_002468.5	TSC1	NM_000368.5
ERBB2	NM_004448.4	*NBN*	NM_002485.4	TSC2	NM_000548.5
ERBB3	NM_001982.4	*NF1*	NM_000267.3	U2AF1	NM_006758.3
ERBB4	NM_005235.3	*NF2*	NM_000268.3	VHL	NM_000551.3
				WT1	NM_024426.5

Supplemental Table 2: Next-Generation Sequencing Oncoplus Panel: Listed above are the 151 genes included on the Oncoplus panel. In addition to the listed genes, sequencing data for *PPM1D* was collected but not clinically published. For each patient with t-MN and available Oncoplus data no *PPM1D* mutations were detected.



Supplemental Figure 1: **Bone marrow biopsy and aspirate findings for patient with spontaneous remission of t-MDS after olaparib discontinuation.** A. Bone marrow biopsy immediately after olaparib therapy showing erythroid hyperplasia on core biopsy with prominent cell drop out and apoptosis with irregular nuclear countours (Hematoxylin & Eosin stain, 400x) B. In the same marrow, aspirate smears showing left shifted binucleate (black arrow head) early pronormoblasts (Wright-Giemsa, 400x) C. Other areas showing megaloblastoid intermediate erythroid precursors (black arrow) with binucleaate late erythroid precursors (white arrowhead & inset) D. Bone marrow biopsy after early cessation of olaparib showing striking reduction in erythroid atypia after cessation. (H&E, 200x) E. Aspirate smears after early cessation showing normoblastic intermediate erythroid precursors (black arrowhead, Wright-Giemsa, 400x) F. Same aspirate smears as panel E showing normoblastic late erythroid precursors G. Bone marrow biopsy after late cessation of olaparib showing normalized cellularity with more intermingled myeloid precursors (H&E, 200x) H. Aspirate smears at the late time point showing normoblastic erythroid precursors (black arrowhead) without any atypia of nuclear contours (Wright-Giemsa, 400x) I. Other areas in the same aspirate smears with normoblastic intermediate and late erythroid precursors (Wright-Giemsa, 400x)