Supplementary Material

Methods

This single-center, single-arm, two-stage phase II study examined the activity of olaparib and durvalumab combination therapy in recurrent ovarian carcinoma patients. Inclusion criteria included patients with histologically or cytologically confirmed persistent or recurrent ovarian, fallopian tube, or primary peritoneal cancer who were either platinum-sensitive, platinum resistant or refractory during or after a first platinum-containing regimen. For platinum-sensitive recurrent disease, the patients must have received at least two prior regimens prior to study enrollment. Documentation of germline *BRCA* mutation status from a CLIA-certified laboratory, including but not limited to Myriad Genetics, either by multi-gene panels or individual testing was requested prior to study enrollment. Variants of uncertain significance (VUS) of BRCA were not considered as deleterious mutation. Patients had to have measurable disease as defined by RECIST v1.1 and at least one lesion deemed safe to biopsy. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status 0–2, and adequate organ and marrow function, defined as hemoglobin ≥ 9g/dL, in the absence of packed red blood cell transfusion 28 days prior to dosing, absolute neutrophil count ≥1500/mcL, platelet count ≥ 100×10^9 per L, total bilirubin ≤ 1.5 × the upper limit of normal (ULN), ALT and AST ≤ 2.5 × ULN, and serum creatinine ≤ 1.5 × within normal institutional limits or measured creatinine clearance ≥ 50 mL/min per 1.73 m^2. Additional criteria included adequately controlled blood pressure (<140/90 mmHg) on no more than three antihypertensive agents. Patients were allowed to have received prior PARPi. Patients of reproductive potential needed a serum pregnancy test upon study entry and agreed to use contraception or abstinence.

Study exclusion criteria included patients who have received chemotherapy, radiotherapy, or any other investigational agents within 3 weeks (4 weeks for platinum agents and 6 weeks for nitrosoureas or mitomycin) prior to study enrollment; patients who were treated with both olaparib and cediranib, either in combination or sequentially; patients who have previously been treated with immune checkpoint inhibitors; patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A4; concomitant or prior invasive malignancies ≤5 years prior to enrollment; patients with evidence of central nervous system metastasis, spinal cord compression, or leptomeningeal disease within one year prior to enrollment; history of auto-immune disease requiring steroid maintenance, or history of primary immunodeficiency; persistent adverse events from prior anticancer therapy ≥ grade 2 per CTCAE Version 4.03; current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab; active or prior documented inflammatory bowel disease; receipt of live attenuated vaccination within 30 days before the first dose of durvalumab; HIV-positive patients on retroviral therapy due to potential pharmacokinetic interactions with study drugs; known history of previous clinical diagnosis of tuberculosis; prior or current evidence of coagulopathy, myelodysplastic syndrome, or acute myelogenous leukemia; patients with any cardiac history of the following conditions within 1 year prior: myocardial infarction, clinically significant pericardial effusion, myocarditis, prior cardiac arrhythmia including atrial fibrillation (except chronic atrial fibrillation with controlled vascular rate), atrial flutter, requiring concurrent use of drugs or biologics with pro-arrhythmic potential, NYHA Class

II or greater heart failure, mean QT interval corrected for heart rate (QTc) ≥470 ms or other significant ECG abnormality noted within 14 days of treatment, clinically significant peripheral vascular disease or vascular disease, or unstable angina.

Correlative studies

A pre-treatment fresh core biopsy was mandatory for all patients and second biopsy on cycle 1 day 15 was optional because of patient's refusal or safety concerns. Serial blood samples were collected from all patients at baseline and prior to cycle 1 day 15 (C1D15) as described[1]. Mandatory baseline fresh frozen and formalin-fixed core biopsies were obtained in 32 of 35 patients, with the biopsy procedure aborted in the remaining three patients for safety concerns (one with uncontrollable hypertension and two with lesions too small and/or close to vital adjacent structures). An on-treatment biopsy was obtained in 22 patients prior to C1D15. Percutaneous biopsies were obtained by interventional radiologists under CT or ultrasound guidance using local anesthesia. The first core sample was formalin/PFA-fixed and paraffin-embedded for immunohistochemistry (IHC) and other core samples were processed in real time into optimal cutting temperature compound and stored at −80°C until use for sequencing. Optimal quality of tissue was defined as core biopsy samples with solid tissue areas containing at least 40% tumor cells and less than 25% necrosis[2].

Mutations in DNA repair pathways

All patients had BROCA-HR testing performed to detect mutations in DNA repair genes by targeted sequencing of tumor DNA[3].

RNA-seq

Total RNA was prepared from 22 matched pairs of core biopsies collected at baseline and C1D15 of treatment and RNA-seq performed as previously detailed[4]. Pretreatment RNA-seq was not conducted in 10 patients without on-treatment biopsy samples because not enough tissue samples remained after whole exome sequencing and BROCA-HR sequencing. Reads were aligned against the Human reference genome Hg38 and gene expression data was generated as counts per million mapped reads (CPM) values. Raw CPM values were processed to remove zero values and low expressing genes using 0.5 CPM as cutoff. The dataset was quartile normalized and log2 transformed using the Palantir Foundry™ platform at NIH. Gene similarity index (GSI) analysis using Morpheus® (https://software.broadinstitute.org/morpheus) and PCA analysis on Palantir™ identified 2 patient samples (matched pairs from study IDs 88 and 42) containing mostly normal tissues which were therefore removed to generate a dataset with 20 matched pairs of samples. Changes in pre- vs on-treatment gene expression were evaluated with Wilcoxon signed-rank tests. Gene expression plots for a clinical benefit group (PR+SD≥6 months) and no clinical benefit group (PD+SD<6 months) at baseline was generated using Graphpad prism® and Microsoft Excel. T cell inflamed gene expression profiles (GEPs) predicted by Ayers *et al*[5] were used to generate 2 genesets for an IFNγ signature (6 genes including *ID01, CXCL10, CXCL9, HLA-DRA, STAT1,* and *IFNG*) and for expanded immune gene signature (18 genes including *CD3D, ID01, CIITA, CD3E, CCL5, GZMK, CD2, HLA-DRA, CXCL13, IL2RG, NKG7, HLA-E, CXCR6, LAG3, TAGAP, CXCL10, STAT1,* and *GZMB*) for performing single sample gene set enrichment

analysis (ssGSEA). SsGSEA and hierarchical clustering analysis (Euclidean with paired average linkage) was done using Genepattern®[6]. High grade serous ovarian cancer (HGSOC) molecular subtype analysis using prognostically relevant gene signatures[7,8] was performed using ssGSEA. Signature scores were calculated by averaging the enrichments scores (Z-scores; Z-score = (Log2CPM of gene1 – average Log2CPM for gene1 for N samples)/standard deviation of Log2CPM for gene1 for N samples) of the included genes for the two genesets and plotted using Graphpad Prism®. Expression of the immunoreactive subtype was associated with clinical response using a Fisher's exact test.

Angiome

EDTA plasma was collected, processed, and frozen at −80°C until use from 32 patients at baseline and C1D15. Upon study completion, samples were shipped to Duke University Medical Center for biomarker testing by multiplex enzyme-linked immunosorbent assay (ELISA)[9]. The following 33 cytokines and factors were evaluated: interleukin (IL) 6 (IL-6), IL-7, IL-15, IL-10, IL-2, stromal cell-derived factor 1 (SDF1), VEGF, VEGF-D, VEGF-C, VEGF receptor 1 (VEGF-R1), VEGF-R2, VEGF-R3, angiopoietin 2 (Ang-2), hepatocyte growth factor (HGF), placental growth factor (PlGF), platelet-derived growth factor bb (PDGFbb), PDGFaa, thrombospondin 2 (TSP2), intracellular adhesion molecule 1 (ICAM1), tissue inhibitor of metalloproteinases 1 (TIMP-1), vascular cell adhesion molecule 1 (VCAM-1), glycoprotein 130 (GP130), osteopontin (OPN), transforming growth factor beta 1 (TGF-β1), TGF-β2, bone morphogenetic protein 9 (BMP-9), cluster of differentiation 73 (CD73), transforming growth factor beta receptor 3 (TGFβ-R3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), IFNγ, IL6 meso scale detection (IL6-MSD), tumor necrosis factor alpha (TNFα), and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Most circulating biomarkers were measured using the SP-X multiplex platform (Quanterix Inc., Billerica, MA, USA). TIM-3 and VEGF-C were measured using the Ella system (Proteinsimple, San Jose, CA, USA). BMP-9, CD73, and TGFβ-R3 were measured using the MSD platform (Meso Scale Discovery, Rockville, MD, USA). Optimized ELISA tests for BMP-9[10], CD73[11], and TGFβ-R3[9] were described previously.

To evaluate on-treatment biomarker change, L-ratios were calculated using the formula: log2 (C1D15/ baseline level) for each biomarker. Signed-rank tests were used to identify markers that underwent significant modulation upon treatment. *P*-values were adjusted for multiple testing. Fold-changes from baseline were associated with PFS using Cox proportional hazards model by dichotomizing the ratios into a higher and a lower group as suggested by the Kaplan-Meier analysis. The multivariate model adjusted for *BRCAm* status, platinum-sensitivity, previous lines of therapy (<=3 vs 4 or more) and previous bevacizumab and analysis was performed by dichotomizing the ratios from baseline based on Kaplan-Meier and log-rank analysis.

Tissue PD-L1 expression and TILs analysis

IHC for PD-L1 and TIL analysis was performed at Johns Hopkins Medical Institution (Baltimore, MD, USA). Pre-treatment tissue samples from 32 patients were obtained for pathologic correlative studies; two of the pre-treatment core biopsies did not contain carcinoma, allowing for evaluation of 30 (94%) biopsies of patients enrolled in the study. Baseline tumor samples were evaluable for TILs in 29 of 32 patients because two core

biopsies contained no carcinoma cells and one had detached carcinoma fragments lacking stroma on histological examination. Paired pre- and on-treatment samples were evaluable from 16 of 22 patients who underwent second biopsy as 6 were insufficient for analysis due to nonviable or benign tissue without carcinoma cells or detached cancer from stroma. H&E stained slides were evaluated to confirm the pathologic diagnosis of malignancy of gynecologic origin and were used to score the presence of TILs. Tumoral TIL were scored as the percentage (0-100%) of tumor stroma area occupied by mononuclear inflammatory cells.

Of the 30 patients with evaluable pre-treatment formalin-fixed paraffin-embedded core biopsies by histological examination, 28 were available for PD-L1 IHC; in one sample the carcinoma cells were cut through while in the other the IHC was uninterpretable due to high background noise. Of the 16 evaluable post-treatment biopsies, PD-L1 IHC was available in 14 because the carcinoma cells were cut through and insufficient for analysis in two samples. PD-L1 status was evaluable in paired pre- and on-treatment samples from 12 patients. IHC for PD-L1 was performed manually on unstained slides (PD-L1 clone SP142, 0.096 μg/mL concentration; Spring Bioscience, Pleasanton, CA, USA). Briefly, slides were deparaffinized and rehydrated using standard methods, followed by antigen retrieval in pH 6.0 CB buffer in a decloaking chamber (Biocare Medical, Pacheco, CA, USA). Slides were treated with peroxidase, protein, avidin and biotin blocking and incubated with the primary antibody overnight at 4°C. Slides were subsequently treated with a biotin-labeled anti-rabbit secondary antibody (1 μg/μl concentration). The signal was developed with horseradish peroxidase using the VECTASTAIN Elite ABC Kit (Vector Laboratories, Burlingame, CA, USA), amplified using a Tyramide Signal Amplification PLUS Biotin KIT (dilution 1:50; Perkin Elmer), and visualized by DAB. PD-L1 labeling by carcinoma cells was scored as percentage (0-100%) of cells with membranous labeling, with a cut-off of >1% carcinoma cell labeling considered positive. Statistical analyses of biomarker results were performed using Microsoft Excel (t-test) or GraphPad Online (Fisher's exact test).

STING pathway immunohistochemistry

STING pathway expression was evaluated using multiplex fluorescent IHC on formalin-fixed paraffin-embedded biopsy sections collected at baseline and C1D15 at the National Cancer Institute's (NCI) Center for Cancer Research (CCR; Bethesda, MD, USA). Analysis of human ovarian tissue labeling STING (green) with ab92605 (anti-STING/TMEM173 antibody, Abcam, Cambridge, MA, USA) at a dilution of 1:50, and CD3+ (yellow) with ab135372 (Abcam) and p53 (red) with ab32389 (Abcam) at a dilution of 1:100. Briefly, paraffin was removed by washing slides in 100% xylene solution 10 minutes 3 times, followed by washing in ethanol at dilutions of 100%, 90%, and 70%, 10 minutes each. Slides were fixed in neutral buffered formalin (10%) for 20 minutes. Heat-mediated antigen retrieval was performed using AR9 antigen retrieval solution (Perkin Elmer, Waltham, MA, USA) and microwave treatment of 3 minutes at 100% power and 20 minutes at 20% power as optimized according to Perkin Elmer Opal staining protocol. Anti-Rabbit/Mouse HRP polymer (PerkinElmer Opal Polymer HRP Ms Plus Rb) was used

as secondary antibody. Opal tyramide amplification was performed using Opal 520, Opal 690, and Opal 570 fluorophores. DAPI was used for counterstaining.

Images were created using a Leica DMI4000B microscope and analyzed via Fiji software. The nuclei of 10 random cells across each sample were measured by the software analysis tool and averaged for surface area. The surface area for the entire sample was measured by color threshold, excluding areas where measurement could not be accurately quantified. Cell number for each sample was extrapolated by surface area of sample/average surface area of nuclei. Bright staining surrounding nuclei in the measured sample were quantified, and the percent was calculated with regard to total cell number. Signed-rank tests were used to compare matched pre- versus on-treatment biopsy STING expression levels.

Whole exome sequencing

Tumor mutational burden (TMB) and *JAK1/2* mutations were analyzed using whole exome sequencing[12,13]. Total DNA was isolated from frozen biopsies of 32 patients isolated at baseline, as well as from matched normal peripheral blood mononuclear cells (PBMCs). 22 of 32 patients had matched pairs. Whole exome sequencing on DNA samples were performed at the NCI's CCR (Frederick, MD, USA) on the Novaseq6000-S2 system using the Agilent Sureselect V7 exome library[14,15], with >100x coverage across 86 samples (32 pre- and 22 on-treatment biopsy samples with 32 matching normal samples). Datasets were later analyzed by NCI's Bioinformatics core (Bethesda, MD, USA) and mutations (frame shift del/ins, inframe del/ins, missense, nonsense, non-stop, splice-site and translation start-site mutations) in exomes of all patients were enumerated. Total exome covered (Mb) for each patient was selected for a 30x coverage and used to generate mutations/Mb. Data was further analyzed using Graphpad Prism and *p*-values were generated using the unpaired Mann-Whitney U test.

Supplementary Table 1. Evaluation of DNA repair deficiency by BROCA-HR analysis

Platinum sensitivity	PFS* (months)	Best response	Germline BRCA analysis	Somatic Mutation in HRR pathway	HRD status	Prior PARPi
Resistant	4.8	SD	wild type		No	No
Resistant	12.7	SD	BRCA1 c4327 C>T		Yes	No
Resistant	24.7	PR	wild type		No	No
Resistant	4.2	SD	wild type	BRIP1 c.200_201dupTT, somatic	Yes	No
Resistant	3.9	SD	wild type		No	No
Resistant	8.6	PR	BRCA2 4677 delA		Yes	Yes
Resistant	1.5	SD	wild type		No	No
Resistant	1.9	PD	BRCA1,c.5166 C>A, heterozygous		Yes	No
Sensitive	4.5	SD	BRCA1, 187 delAG		Yes	No
Resistant	1.8	PD	wild type		No	No
Resistant	7.2	SD	wild type		No	No
Resistant	7.3	SD	wild type	BRCA1 exon 15-23del, somatic	Yes	No
Resistant	2.0	PD	wild type		No	No
Resistant	3.7	SD	wild type		No	No
Resistant	9.3	SD	wild type		No	No
Resistant	6.5	SD	wild type		No	No
Resistant	1.7	PD	wild type		No	No
Resistant	2.8	SD	wild type		No	No
Resistant	7.3	SD	wild type		No	No
Resistant	17.2	PR	wild type		No	No
Resistant	2.9	SD	wild type	PALB2 c.1073C>T, p.P358L, somatic	Yes	No
Resistant	5.0	SD	BRCA1, c.68_69 del, heterozygous		Yes	No

Sensitive	6.5	PR	wild type	BRCA2 c.767_768delCA, somatic	Yes	No
Resistant	1.4	PD	wild type		No	No
Resistant	9.5	SD	wild type		No	No
Resistant	2.9	SD	wild type		No	No
Sensitive	21.0+	PR	BRCA2, c.8575delC, heterozygous		Yes	No
Resistant	1.3	PD	wild type		No	No
Resistant	2.1	PD	wild type		No	No
Resistant	1.6	PD	wild type		No	No
Resistant	3.7	SD	wild type	BRIP1 c.2348G>A, p.G783E, somatic	Yes	Yes
Resistant	5.9	SD	wild type		No	No
Sensitive	2.0	PD	wild type		No	No
Resistant	2.8	SD	wild type	CDK12 c.301delG:p.G101fs, somatic	Yes	No
Sensitive	1.8	PD	wild type		No	No

* Data cutoff date is February 12, 2019. All patients progressed on study treatment except one patient with *BRCA2m* platinum-sensitive disease who was receiving treatment at the time of data cutoff, at >21 months continuous treatment.
Abbreviations: PFS = progression-free survival, HRR = homologous recombination repair, PARPi = PARP inhibitor.

Supplementary Table 2. Relationship of treatment response with the degree of TIL and PD-L1 labeling in pre-treatment and post-treatment tumor samples

	Patients with Evaluable Pre-Treatment Biopsy					**Patients with Evaluable Post-Treatment Biopsy**				
	all	**PR**	**SD**	**PD**	***p-value****	**all**	**PR**	**SD**	**PD**	***p-value****
Number (%)	30[1]	5 (17%)	17 (57%)	8 (27%)		16[3]	2 (%12)	9 (57%)	5 (31%)	
% TIL	n = 29	n = 5	n = 16	n = 8						
Average % TIL	17% TIL	18% TIL	23% TIL	5% TIL	*0.008*	23%	39%	22%	19%	*n.s.*
<5% (n, %)	9 (31%)	1 (20%)	5 (31%)	3 (38%)		3 (19%)	1 (50%)	1 (11%)	1 (20%)	
5-10% (n, %)	11 (38%)	1 (20%)	5 (31%)	5 (62%)		5 (31%)	0	4 (44%)	1 (20%)	
11-50% (n, %)	6 (21%)	3 (60%)	3 (19%)	0		5 (31%)	0	2 (22%)	3 (60%)	
51-100% (n, %)	3 (10%)	0	3 (19%)	0		3 (19%)	1 (50%)	2 (22%)	0	
any >10% (n, %)	9 (31%)	3 (60%)	6 (38%)	0	*0.035*	8 (50%)	1 (50%)	4 (44%)	3 (60%)	*n.s.*
PD-L1 labeling in carcinoma**	n = 28[2]	n = 5	n = 16	n = 7		n = 14	n = 1	n = 8	n = 5	
N (%) Positive, 1-50%	14 (50%)	2 (40%)	9 (56%)	3 (43%)	*n.s.*	9 (64%)	1 (100%)	5 (63%)	3 (60%)	*n.s.*
N (%) Positive, 51-100%	0	0	0	0		1 (7%)	0	1 (13%)	0	
N (%) Negative	14 (50%)	3 (60%)	7 (44%)	4 (57%)		5 (36%)	0	3 (38%)	2 (40%)	

*p-values are based upon a comparison of patients with PR to those with PD.

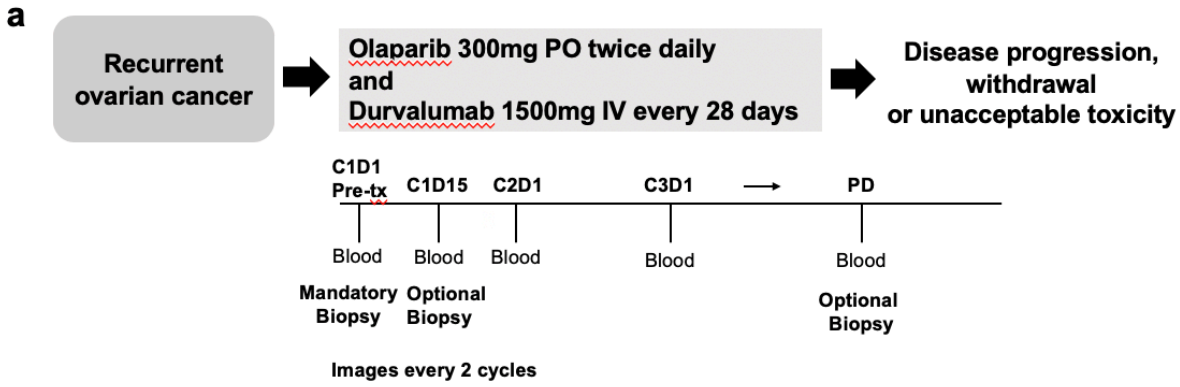
**No tumors completely lost PD-L1 expression (positive to negative) after one dose of durvalumab on cycle 1 day 1 although two tumors displayed a decrease in the proportion of PD-L1 positive cells (20% to 2% and 10% to 8% PD-L1+ carcinoma cells, respectively), both with PD compared to no patients with SD or PR (p=0.09).

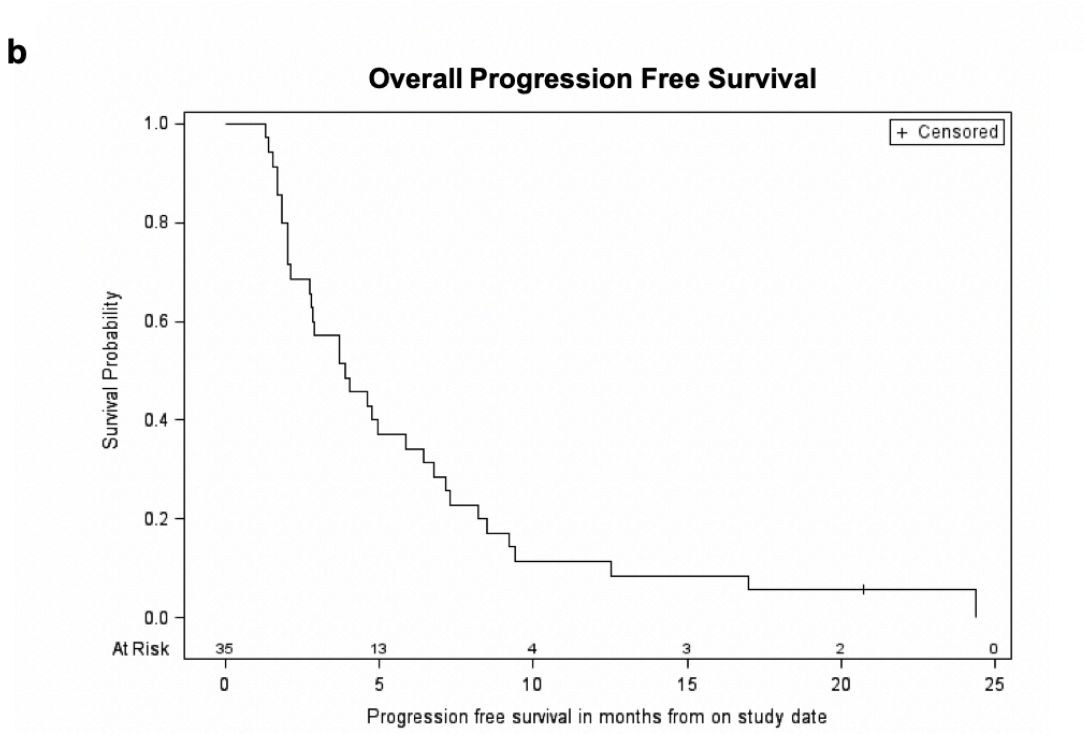
[1] 2 of the 32 pre-treatment biopsies contained <5% tumor samples; [2] PD-L1 IHC was unevaluable in 2 of 30 biopsy samples (technical issues); [3] 6 of the 22 post-treatment biopsies were insufficient for biomarker studies (technical issues).

Abbreviations: n, number; n.s., not significant ($p \geq 0.05$); PD, progressive disease; PR, partial response; SD, stable disease; TIL, tumor infiltrating lymphocytes.

Figures

Supplementary Figure 1. Study design and progression free survival

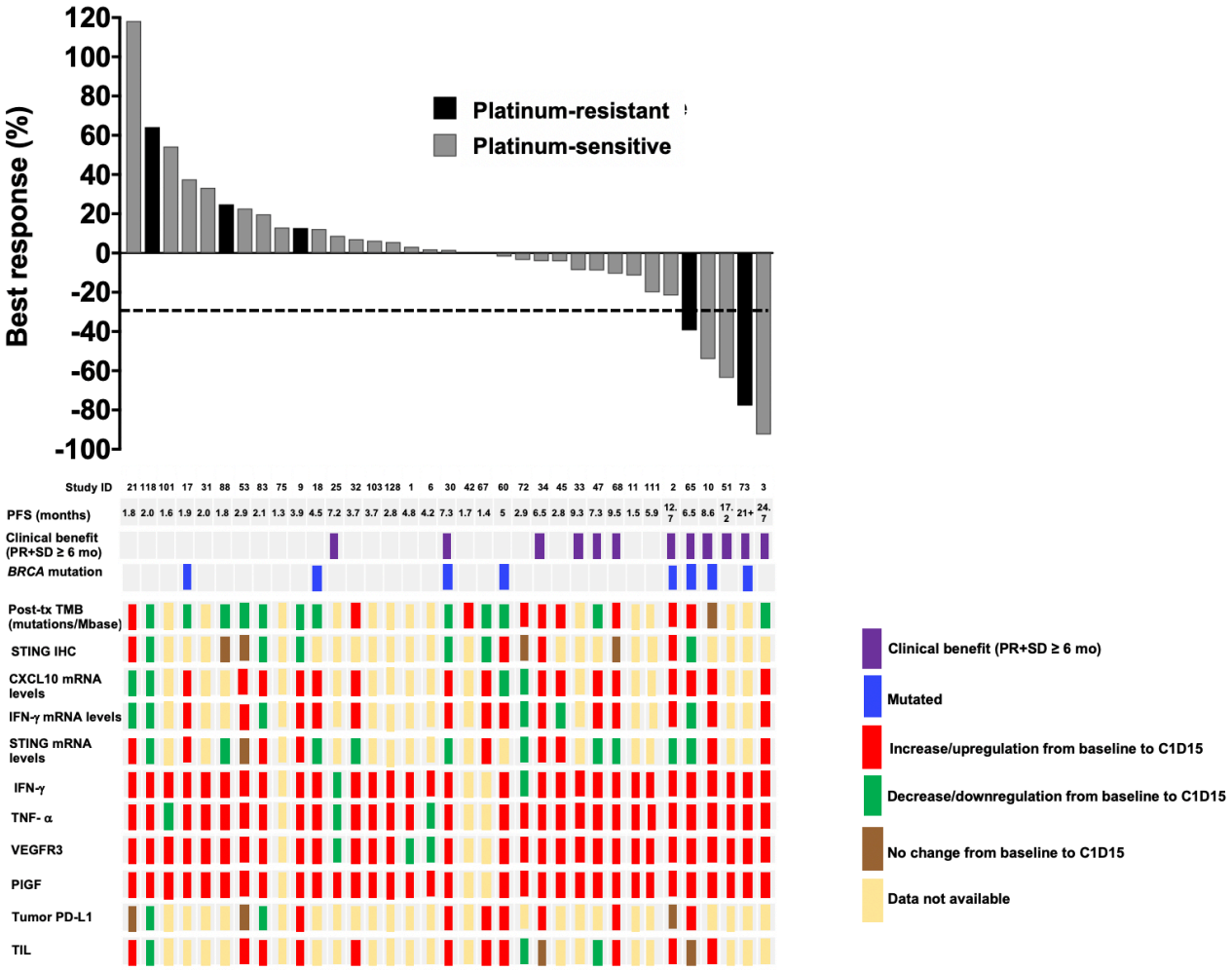




Supplementary Figure 1 Legend:
a) Study design and sample collection timepoints. Pretreatment C1D1 biopsy was mandatory, and other timepoints were optional because of patient's refusal or safety concerns.
b) Overall progression free survival. Median potential follow-up: 24.6 months, Median PFS 3.9 months (95% CI: 2.8 to 5.9 months).

Abbreviations**:** C1D1 = cycle 1 day 1, C1D15 = cycle 1 day 15, C2D1 = cycle 2 day 1, C3D1 = cycle 3 day 1, PD = progressive disease, PO = per os, tx = treatment, PFS = progression free survival.

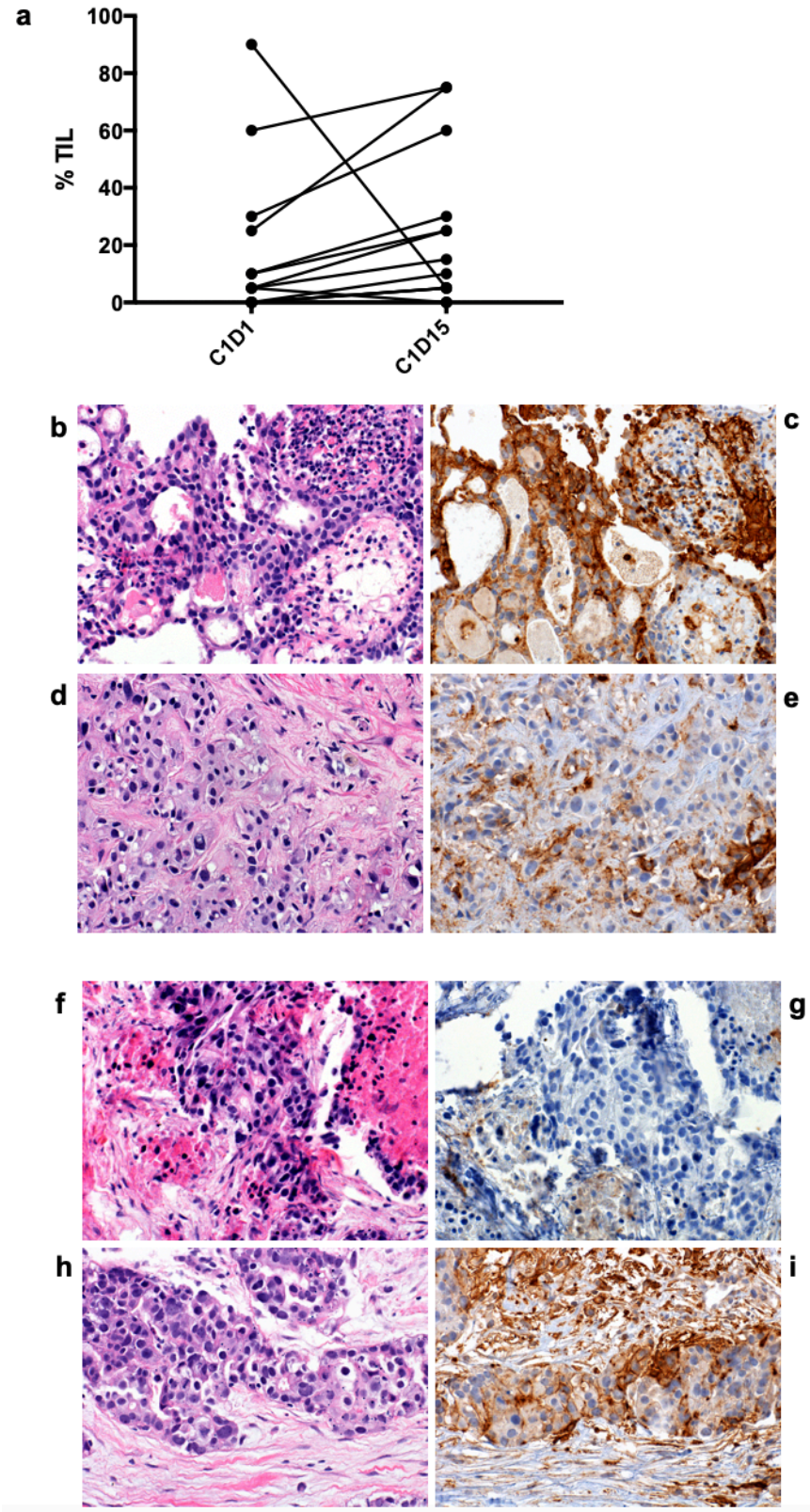
Supplementary Figure 2. Changes of biomarker endpoints in relation to best responses



Supplementary Figure 2 Legend: Best responses (percentage change in tumor size) are shown according to study ID, PFS, clinical response, *BRCA* mutation status, and change in TMB, tissue expression of STING, mRNA expression of CXCL10, IFNγ, and STING, plasma levels of IFNγ, TNFα, VEGFR3, and PlGF, tumor expression of PD-L1, amount of TILs, all calculated as C1D15/C1D1.

Abbreviations: ID = identification, PFS = progression-free survival, PR = partial response, SD = stable disease, mo = months, tx = treatment, TMB = tumor mutational burden, STING = stimulator of interferon genes, IHC = immunohistochemistry, IFNγ = interferon gamma, TNFα = tumor necrosis factor alpha, VEGFR3 = vascular endothelial growth factor receptor 3, PlGF = placental growth factor, PD-L1 = programmed death-ligand 1, TIL = tumor infiltrating lymphocyte.

Supplementary Figure 3. PD-L1 and tumor infiltrating lymphocytes staining (representative figures)



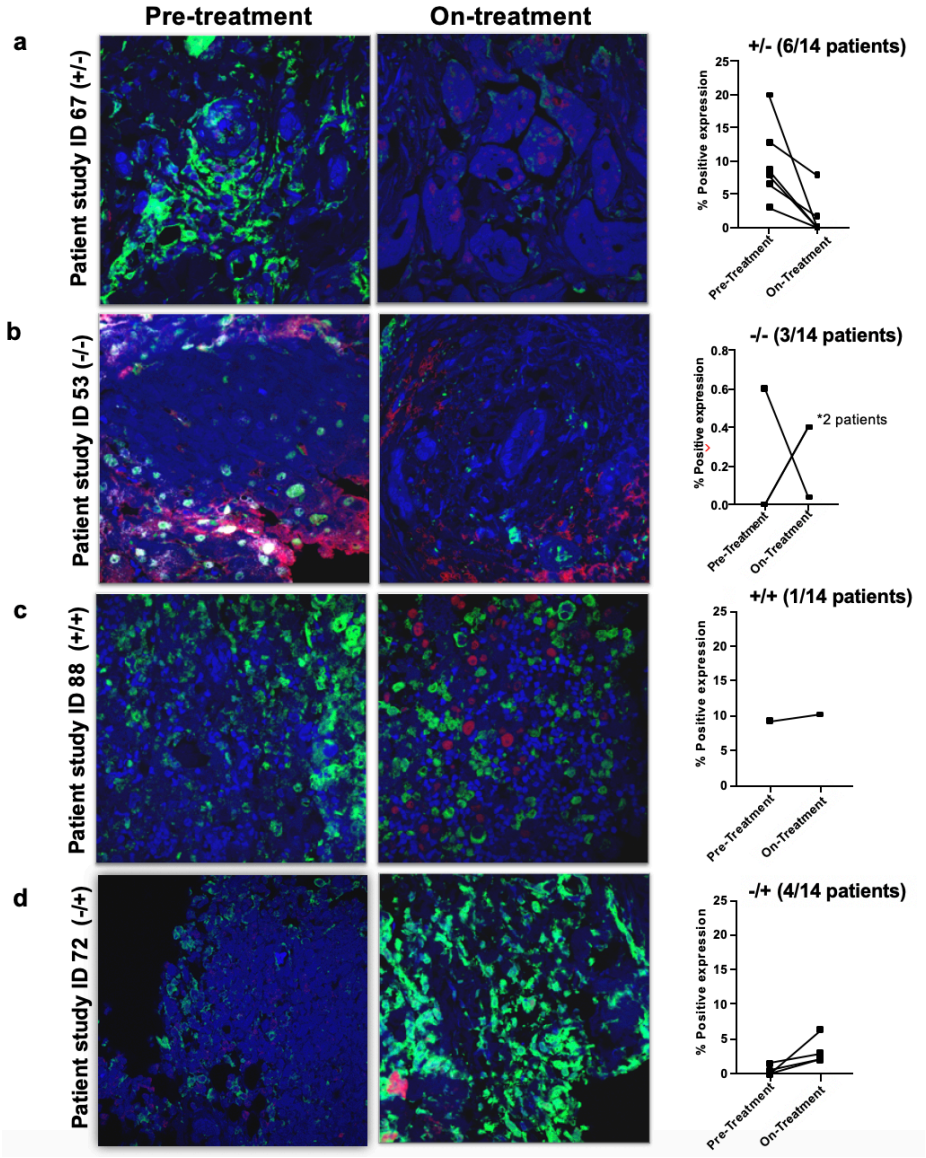
Supplementary Figure 3 Legend:
a) %TIL in tumor tissue at C1D1 and C1D15 among 15 available matched pairs of patients. An increase in %TIL was observed among 11/15 patients, and there was an overall significant increase in %TIL from median 5% to 10%, p=0.035.

b-e: The degree of TIL but not PD-L1 labeling in the pre-treatment tumor is associated with treatment response to anti-PD-L1 therapy.
b,c) The patient ID#3 with a partial response; her pre-treatment tumor displayed 25% tumoral TIL and 25% PD-L1+ carcinoma cells, respectively but no changes after treatment.
d,e) The patient ID#118 with progressive disease; her pre-treatment tumor displayed 5% tumoral TIL tumor biopsy and 20% PD-L1+ carcinoma, respectively.

f-i Gain of carcinoma cell PD-L1 expression in a patient with stable disease (3.9 months) after PARPi.
f,g) The patient ID#9 with stable disease; pre-treatment tumor was negative for PD-L1 labeling by the carcinoma cells.
h,i) However, her on-treatment tumor biopsy displayed PD-L1+ carcinomas cells, as well as increased degree of PD-L1+ TIL.

Abbreviations*:* C1D1 = cycle 1 day 1, C1D15 = cycle 1 day 15, PD-L1 = programmed death ligand 1, TIL = tumor-infiltrating lymphocyte.
All images, 200X.

Supplementary Figure 4. STING expression in paired pre- and on-treatment tumor biopsies

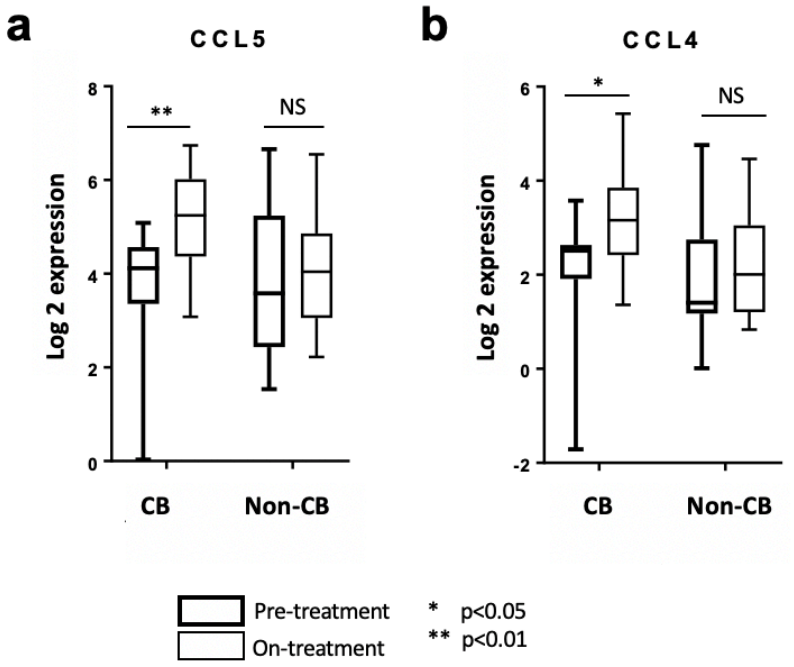


Supplementary Figure 4 Legend:
Representative immunohistochemical figures are shown on the left.
All images: 10x magnification, STING (green), p53 (red), CD3 (yellow) and DAPI (blue).

a) 6/14 (43%) patients had decreased STING expression post-treatment (median 8.3% vs 0.03%, pre vs on-therapy, p=0.03).
b) 3/14 (21%) patients maintained unchanged, negative STING staining on-treatment.
c) 1 patient (7%) maintained unchanged, positive STING staining on-treatment.
d) 4/14 (29%) patients had increased STING expression post-treatment (median 0.26% vs 2.6%, pre vs on-therapy, p=0.125).

Abbreviations: STING = stimulator of interferon genes.

Supplementary Figure 5. CCL5 and CCL4 expression analysis by RNA-seq



Supplementary Figure 5 Legend:
a) Change in log2 CCL5 expression among 20 paired pre- vs on-treatment tumor biopsies, with significant change observed among responders (median pre 4.12 vs on-therapy 5.24, p=0.008, Wilcoxon signed-rank test).
b) Change in log2 CCL4 expression among 20 paired pre- vs on-treatment tumor biopsies, with significant change observed among responders (median pre 2.51 vs on-therapy 3.16, p=0.01, Wilcoxon signed-rank test).

Abbreviations: NS = non-significant, CB = clinical benefit, non-CB = non-clinical benefit.

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