

## Priority Report

## PARP-1 Inhibition as a Targeted Strategy to Treat Ewing's Sarcoma

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## Abstract

Ewing's sarcoma family of tumors (ESFT) refers to aggressive malignancies which frequently harbor characteristic EWS-FLI1 or EWS-ERG genomic fusions. Here, we report that these fusion products interact with the DNA damage response protein and transcriptional coregulator PARP-1. ESFT cells, primary tumor xenografts, and tumor metastases were all highly sensitive to PARP1 inhibition. Addition of a PARP1 inhibitor to the second-line chemotherapeutic agent temozolamide resulted in complete responses of all treated tumors in an EWS-FLI1-driven mouse xenograft model of ESFT. Mechanistic investigations revealed that DNA damage induced by expression of EWS-FLI1 or EWS-ERG fusion genes was potentiated by PARP1 inhibition in ESFT cell lines. Notably, EWS-FLI1 fusion genes acted in a positive feedback loop to maintain the expression of PARP1, which was required for EWS-FLI-mediated transcription, thereby enforcing oncogene-dependent sensitivity to PARP-1 inhibition. Together, our findings offer a strong preclinical rationale to target the EWS-FLI1:PARP1 intersection as a therapeutic strategy to improve the treatment of ESFTs. *Cancer Res*; 72(7); 1608–13. ©2012 AACR.

## Introduction

The Ewing's sarcoma family of tumors (ESFT) refers to malignant neoplasms of bone and soft tissue which frequently harbor reciprocal chromosomal translocations that result in the production of chimeric proteins containing the transcriptional activation domain from the Ewing's sarcoma breakpoint region 1 gene (*EWS*) fused to the DNA-binding domain of an E26 transformation-specific sequence (*ETS*) transcription factor (*FLI1* or *ERG*; refs. 1, 2). Dysregulation of these chimeric proteins have previously been implicated in abnormal proliferation, invasion, and tumorigenesis (3, 4). Although the EWS-FLI or EWS-ERG fusion proteins represent potential disease-specific molecular targets, transcription factors such as these have been notoriously difficult to inhibit therapeutically. How-

ever, given the poor outcomes of patients with metastatic ESFT (5), there is a clear need to improve therapy for these patients.

We have recently shown that an alternative strategy to inhibit transcription factor activity is to target critical interacting enzymes (6). Similar to ESFTs, 50% of prostate cancers harbor genomic rearrangements of *ETS* transcription factors (7). However, unlike the EWS-FLI or EWS-ERG fusions which produce a multifunctional chimeric protein, prostate cancer rearrangements usually place an androgen-regulated promoter upstream of an *ETS* gene (*ERG* or *ETV1*), resulting in increased *ETS* transcription factor activity by overexpression (3). We have previously shown that PARP1 and DNA-dependent protein kinase (DNA-PKcs) are key *ETS* protein family cofactors in prostate cancer, and therapeutic inhibition of PARP1 disrupts the growth of *ETS* positive, but not *ETS* negative, prostate cancer xenografts (6). Importantly, we showed that this *ETS* protein interaction axis is mediated by the *ETS* DNA-binding domain (6). Although this interaction site is present in the EWS-FLI1 and EWS-ERG chimeras, these fusion proteins activate oncogenic pathways independent of their DNA-binding domain (8). As such, despite the presence of the *ETS* DNA-binding domain, the effectiveness of PARP inhibitors against these multifunctional gene fusion proteins is unclear.

Mechanistically, PARP1 is a functionally complex enzyme that has been shown to both drive transcription and to accelerate base excision repair (9–11). PARP1 inhibitors have shown promising activity in early clinical trials (12), particularly in BRCA-mutant cancers defective in homologous repair (HR), in which they may cause replication fork stalling and subsequent synthetic lethal cell death (13, 14). We now

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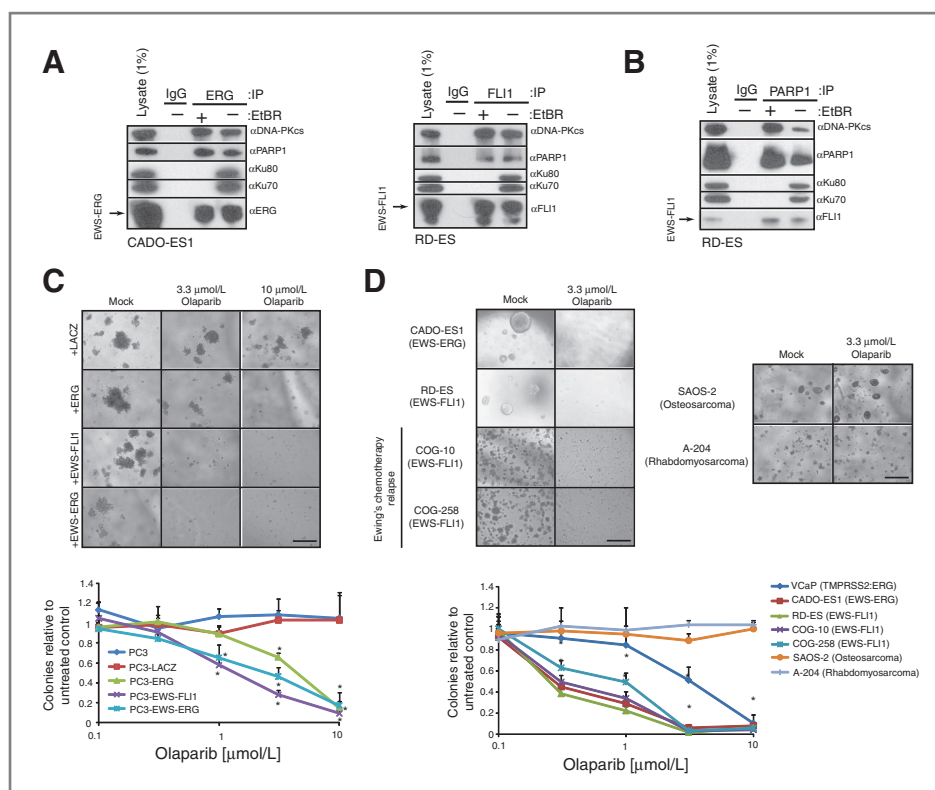
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**Figure 1.** Ewing's sarcoma gene fusion products (EWS-FLI1 and EWS-ERG) interact with PARP1 and DNA-PKcs and confer sensitivity to PARP1 inhibition. A, IP-immunoblot analysis conducted on CADO-ES1 (EWS-ERG) cells with an ERG antibody and RD-ES (EWS-FLI1) cells using a FLI1 antibody. IPs were treated  $\pm$ 100  $\mu$ g/mL ethidium bromide. B, as in A, except using a PARP1 antibody on RD-ES cells. C, soft agar colony formation assays were conducted using PC3 cells, overexpressing ERG, EWS-FLI1, EWS-ERG, or LACZ. Colonies counted after 3 weeks in culture. Representative photomicrographs shown. Scale bar, 50  $\mu$ mol/L. D, as in C, except in ETS-rearranged cells (VCaP, RD-ES, CADO-ES1, COG10, and COG258) and ETS-negative sarcoma controls (SAOS-2 and A-204). Error bars, SEM of 3 replicates. \*,  $P < 0.05$ .



hypothesize that the *EWS-FLI1* and *EWS-ERG* gene fusions in ESFTs depend on the activity of PARP1 and may be targeted with PARP1 inhibition.

## Materials and Methods

### Cell lines and inhibitors

PC3, RD-ES, SAOS-2, A-204 (ATCC), CADO-ES1 (DSMZ), COG10, and COG258 cell lines were grown in RPMI-1640 (Invitrogen) supplemented with 10% FBS (Invitrogen). The genetic identity of each cell line was confirmed by genotyping samples. Olaparib was purchased from Axon Biochem.

### RNA interference

Gene-specific knockdown was accomplished with commercially available siRNA duplexes for EWS, ERG, FLI1, DNA-PKcs, or PARP-1 (Dharmacon). Two independent siRNA sequences were used for each gene for knockdown experiments.

### In vitro assays

Soft agar colony formation, chemosensitivity, and basement membrane matrix invasion assays were conducted per standard protocols (see SOM). Approaches for immunofluorescence, immunoprecipitation, Western blot, COMET assays, luciferase reporter assays, and Oncomine analysis are also detailed in the SOM. Primer sequences available in Supplementary Table S1.

### Xenografts

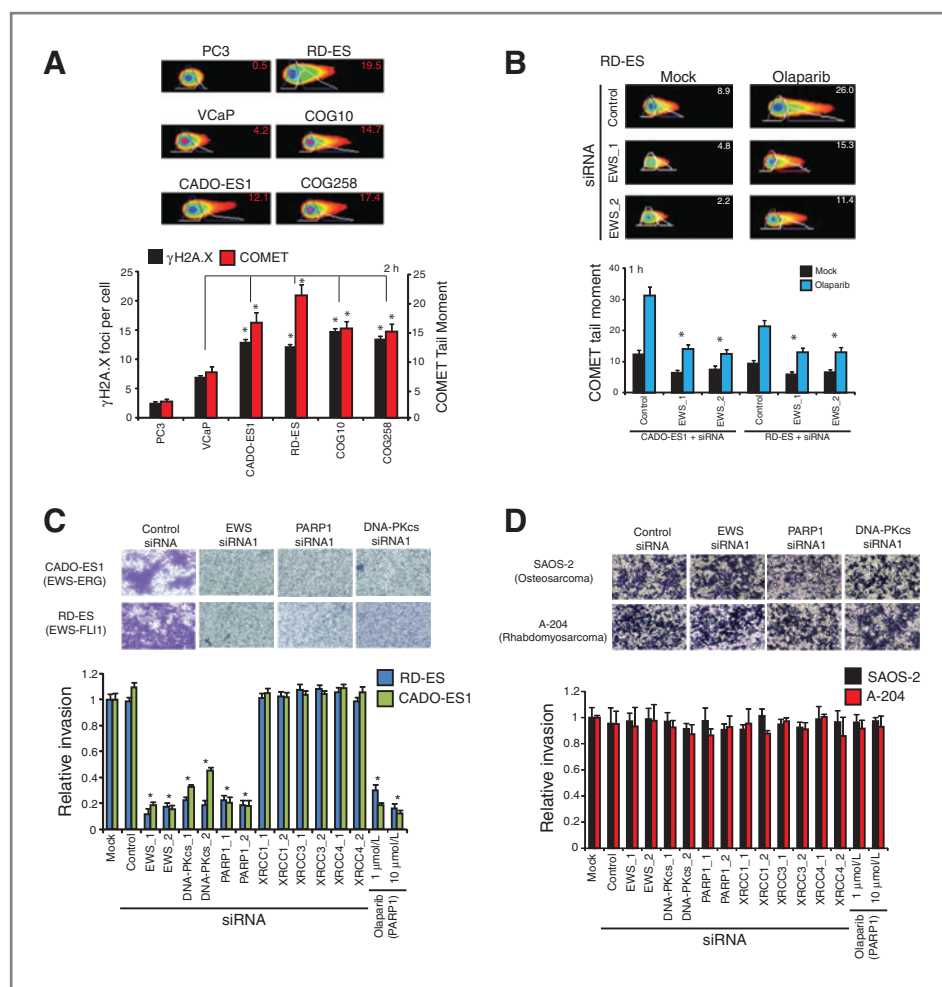
Severe combined immunodeficient mice were purchased from Charles River, Inc. (Charles River Laboratory) and

implanted subcutaneously with RD-ES, PC3-luciferase-LACZ, or PC3-luciferase-EWS-FLI1 ( $1 \times 10^6$  cells per injection). After 2 weeks, mice with tumors were treated with Olaparib and/or Temozolamide. All procedures involving mice were approved by the University of Michigan, The University Committee on Use and Care of Animals (UCUCA) and conform to their relevant regulatory standards. Additional experimental details are available in the SOM.

## Results and Discussion

To test the hypothesis that EWS fusions interact with PARP1, we carried out immunoprecipitation (IP)-immunoblot analysis on cell lines naturally harboring the rearrangements. Using an ERG or FLI1 antibody that recognizes the EWS-ERG and EWS-FLI1 fusion proteins, respectively, we pulled down both PARP1 and DNA-PKcs in a DNA-independent manner from 2 cell lines, CADO-ES1 (EWS-ERG) or RD-ES (EWS-FLI1; Fig. 1A). Reverse IP from RD-ES cells carried out using a PARP1 antibody enriched for EWS-FLI1 and DNA-PKcs in a DNA-independent manner (Fig. 1B), confirming the interaction between EWS fusions and PARP1.

We then tested the sensitivity of ESFT cells to the PARP1 inhibitor Olaparib. To analyze the sensitivity of ESFT cells overexpressing the *EWS-FLI1* and *EWS-ERG* fusions, compared with the prostate cancer harboring the *TMPRSS2-ERG* fusion, we carried out soft agar colony formation assays on PC3 cells in which we had stably overexpressed these fusion products. Overexpression of any of these 3 *ETS* fusion genes caused sensitivity to Olaparib ( $P < 0.05$  at 3 and 10  $\mu$ mol/L), and the



**Figure 2.** Ewing sarcoma gene fusion products confer increased DNA damage and cell invasion, which can be modulated by genetic or pharmacologic approaches. **A**, staining and quantification of  $\gamma$ H2A.X foci in prostate and EFST cells shown on left axis. On right axis, average tail moments from neutral COMET assays are shown. Representative COMET tails are shown, with calculated tail moments depicted numerically. **B**, neutral COMET assays conducted on cells treated with siRNA and/or 1  $\mu$ mol/L Olaparib as indicated. **C**, Boyden chamber Transwell migration assays were conducted 48 hours after siRNA transfection or Olaparib treatment. For siRNA experiments, cells were plated in serum-free media and incubated for another 48 hours before fixing and staining. Representative photomicrographs are shown. **D**, as in **C**, except sarcoma control cell lines that do not harbor ETS gene fusions were used. Error bars, SEM of 3 replicates. \*,  $P < 0.05$ .

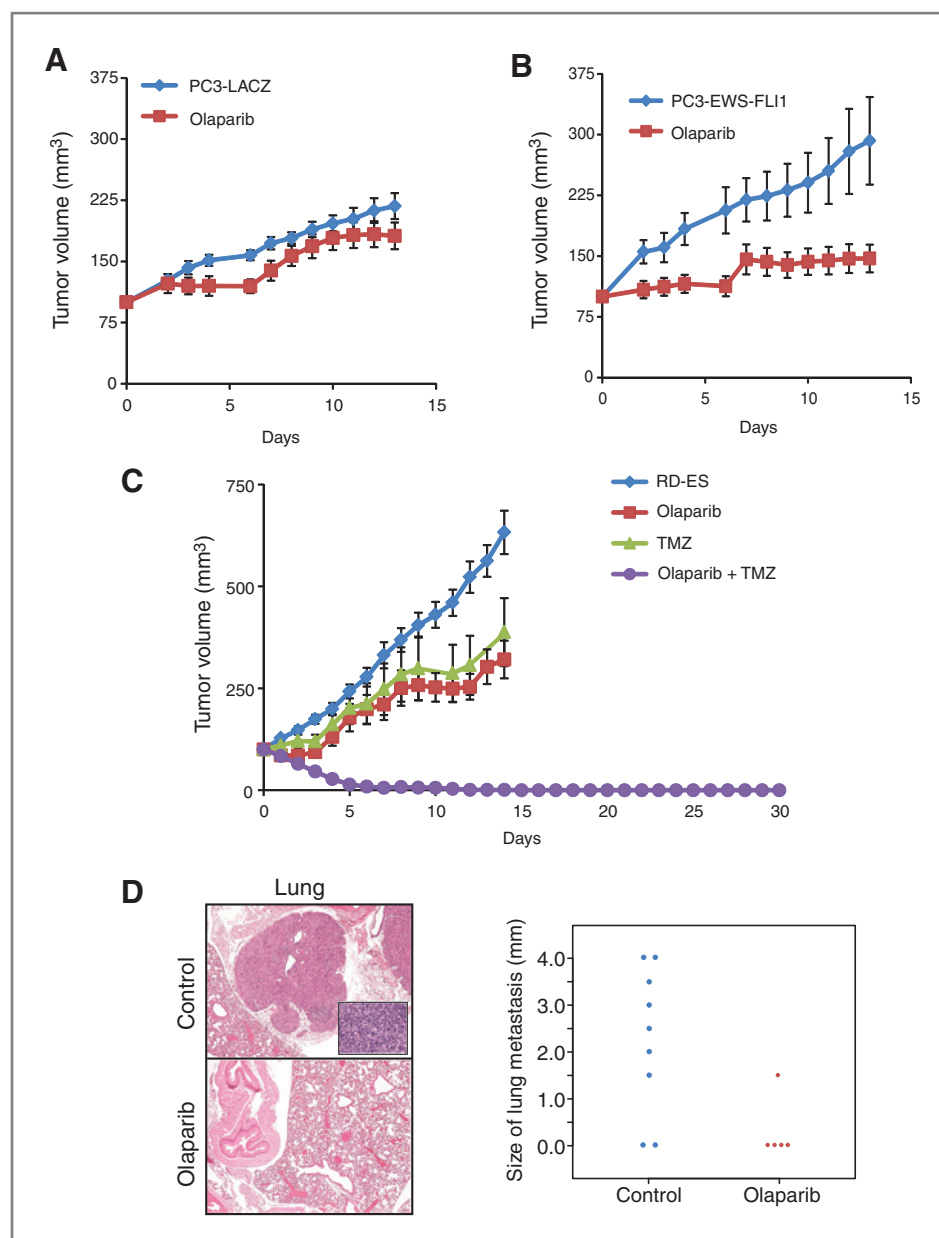
*EWS-FLI1* and *EWS-ERG* fusions were more sensitive than the *TMPRSS2-ERG* fusion ( $P < 0.05$  at 1  $\mu$ mol/L; Fig. 1C). Soft agar assays conducted with CADO-ES1, RD-ES, or VCaP (*TMPRSS2-ERG* rearranged prostate cancer) cells confirmed that while all *ETS*-positive cell lines were more susceptible to Olaparib than the *ETS*-negative cell line PC3, ESFT cell lines were even more sensitive than VCaP cells ( $P < 0.05$ ; Fig. 1D). Importantly, Olaparib did not have an effect on an osteosarcoma cell line, SAOS-2, or a rhabdomyosarcoma cell line, A-204, which were used as sarcoma model controls without *ETS* rearrangement (Fig. 1D). We also found that 2 Ewing's cell lines [COG10 and COG258 (both *EWS-FLI1*)] derived from front-line chemotherapy patient relapses (and thus heavily pretreated) were also extremely sensitive to PARP1 inhibition (Fig. 1D).

Given the sensitivity of ESFTs to PARP inhibition, we sought to explore the mechanism underlying this sensitivity. In prostate cancer, *TMPRSS2-ERG* overexpression causes DNA damage, which is then potentiated by PARP inhibition (6). Surprisingly, Ewing's cells showed significantly more  $\gamma$ H2A.X foci (a marker of DNA double-strand breaks) per cell than *TMPRSS2-ERG*-positive VCaP cells ( $P < 0.05$  for all EFST cells; Fig. 2A) and 1  $\mu$ mol/L Olaparib caused massive induction of  $\gamma$ H2A.X foci

(Supplementary Fig. S1A). Neutral COMET assays confirmed that natural EFST cells have more DNA double-strand breaks per cell than VCaP cells ( $P < 0.05$ ; Fig. 2A). Importantly, overexpression of *EWS-FLI1* in PC3 cells led to increased DNA breaks ( $P < 0.05$ ; Supplementary Fig. S1B), and knockdown of either *EWS-FLI1* or *EWS-ERG* fusions caused a reduction in COMET tail moment, and significantly decreased the induction of DNA damage after Olaparib treatment ( $P < 0.05$ ; Fig. 2B and Supplementary Figs. S2A, S2B, S3A, and S3B) suggesting that Olaparib-potentiated DNA damage is due to expression of the *EWS-FLI1* and *EWS-ERG* fusion genes. Inhibition of nonhomologous end-joining (NHEJ) can synergistically potentiate DNA damage in the context of deficient HR. However, siRNA knockdown of XRCC4 (needed for NHEJ) had little effect (Supplementary Fig. S4), suggesting that EFST cells have functional HR. Although PARP1 inhibition dramatically accentuated DNA damage, it did not have an effect on short-term cell viability (Supplementary Fig. S5A and S5B).

We next assessed the effect of PARP1 inhibition on short-term cell invasion. Intriguingly, siRNA against *EWS*, *PARP1*, or *DNA-PKcs* reduced CADO-ES1 and RD-ES cell invasion ( $P < 0.05$ ), while knockdown of key components of DNA repair

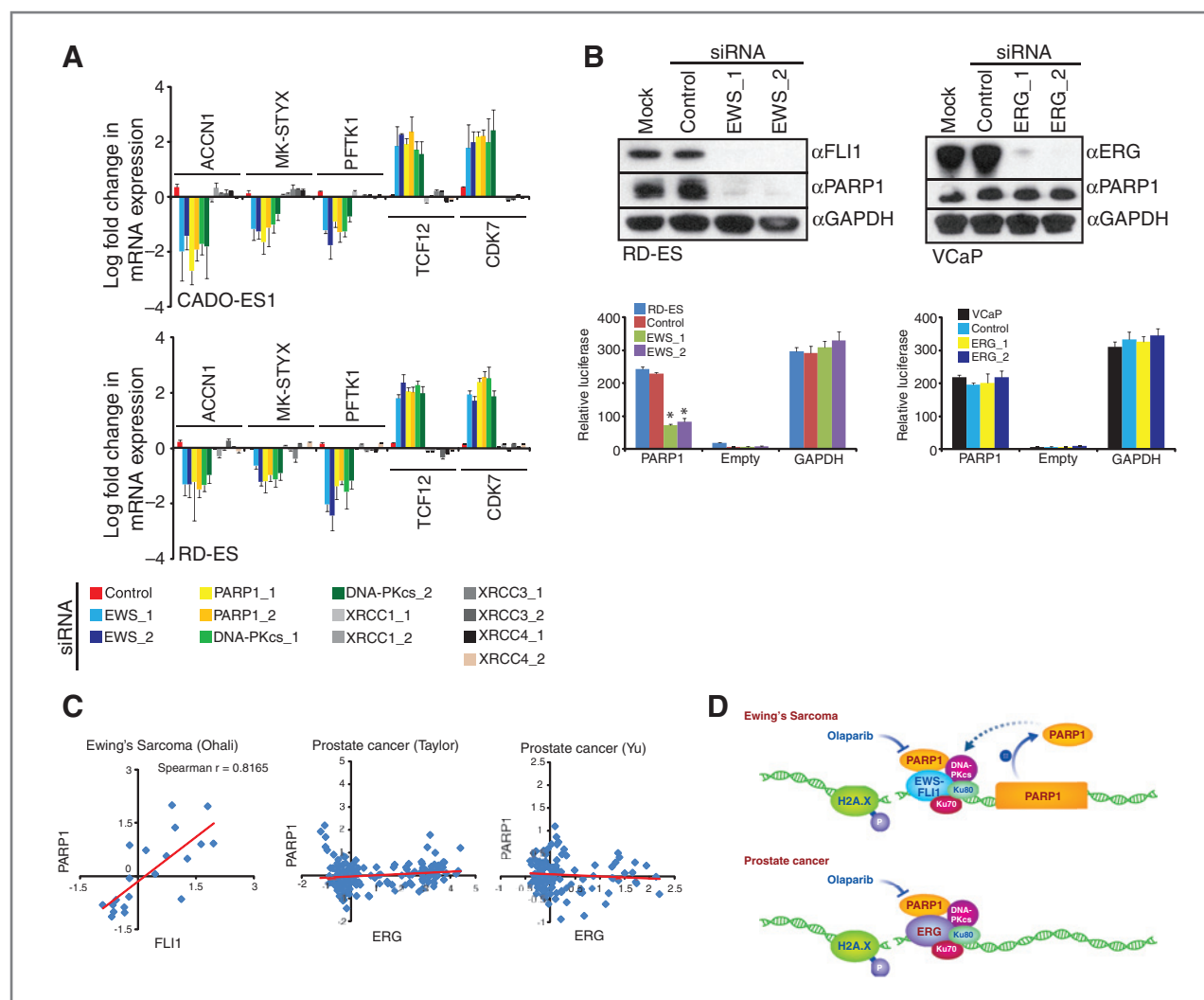
**Figure 3.** PARP inhibition prevents EWS-FLI1-positive xenograft growth and metastasis. A, two weeks after engraftment, PC3-LACZ xenografts were treated with 100 mg/kg Olaparib twice a day. Tumor volume measurements were recorded daily. B, as in A, except with PC3-EWS-FLI1 xenografts. C, as in A, except RD-ES were treated with Olaparib (100 mg/kg BID) alone, TMZ (50 mg/kg QD) alone, or in combination. D, at the RD-ES xenograft assay endpoint, lungs were analyzed for metastases. Representative images were taken with a  $\times 4$  objective (inset at  $\times 40$ ). In the plot, each dot represents an individual lung metastasis for different treatments as indicated along the x-axis. Metastasis diameter was measured and depicted along the y-axis.



pathways (*XRCC1* for base excision repair, *XRCC3* for HR, and *XRCC4* for NHEJ) had no effect (Fig. 2C and Supplementary Figs. S2A and S2B), supporting a DNA repair-independent role of the enzymes. Importantly, Olaparib disrupted ESFT cell invasion ( $P < 0.05$ ) at approximately 1 log-fold lower concentration than VCaP cell invasion (6) and did not affect ETS negative, control sarcoma cell invasion (Fig. 2D and Supplementary Figs. S2A and S2B).

Because PARP inhibition disrupts the long-term growth and invasion of ESFT cells, we assessed the ability of *EWS-FLI1* to sensitize xenografts to Olaparib. Surprisingly, Olaparib significantly impeded PC3-EWS-FLI1 ( $P < 0.001$ ), but not PC3-LACZ, xenograft growth (Fig. 3A and B), showing that *EWS-FLI1* overexpression is alone sufficient to sensitize PC3 xenografts

to Olaparib. Because PARP1 inhibitors are unlikely to be used clinically as a monotherapy, we also combined PARP1 inhibition with the DNA alkylating agent temozolomide (TMZ) to treat a highly aggressive ESFT xenograft model (RD-ES) harboring an endogenous *EWS-FLI1* rearrangement. TMZ potentiates the effects of PARP1 inhibitors (15) and is currently being assessed in Ewing's sarcoma patients as second-line therapy (16). Surprisingly, TMZ alone only delayed RD-ES xenograft growth ( $P < 0.001$ ; Fig. 3C). However, Olaparib also caused significant delay in RD-ES xenograft growth ( $P < 0.001$ ), and, when administered in combination with TMZ, led to an immediate tumor regression and a highly significant sustained complete response. Mice were maintained without therapy for an additional 30 days without any observable recurrence



**Figure 4.** EWS-FLI1 maintains a feed forward loop that drives PARP1 expression. **A**, CADO-ES1 or RD-ES cells were treated with siRNA for 48 hours. Quantitative PCR was then carried out for several *EWS-ETS* target genes. **B**, immunoblot analysis of cells treated with control or *EWS* siRNA. Bar graphs are *PARP1* promoter reporter luciferase assays conducted on cells treated with siRNA for 24 hours and then transfected with the promoter reporter for an additional 24 hours. **C**, Oncomine scatter plots of publicly available gene expression data sets. Each point represents gene expression values from an individual patient. First author of each published study is indicated and referenced in the SOM. **D**, model depicting proposed mechanism of increased PARP1 sensitivity of ESFTs as compared with ETS-positive prostate cancers. Error bars, SEM of 3 replicates. \*,  $P < 0.05$ .

( $P < 0.001$ ). Furthermore, we harvested lungs from RD-ES-xenografted mice, assessed metastasis and found only 1 of 5 mice treated with Olaparib developed lung metastasis as compared with 6 of 8 untreated mice ( $P = 0.058$ ; Fig. 3D). This is the first mouse model showing that PARP1 activity is required for metastasis.

Given that PARP1 has roles in both DNA repair and transcriptional regulation (9, 10), we hypothesized that the sensitivity of ESFT xenograft growth and metastasis depends on both PARP1-mediated roles. Consistent with this, knockdown of PARP1 or DNA-PKcs, but not other DNA repair proteins, disrupted transcriptional activity to a similar extent as fusion targeting *EWS* siRNA as evidenced by disruption of consensus EWS-FLI1 target genes (ref. 17; Fig. 4A and Supplementary Figs. S2A, S2B).

In modulating EWS-FLI1 and EWS-ERG expression, we observed that both EWS fusions maintain *PARP1* mRNA expression levels ( $P < 0.05$ ; Supplementary Figs. S2A, S3A, S6A, and S6B). This was unexpected because the *ETS* gene fusions found in prostate cancer do not regulate *PARP1* mRNA expression (6), but consistent with reports showing that ETS transcription factors drive PARP1 expression in ESFTs (18, 19). Likewise, in EFST cells, knockdown of the EWS-FLI1 fusion led to a decrease in PARP1 protein expression and promoter activity ( $P < 0.05$ ), while ERG siRNA did not have these effects in VCaP cells (Fig. 4B). Conversely, EWS-FLI1 expression was not altered by Olaparib in RD-ES cells (Supplementary Figs. S6C and S6D). Finally, Oncomine tumor microarray compendium analysis showed that *PARP1* mRNA expression correlates with *FLI1* expression in EFST patient samples ( $P < 0.01$ ,

Spearman correlation shown in figure), but did not correlate with *ERG* expression in prostate cancer (Fig. 4C). Taken together, our data suggest that PARP1 is critical to a positive-feedback loop in EFST, in which the EWS-FLI fusion product drives expression of PARP1, which then further promotes transcriptional activation by EWS-FLI.

In conclusion, our data show that ESFT cells and xenografts are sensitive to PARP1 inhibition, to a significantly greater degree than their *ETS* fusion-positive prostate cancer counterparts. This increased sensitivity may stem from both greater potentiation of DNA damage by PARP1 inhibition, as well as a EWS-FLI:PARP1-positive feedback loop in transcriptional activation (Fig. 4D). Our findings suggest that PARP1 inhibition should be explored as a strategy for targeted therapy in Ewing's sarcoma, which may represent a tumor type that may be as profoundly affected by PARP inhibitors as *BRCA1/2* mutated carcinomas (12–14).

## References

- Burchill SA. Ewing's sarcoma: diagnostic, prognostic, and therapeutic implications of molecular abnormalities. *J Clin Pathol* 2003;56:96–102.
- de Alava E, Kawai A, Healey JH, Fligman I, Meyers PA, Huvos AG, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. *J Clin Oncol* 1998;16:1248–55.
- Brenner JC, Chinnaiyan AM. Translocations in epithelial cancers. *Biochim Biophys Acta* 2009;1796:201–15.
- Tomlins SA, Laxman B, Dhanasekaran SM, Helgeson BE, Cao X, Morris DS, et al. Distinct classes of chromosomal rearrangements create oncogenic *ETS* gene fusions in prostate cancer. *Nature* 2007;448:595–9.
- Pinkerton CR, Bataillard A, Guillo S, Oberlin O, Fervers B, Philip T. Treatment strategies for metastatic Ewing's sarcoma. *Eur J Cancer* 2001;37:1338–44.
- Brenner JC, Ateeq B, Li Y, Yocum AK, Cao Q, Asangani IA, et al. Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in *ETS* gene fusion-positive prostate cancer. *Cancer Cell* 2011;19:664–78.
- Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of *TMPRSS2* and *ETS* transcription factor genes in prostate cancer. *Science* 2005;310:644–8.
- Welford SM, Hebert SP, Deneen B, Arvand A, Denny CT. DNA binding domain-independent pathways are involved in EWS/FLI1-mediated oncogenesis. *J Biol Chem* 2001;276:41977–84.
- Kim MY, Mauro S, Gevry N, Lis JT, Kraus WL. NAD<sup>+</sup>-dependent modulation of chromatin structure and transcription by nucleosome binding properties of PARP-1. *Cell* 2004;119:803–14.
- Krishnakumar R, Gamble MJ, Frizzell KM, Berrocal JG, Kininis M, Kraus WL. Reciprocal binding of PARP-1 and histone H1 at promoters specifies transcriptional outcomes. *Science* 2008;319:819–21.
- Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. *Nat Rev Cancer* 2010;10:293–301.
- Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med* 2009;361:123–34.
- Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005;434:913–7.
- Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature* 2005;434:917–21.
- Donawho CK, Luo Y, Luo Y, Penning TD, Bauch JL, Bouska JJ, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res* 2007;13:2728–37.
- Wagner LM, McAllister N, Goldsby RE, Rausen AR, McNall-Knapp RY, McCarville MB, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. *Pediatr Blood Cancer* 2007;48:132–9.
- Siligan C, Ban J, Bachmaier R, Spahn L, Kreppel M, Schaefer KL, et al. EWS-FLI1 target genes recovered from Ewing's sarcoma chromatin. *Oncogene* 2005;24:2512–24.
- Soldatenkov VA, Albor A, Patel BK, Dreszer R, Dritschilo A, Notario V. Regulation of the human poly(ADP-ribose) polymerase promoter by the *ETS* transcription factor. *Oncogene* 1999;18:3954–62.
- Newman RE, Soldatenkov VA, Dritschilo A, Notario V. Poly(ADP-ribose) polymerase turnover alterations do not contribute to PARP overexpression in Ewing's sarcoma cells. *Oncol Rep* 2002;9:529–32.

## Disclosure of Potential Conflicts of Interest

The University of Michigan has filed a patent linking *ETS* fusions in Ewing's sarcoma and prostate cancer as markers of sensitivity to PARP inhibitors and DNA-PKcs inhibitors. A.M. Chinnaiyan and J.C. Brenner are named as inventors. No potential conflicts of interest were disclosed by the other authors.

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