A Unique Subset of Epithelial Ovarian Cancers with Platinum Sensitivity and PARP Inhibitor Resistance

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Abstract

Platinum and PARP inhibitor (PARPi) sensitivity commonly coexist in epithelial ovarian cancer (EOC) due to the high prevalence of alterations in the homologous recombination (HR) DNA repair pathway that confer sensitivity to both drugs. In this report, we describe a unique subset of EOC with alterations in another DNA repair pathway, the nucleotide excision repair (NER) pathway, which may exhibit a discordance in sensitivities to these drugs. Specifically, 8% of high-grade serous EOC from The Cancer Genome Atlas dataset exhibited NER alterations, including nonsynonymous or splice site mutations and homozygous deletions of NER genes. Tumors with NER alterations were associated with improved overall survival (OS) and progression-free survival (PFS), compared with patients without NER alterations or BRCA1/2 mutations. Furthermore, patients with tumors with NER alterations had similar OS and PFS as BRCA1/2-mutated patients, suggesting that NER pathway inactivation in EOC conferred enhanced platinum sensitivity, similar to BRCA1/2-mutated tumors. Moreover, two NER mutations (ERCC6-Q524* and ERCC4-A583T), identified in the two most platinum-sensitive tumors, were functionally associated with platinum sensitivity in vitro. Importantly, neither NER alteration affected HR or conferred sensitivity to PARPi or other double-strand break–inducing agents. Overall, our findings reveal a new mechanism of platinum sensitivity in EOC that, unlike defective HR, may lead to a discordance in sensitivity to platinum and PARPi, with potential implications for previously reported and ongoing PARPi trials in this disease. Cancer Res; 75(4); 1–7. ©2014 AACR.

Introduction

Platinum analogues (cisplatin and carboplatin) are active agents against epithelial ovarian cancer (EOC) and constitute the backbone of first-line chemotherapy used in this disease (1, 2). The enhanced platinum sensitivity of EOC tumors is thought to be related to an underlying defect in homologous repair (HR)–mediated DNA repair, particularly in those tumors with high-grade serous histology. Specifically, approximately 50% of the high-grade serous EOCs in The Cancer Genome Atlas (TCGA) dataset harbored genetic or epigenetic alterations involving the HR pathway, with germline and somatic BRCA1/2 mutations occurring in 15% and 6% to 7%, respectively (3). Tumors with defective HR have also been shown to be exquisitely sensitive to inhibitors of PARP inhibitor (PARPi), a novel class of anticancer agents, which exhibit synthetic lethality in tumors with a defective HR pathway (4, 5).

Although defective HR is an important mediator of platinum sensitivity in EOC, repair of platinum-induced DNA damage does not involve only the HR pathway. The nucleotide excision repair (NER) pathway is a highly conserved and remarkably versatile DNA repair pathway that functions to identify and repair bulky DNA cross-links generated by a variety of genotoxic agents including platinum (6). Indeed, more than 90% of platinum–DNA lesions are intrastrand cross-links, which are repaired by the NER pathway (6–8). Furthermore, biallelic germline mutations of NER pathway genes lead to extreme platinum sensitivity observed in patients with Xeroderma pigmentosum or Cockayne syndrome (9, 10).

Defective HR contributes to sensitivity to both platinum and PARPi, explaining why responsiveness to PARPi is closely associated with platinum sensitivity in EOC (11). In fact, completed and on-going clinical trials of PARPi routinely enroll patients with platinum-sensitive disease in an attempt to enrich for HR-defective tumors that are likely to respond to PARPi (12). However, platinum and PARPi sensitivity do not always coexist in EOC. Specifically, not all platinum-sensitive tumors respond to PARPi (11), and EOC tumors that become PARPi-resistant retain the potential to respond to subsequent platinum-based chemotherapy (13). Understanding the mechanisms of discordance between platinum and PARPi sensitivity may help optimize the administration of these agents in the clinical management of EOC and may also aid in the development of novel therapies to overcome resistance.

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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doi: 10.1158/0008-5472.CAN-14-2593

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Published OnlineFirst January 29, 2015; DOI: 10.1158/0008-5472.CAN-14-2593
In this study, we show that NER alterations are present in EOC and that these alterations are associated with a phenotype of clinical platinum sensitivity that is similar to that of BRCA1/2-mutated tumors with improved overall survival (OS) and progression-free survival (PFS). Moreover, we show that NER alterations are associated with increased cellular platinum sensitivity and that, unlike defective HR, lead to discordance between platinum and PARPi sensitivity, a finding that may have important clinical and translational implications.

Materials and Methods

Evaluation of NER alterations in TCGA dataset

We accessed data for 316 patients with high-grade serous EOCs in the TCGA dataset for which DNA copy number, promoter methylation, and whole-exome sequencing information was available (3, 14, 15). We evaluated for nonsynonymous or splicing site mutations, promoter hypermethylation, and homozygous deletions in the following NER genes: XPA, XPC, DDB1, ERCC4, ERCC5, ERCC2, ERCC3, ERCC1, ERCC6, PCNA, ERCC8, LIG1, RAD23B, MNT1, MMS19, RFC1, and XAB2. For each NER mutation, we also evaluated the copy-number status to assess whether it was accompanied by heterozygous loss. Homozygous deletion status was determined by GISTIC methodology (as applied in the ovarian TCGA dataset), and we focused only on those with concurrent low mRNA expression levels of the corresponding NER gene (i.e., mRNA expression z score of less than −3). Promoter hypermethylation was assessed using the same criteria described in the ovarian TCGA dataset publication (3).

Cell culture

ERCC6 (GM16095) and ERCC4 (GM08437)-deficient immortalized fibroblast cell lines (Coriell Cell Repository) were cultured in DMEM (Invitrogen), supplemented with 10% FBS, 1% Penicillin Streptomycin, and 1-glutamine. ERCC6-deficient line was complemented with either wild-type or mutant N-terminal Flag-tagged ERCC6, cloned in a pOZ vector. The ERCC4-deficient line was complemented with C-terminal Myc-tagged wild-type or mutant ERCC4, cloned in a plenti vector (Origene).

For Western blotting, whole cell extracts were prepared by lysing cells in RIPA with complete protease inhibitor. Lysates were resolved on a polyacrylamide gel, transferred to a PVDF membrane, and incubated with primary antibodies [BRCA2 (ab-1; Calbiochem), BRCA1 (ab-1; Calbiochem), ERCC4 (D3G8C; Cell Signaling Technology), ERCC6 (D-7; Santa Cruz Biotechnology), Flag (M2; Sigma), and β-actin (Cell Signaling Technology)]. Signal was detected using an ECL kit (Pierce) and visualized with a Fuji LAS-3000 luminescent image analyzer system.

Transfection

Targeted genes were depleted by transient transfection of siRNA directed against BRCA2 (5'-GAAGAAGGCAGGUGUAAUAdTdT-3'), ERCC4 (ERCC4-5), or ERCC6 (ERCC6-2). All siRNA duplexes were from Qiagen. siRNA duplexes were transfected at a final concentration of 100 nmol/L using the Lipofectamine Reagent (Life Technologies) according to the manufacturer’s recommendations. In all experiments, a fraction of transfected cells was analyzed by immunoblot to assess knockdown efficiency. Transfection of plasmid cDNA was achieved using Lipofectamine LTX (Life Technologies). Functional assays were performed 48 hours after transfection, and protein expression was concurrently analyzed by immunoblot.

HR efficiency

HR efficiency was measured using the DR-GFP reporter assay. Briefly, 48 hours before SceI transfection, U2OS-DR-GFP cells were transfected with Control siRNA or siRNA targeting BRCA2, ERCC4, or ERCC6. The HR activity was determined by FACS quantification of viable GFP-positive cells 96 hours after SceI cDNA transfection. For RAD51 immunofluorescence, cells were fixed with 4% paraformaldehyde for 10 minutes at room temperature, followed by extraction with 0.3% Triton X-100 for 10 minutes on ice. Incubation with the primary antibody (anti-RAD51; Santa Cruz Biotechnology) was performed at 37°C.

Cell survival assays

Cells were seeded in 96-well plates and treated with increasing concentrations of cisplatin (Sigma), Doxorubicin (Sigma), and Rucaparib (AG-D14699; Selleckchem). After 72 hours, viability was assessed 72 hours by adding CellTiter-Glo (Promega) and measuring luminescence using a luminescence plate reader. Survival at each drug concentration was plotted as a percentage of the survival in drug-free media.

Statistical analysis

The t test and the Fisher exact test were used to analyze the clinical and experimental data. Significance was defined as a P < 0.05; all reported P values are two sided. OS and PFS curves were generated by the Kaplan–Meier method, and statistical significance was assessed using the log-rank test. Tumors that harbored both NER and BRCA1/2 mutations (n = 4) were not included in the PFS or OS survival analysis. Inclusion of these tumors did not significantly change the results of the PFS and OS analyses.

Results and Discussion

NER alterations are present in EOC and are associated with clinical platinum sensitivity

We curated the EOC TCGA dataset to assess potential inactivating events of the NER pathway, including mutations, homozygous deletions, and promoter hypermethylation of NER genes (3, 14, 15). We found that a total of 24 (8%) of 316 EOCs harbored either NER mutations or homozygous deletions of NER genes. Specifically, we identified 19 cases with nonsynonymous or splice site NER gene mutations (all somatic) and 6 cases with homozygous deletions of NER genes among the 316 sequenced EOCs of the TCGA dataset (Fig. 1A). None of the NER genes were found to harbor promoter hypermethylation. All NER mutations were mutually exclusive, i.e., no individual tumor harbored mutations in more than one NER gene. Furthermore, NER mutations were mutually exclusive with homozygous deletions of the NER genes with the exception of one case that harbored both an ERCC5 mutation and homozygous deletion of ERCC2. Of the 19 cases with NER mutations, 7 (36.8%) were accompanied by heterozygous loss of the respective NER gene (Fig. 1A), indicating that in these cases both wild-type alleles had been lost.

Importantly, patients with tumors with NER alterations exhibited statistically significantly higher median OS (63.5 vs. 41.5 months, respectively; log-rank P = 0.048) and a trend toward statistically significantly higher median PFS (30.4 vs. 14.7 months, respectively; log-rank P = 0.069) compared with patients...
with tumors without NER alterations and BRCA1/2 mutations (Fig. 1B and C). Furthermore, patients with tumors with NER alterations exhibited similar outcome (OS and PFS), with tumors without NER alterations and BRCA1/2 mutations exhibiting similar median OS (63.5 vs. 41.5 months, respectively, P = 0.048) compared with the remaining tumors. For both B and C, tumors that harbored both NER and BRCA1/2 mutations (Fig. 1B and C) exhibited similar outcome (OS and PFS), with tumors without NER alterations and BRCA1/2 mutations exhibiting similar median OS (63.5 vs. 41.5 months, respectively, P = 0.048) compared with the remaining tumors. For both B and C, tumors that harbored both NER and BRCA1/2 mutations (n = 4) were not included in the PFS or OS analysis. Inclusion of these tumors did not significantly change the results of the PFS and OS analyses.

NER alterations are functionally associated with platinum sensitivity in vitro

As a proof of principle that NER alterations are functionally associated with platinum sensitivity, we evaluated two NER mutations (ERCC6-Q524* and ERCC4-A583T) that were identified in 2 patients (cases 9 and 19, respectively, Fig. 1A) with advanced-stage high-grade serous EOC that demonstrated the best response to first-line platinum-based chemotherapy. The ERCC6-Q524* nonsense mutation was present in a patient with stage IV suboptimally debulked high-grade serous tumor that had complete response to first-line platinum chemotherapy and remained in complete remission for 31.5 months after diagnosis. The ERCC4-A583T missense mutation was present in a patient with stage IIIC optimally debulked high-grade serous tumor who remained in complete remission for 31.5 months after diagnosis.

To determine the functional significance of ERCC6-Q524* on platinum sensitivity, we evaluated whether this variant could rescue platinum sensitivity in an ERCC6-deficient cell line. An ERCC6-deficient immortalized fibroblast cell line (GM16093) was complemented with either wild-type ERCC6 or the mutant ERCC6-Q524*. Expression of wild-type ERCC6 rescued cisplatin sensitivity of ERCC6-deficient cells, whereas complementation with mutant ERCC6-Q524* did not impact cisplatin sensitivity (Fig. 2A). To confirm that ERCC6 loss alone is solely sufficient to induce cisplatin sensitivity, we assessed cisplatin cytotoxicity following siRNA knockdown of ERCC6. ERCC6 depletion significantly increased platinum sensitivity, comparable with BRCA2 loss, a major mediator of DNA cross-link repair (Supplementary Fig. S1A).

Given that ERCC6-Q524* was a somatic mutation and not associated with heterozygous loss, we evaluated whether this mutation may exert a dominant-negative effect. We postulated that ERCC6-Q524* may interfere with the function of the wild-type allele and hence increase sensitivity to cisplatin. Indeed, introduction of the ERCC6-Q524* variant in ERCC6 wild-type 293T cells dramatically increased cisplatin sensitivity compared with cells transfected either with wild-type ERCC6 or control empty vector, suggesting that this mutation sensitizes cells to cisplatin by a dominant-negative mechanism (Fig. 2B). This finding suggests that even in the absence of heterozygous loss, NER mutations may still be functionally relevant in terms of platinum sensitivity in EOC. Heterozygous NER mutations associated with platinum sensitivity have been reported in other tumor types (other than EOC) and more recently in bladder cancer (18). How mutation of one NER allele can exert a dominant-negative phenotype is unclear and several mechanisms are possible. First, because NER proteins are assembled into large, multisubunit complexes, the presence of a mutant protein may have a deleterious effect on DNA repair, even when the wild-type protein is present. Alternatively, the mutated protein may bind, but not adequately repair, damaged DNA, thereby preventing...
repair by an alternative DNA-repair pathway, thus explaining a dominant-negative phenotype as previously described for ERCC2 in yeast (19).

Similarly, we evaluated whether the ERCC4-A583T mutant could rescue the platinum sensitivity of ERCC4-deficient (GM08437) cells. Reinroduction of wild-type ERCC4, but not the mutant protein, was able to rescue cisplatin sensitivity of ERCC4-deficient cells (Fig. 2C). Importantly, ERCC4-A583T was a somatic mutation associated with heterozygous loss arguing for a complete loss of functional ERCC4 in this patient. Furthermore, ERCC4 knockdown alone was able to confer platinum sensitivity in 293T cells to levels comparable with BRCA2 depletion (Supplementary Fig. S1B).

Our experiments indicate that the ERCC4-A583T and ERCC6-Q524* mutations confer platinum sensitivity in vitro and may be responsible for the extreme platinum sensitivity observed in these 2 patients. It is important to underscore that, in both tumors, we could not detect any concurrent HR pathway alterations that
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would otherwise explain the extreme platinum sensitivity of these patients. Specifically, there were no BRCA1/2 mutations, epigenetic silencing of BRCA1, mutations in Fanconi Anemia genes, mutations in core HR RAD genes, mutations in DNA damage response HR genes, amplification of EMSY, and homozygous deletion of PTEN detected in these tumors. Taken together, our findings provide the proof of principle that platinum sensitivity may occur in EOC as a result of NER alterations.

**ERCC6-Q524* and ERCC4-A583T mutations do not affect HR nor sensitivity to PARPi**

We evaluated the association of these NER alterations with sensitivity to the PARPi rucaparib. Unlike in the case of cisplatin, expression of wild-type or mutant ERCC6 or ERCC4 did not affect PARPi sensitivity of ERCC6- and ERCC4-deficient fibroblasts (Fig. 3A). Furthermore, because defective HR is a critical mediator of platinum and PARPi sensitivity in EOC, we evaluated whether deficiency in ERCC6 or ERCC4 affected HR in vitro. Inhibition of ERCC4 or ERCC6 did not affect HR efficiency in vitro, as measured by direct-repeat GFP recombination (DR-GFP) assay and by IR-induced RAD51 foci formation, a surrogate for HR efficiency (Fig. 3B and C). Similarly, reintroduction of wild-type or mutant ERCC6 or ERCC4 did not affect sensitivity of ERCC6- and ERCC4-deficient fibroblasts to the topoisomerase-II inhibitor doxorubicin or the topoisomerase-I inhibitor camptothecin (Fig. 3D and Supplementary Fig. S2), which induce DNA double-strand breaks that are repaired by HR. Together, these results indicate that functional loss of ERCC6 or ERCC4 does not impair HR efficiency nor alters sensitivity to PARPi or other double-strand break-inducing agents such as camptothecin and doxorubicin.

Our findings suggest a novel mechanism of discordance between platinum and PARPi sensitivity in EOC, which may have important clinical and translational implications. Platinum sensitivity has been traditionally used as an eligibility criterion for selection of participation in PARPi clinical trials in an attempt to enrich for HR-defective tumors that may respond to PARPi (12).

**Figure 3.**

Inactivation of ERCC6 or ERCC4 does not impair HR efficiency and does not confer sensitivity to rucaparib and doxorubicin. A, addition of wild-type (WT) or mutant ERCC6 in ERCC6-deficient fibroblasts does not affect PARPi sensitivity (left). Addition of wild-type ERCC4 to ERCC4-deficient fibroblasts does not affect PARPi sensitivity (right). BRCA2-depleted cells are shown as a positive control. Error bars, ± 1 SEM. Results are representative of three independent experiments. C, siRNA knockdown of ERCC4 or ERCC6 does not affect HR as measured by a DR-GFP recombination assay in U2OS cells. BRCA2 depletion is shown as a positive control. Error bars, ± 1 SEM. Representative micrographs of irradiated cells are shown (right). D, addition of wild-type ERCC6 (black dashes) or mutant protein (red solid line, ERCC6-Q524*) in ERCC6-deficient fibroblasts does not impact sensitivity to doxorubicin (left). Addition of wild-type ERCC4 (black dashes) or mutant ERCC4 (red solid line, ERCC4-A583T) in ERCC4-deficient fibroblasts does not impact sensitivity to doxorubicin (right). Error bars, ± 1 SEM. Results are representative of three independent experiments.

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Figure 4. Discordance between platinum and PARPi due to NER alterations: potential implications.

A. Potential implications of NER alterations for platinum and PARPi sensitivity in patients with BRCA/HR-deficient (I) and BRCA/HR-proficient (II) tumors. I, if tumors with NER alterations are HR proficient, i.e., they do not harbor concurrent HR alterations that would confer sensitivity to PARPis, they are expected to be platinum sensitive but not PARPi sensitive. II, if tumors with NER alterations are BRCA/HR-deficient they will initially be sensitive to both platinum and PARPis. However, if these tumors develop resistance to PARPi via reversion of the HR defect (e.g., via secondary BRCA1/2 mutations), they are predicted to retain some sensitivity to subsequent platinum therapy due to the underlying NER alterations. B, expression of BRCA1 (BRCA1 + si Ctrl, red solid line) rescues the cisplatin hypersensitivity of BRCA1+/− MDA-MB-436 cells (empty vector (EV) + si ERCC6, black dashed line). However, BRCA1-restored cells with ERCC6-depletion (BRCA1 + si ERCC6, red dashed line) partially retain sensitivity to cisplatin compared with BRCA1-restored line without ERCC6-depletion (BRCA1 + si Ctrl, red solid line; left plot). Sensitivity is measured by 3-day viability. Error bars, ± 1 SEM. IC50 values are shown as a measure of the relative cisplatin sensitivity of MDA-MB-436 cell lines (right plot). An immunoblot showing knockdown efficiency of ERCC6 and reexpression of BRCA1 in MDA-MB-436 cells is shown on the right. C, add-back of BRCA1 cDNA (BRCA1+/− MDA-MB-436 fibroblasts): EV BRCA1−/−, EV + si ERCC6, si ERCC6, BRCA1 + si ERCC6, VINCULIN.

However, our findings suggest that for tumors with NER alterations, platinum sensitivity may not always be an accurate predictor of PARPi sensitivity. Specifically, if tumors with NER alterations are HR proficient, i.e., they do not harbor concurrent HR alterations that would confer sensitivity to PARPis, platinum sensitivity may not necessarily translate into PARPi sensitivity (Fig. 4A). Therefore, the presence of NER alterations may explain why certain patients with platinum sensitive who are enrolled in PARPi trials fail to respond to these agents (11, 12). Specifically, in the phase II multicentre, open-label, nonrandomized study of olaparib in women with advanced high-grade serous and/or undifferentiated ovarian carcinoma (20), the objective response rate to the PARPi olaparib in patients with platinum-sensitive ovarian cancer was 50% in BRCA1/2-negative and 60% in BRCA1/2-mutated tumors. Furthermore, in the phase I dose-escalation and single-stage expansion study of olaparib in BRCA1/2-mutated ovarian cancer (11), the clinical benefit response rate (radiologic or tumor marker complete or partial response or radiologic disease stabilization for 4 months or more) was 69% in patients with platinum-sensitive disease. Overall, as evident by these studies, 30% to 50% of tumors with platinum-sensitive ovarian cancer were resistant to PARPi therapy.

Furthermore, NER alterations may also, at least partly, explain another phenomenon, commonly encountered in clinic, whereby certain patients with BRCA1/2-mutated tumors that become PARPi-resistant retain the potential to respond to subsequent platinum-based chemotherapy, as has been previously reported (13). It is well known that the most common mechanism of PARPi resistance in BRCA/HR-deficient tumors is reversion of the HR defect (i.e., secondary BRCA1 or BRCA2 mutations restoring normal BRCA1/2 function; refs. 21–23). In this regard, if BRCA/HR-deficient tumors also harbor NER alterations, then reversion of the HR defect conferring PARPi resistance (21, 22) will not confer cross-resistance to platinum; therefore, these patients may still benefit from subsequent platinum-based therapy (Fig. 4A). Supporting this, restoration of BRCA1 function in BRCA1- and ERCC6-depleted cells completely rescues PARPi sensitivity but only partially rescues cisplatin sensitivity (Fig. 4B and C). In this regard, in a retrospective review of patients with BRCA1/2-mutated ovarian cancer who received chemotherapy following disease progression on olaparib (i.e., after development of resistance to PARPis), response to platinum-based chemotherapy was 40%, thereby suggesting a discordance between platinum and PARPi sensitivity of 40% in this setting (13). Known mechanisms of
resistance to PARPi in patients with BRCA1/2-mutated EOCs or EOCs with BRCA-ness phenotype (apart from secondary BRCA1/2 mutations) include loss of PARP1 expression, upregulation of Poly-glyceroprotein efflux Pump transporter, and loss of 53BP1 in BRCA1 mutant cells. Of these mechanisms, loss of 53BP1 has been experimentally proven to confer platinum sensitivity in BRCA1-mutated tumors (24), but its exact clinical relevance in patients with ovarian cancer is unclear.

In conclusion, we report for the first time that NER pathway alterations (mutations and homozygous deletions) occur in EOC and that these alterations are associated with a phenotype of clinical platinum sensitivity that is similar to that of BRCA1/2-mutated tumors characterized by improved OS and PFS. We showed that the NER mutations identified in the most platinum-sensitive tumors (ERCC6-Q524* and ERCC4-A583T) were functionally associated with platinum sensitivity in vitro. Importantly, these NER alterations did not affect HR and did not confer sensitivity to PARPi, thus providing a novel mechanism of discordance between platinum and PARPi sensitivity in EOC. Our findings suggest that NER alterations may have a previously unrecognized role as biomarkers for selection of patients for participation in PARPi trials as well as for deciding therapy after development of PARPi resistance.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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Acknowledgments
The authors thank Timur Yusufzai for providing the pOZ-ERCC6 construct and Shawn Johnson and Geoffrey Shapiro for providing the MDA-MB-436 (± BRCA1 cDNA) cell line.

Grant Support
R. Ceccaldi is a recipient of the Ovarian Cancer Research Fellowship. P.A. Konstantinopoulos is recipient of DOD Ovarian Cancer Research Program Ovarian Cancer Academy Award W81XWH010-1-0585.

Received September 3, 2014; revised October 29, 2014; accepted November 18, 2014; published OnlineFirst January 29, 2015.
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Cancer Res  Published OnlineFirst January 29, 2015.