Metastatic solid tumors are almost invariably fatal. Patients with disseminated small-cell cancers have a particularly unfavorable prognosis, with most succumbing to their disease within two years. Here, we report on the genetic and functional analysis of an outlier curative response of a patient with metastatic small-cell cancer to combined checkpoint kinase 1 (CHK1) inhibition and DNA-damaging chemotherapy. Whole-genome sequencing revealed a clonal hemizygous mutation in the Mre11 complex gene RAD50 that attenuated ATM signaling which in the context of CHK1 inhibition contributed, via synthetic lethality, to extreme sensitivity to irinotecan. As Mre11 mutations occur in a diversity of human tumors, the results suggest a tumor-specific combination therapy strategy in which checkpoint inhibition in combination with DNA-damaging chemotherapy is synthetically lethal in tumor cells but not normal cells with somatic mutations that impair Mre11 complex function.

**SIGNIFICANCE:** Strategies to effect deep and lasting responses to cancer therapy in patients with metastatic disease have remained difficult to attain, especially in early-phase clinical trials. Here, we present an in-depth genomic and functional genetic analysis identifying RAD50 hypomorphism as a contributing factor to a curative response to systemic combination therapy in a patient with recurrent, metastatic small-cell cancer. Cancer Discov; 4(9); 1–8. © 2014 AACR.
INTRODUCTION

Curative therapy for patients with metastatic solid tumors remains elusive. Even with the much-heralded advent of targeted inhibitors of oncopgenic signaling pathways, drug resistance and disease progression occur in essentially all patients. We sought to define the mechanistic basis of a dramatic and durable response to systemic therapy in a 51-year-old woman originally diagnosed with an invasive small-cell cancer of the ureter (Supplementary Fig. S1A and S1B). Small-cell variant, a rare histologic subtype that can arise throughout the urothelial tract, is associated with a particularly poor prognosis. Following initial surgical resection and a short course of adjuvant chemotherapy (etoposide and cisplatin), her disease rapidly recurred. After a second surgery to remove recurrent and metastatic tumors in her kidney and retroperitoneal lymph nodes, the patient again recurred with progressive metastatic disease, prompting enrollment in an open-label phase I clinical trial of AZD7762, an ATP-competitive checkpoint kinase inhibitor (CHK1/2), and weekly irinotecan, a topoisomerase I inhibitor (1). Within 5 months, the patient achieved a complete response that has proved durable despite discontinuation of drug therapy nearly 3 years ago (Fig. 1A and B). We performed whole-genome sequencing (WGS) of the tumor and matched normal tissue from this patient to investigate the genetic basis of this outlier example of curative systemic cancer therapy.

RESULTS

WGS of tumor DNA from the second surgery and matched normal blood revealed a complex somatic tumor genome (Fig. 1C). We identified 19,011 somatic point mutations and small insertions and deletions (indels), of which 147 were located in protein-coding or noncoding RNA regions of the genome (Supplementary Table S1). Overall, the somatic mutation rate was 7.06 mutations per million bases, similar to the only other reported WGS of a metastatic urothelial cancer reported to date (2). This genome also had a substantial number of DNA copy-number alterations (CNA), as is typical of p53-mutant bladder cancers (the tumor harbored a TP53*461T mutation; ref. 3). CNAs were the source of approximately 60% of all structural rearrangements identified in this tumor genome, the burden of which was high (Supplementary Table S2).

As WGS was performed on the recurrent tumor specimen obtained after etoposide–cisplatin therapy but before trial enrollment, we sought to determine whether the candidate driver mutations identified arose early in molecular time by analyzing the diagnostic tumor sample collected pre-etoposide–cisplatin therapy. Using a capture-based approach partly customized using the WGS findings (see Methods; Supplementary Fig. S2A), we deeply sequenced 281 genes (Supplementary Tables S3 and S4). This confirmed that most of the mutations identified by WGS of the recurrent tumor affecting known cancer genes were present in the treatment-naive diagnostic tumor (Fig. 1D). Others preexisted therapy but were not selected for, and still others arose later in molecular time, as they were present but subclonal only in the post-etoposide–cisplatin tumor.

We then performed an integrated analysis using the mutation, DNA copy number, and tumor clonality data generated by the WGS analysis together with the sum of information on pathways proximal to the mechanism of drug action to prioritize genomic aberrations that may have contributed to this patient’s exceptional response. In addition to the mutation in TP53 (A161T), mutations identified in ATR and RAD50 were particularly noteworthy from the perspective of this patient’s profound response to checkpoint inhibitor–based combination therapy (Supplementary Fig. S2B–S2D). Although both were missense mutations, in silico analyses suggested that whereas ATRH585D was unremarkable, the RAD50L1237F mutant was deemed the likeliest contributor to the profound response to systemic therapy observed in this patient. Several lines of evidence supported this prediction. The ATR mutation was heterozygous, affected the poorly conserved H585 residue (Supplementary Fig. S2C), did not reside in a protein domain or motif of known significance, was not recurrently mutated nor was among a pattern of clustered mutations at this site (data not shown), and was not affected by a focal CNA, arguing against selection for the ATR mutation during tumorigenesis (see Supplementary Data).

Conversely, the weight of the in silico evidence suggested that the novel missense mutation in RAD50 (L1237F) was a potential sensitizing lesion contributing to the profound response to systemic therapy observed in this patient. RAD50 is a component of the Mre11 complex, a multisubunit nucleosome composed of RAD50, MRE11A, and NBN (4), mutations of which are associated with DNA repair deficiency. This RAD50L1237F allele was clonal in the index patient (present in 100% of tumor cells; Supplementary Fig. S3) and accompanied by focal deletion of the wild-type allele (Fig. 2A), with corresponding tumor-specific reduction of RAD50 protein expression confirmed by IHC (Supplementary Fig. S4A–S4D). Furthermore, this mutation is situated in the D-loop of RAD50 (Fig. 2B), a region that influences ATP hydrolysis (5, 6). Recent structural analyses indicate that ATP hydrolysis has a profound effect on the functionality of the Mre11 complex, which senses double-strand breaks (DSB) and governs the DNA-damage response (DDR; ref. 7). Analyzing the mutational landscape of RAD50 in 7,494 sequenced tumors across 28 tumor types (Supplementary Table S5 and Supplementary Data) revealed that not only do approximately 4% of all human tumors harbor Mre11 complex mutations but a subset of these cluster in regions adjacent to the L1237F-mutant D-loop motif of the RAD50 protein (4), mutations of which are associated with DNA repair deficiency. This RAD50L1237F mutant was deemed the likeliest contributor to this patient’s exceptional response. In addition to the prioritize genomic aberrations that may have contributed to the sequential drug therapy, the patient’s profound response correlated with a novel mutant allele of the DNA damage repair pathway.

We next prioritized how the different tumor clones affected the DDR. In the diagnostic tumor (Fig. 2C), analysis of the Mre11 complex revealed that both MRE11A and NBN were mutated at frequencies of 26% and 2.2%, respectively. However, the MRE11A mutation was not recurrently mutated nor was among a pattern of clustered mutations at this site (data not shown), and was not affected by a focal CNA, arguing against selection for the ATR mutation during tumorigenesis (see Supplementary Data).

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the clustering of the L1237F mutation in the index tumor genome with other mutant alleles observed in diverse tumor types, which together affect the D-loop motif and Walker B elements adjacent to ATP binding (Fig. 2D). In summary, in silico analysis predicted that although ATR H585D was likely a passenger mutation, the L1237F mutation and others observed in RAD50 in additional tumors may exert a significant functional impact.

We exploited the high degree of evolutionary conservation of the RAD50 D-loop to assess the functional significance of RAD50 L1237F by modeling this and other tumor-associated alleles in S. cerevisiae. Six rad50-mutant yeast strains were...
Hypomorphism and Curative Response to Cancer Therapy

established: rad50<sup>L1240F</sup> (the yeast version of the mutation in the tumor genome), as well as mutations predicted to exert minor and major effects on D-loop structure (rad50<sup>L1240A</sup> and rad50<sup>L1240R</sup>, respectively; see Methods; Supplementary Table S6). In addition, we established rad50<sup>-</sup>mutant strains harboring D-loop (D1238N, rad50<sup>D1241N</sup>) and non–D-loop but highly conserved (Q1259K, rad50<sup>Q1262K</sup>) mutations identified in breast and endometrial carcinomas, respectively. All three rad50<sup>L1240</sup> mutations appeared to destabilize the Rad50 protein, as the steady-state levels of the rad50<sup>L1240F</sup> and rad50<sup>L1240A</sup> gene products were reduced compared with wild-type, whereas Rad50<sup>L1240R</sup> was nearly undetectable (Fig. 3A). Conversely, the rad50<sup>D1241N</sup> and rad50<sup>Q1262K</sup> mutants had levels of Rad50 similar to wild-type cells. Nevertheless, although these mutations had differing effects on Rad50 expression levels, the Mre11 complex itself remained intact, as indicated by coimmunoprecipitation with Mre11 (Fig. 3A). We further confirmed the apparent selection for RAD50 hemizygosity in the tumor (mutation and LOH), as only diploid strains expressing homozygous rad50<sup>L1240F/L1240F</sup> (or rad50<sup>L1240F</sup> haploid cells) exhibited impaired survival following camptothecin (an analog of irinotecan) treatment (Supplementary Figs. S5 and S6).
These data indicate selection for RAD50 hypomorphism in the index patient through mutation and LOH (Fig. 2A), resulting in the retention of only a single-mutant allele with compromised function.

As the curative response in the index patient occurred in the setting of combined inhibition of topoisomerase I and the DNA-damage checkpoint pathway, we assessed whether checkpoint inhibition coconfers chemotherapy sensitivity. A, although the Rad50L1240F protein level is reduced, the Mre11 complex is intact in rad50Δ cells as well as those harboring similar D-loop or adjacent mutations. The Mre11–Rad50 interaction was assessed by communoprecipitation with Rad50 or Mre11 antibodies (Rad50-IP or Mre11-IP) and Western blot analysis (anti-Rad50 or anti-Mre11) from yeast extracts of the indicated genotypes. Preimmune antibodies (PI) were included as a negative control. Rad50L1240F abundance was too low to rigorously determine whether complex formation was disrupted. B, Mec1 (yeast ortholog of human ATR) deficiency dramatically potentiates the DNA-damage sensitivity of rad50Δ cells. The Mre11 complex is intact in rad50Δ cells as well as those harboring similar D-loop or adjacent mutations. The Mre11–Rad50 interaction was assessed by communoprecipitation with Rad50 or Mre11 antibodies (Rad50-IP or Mre11-IP) and Western blot analysis (anti-Rad50 or anti-Mre11) from yeast extracts of the indicated genotypes. Preimmune antibodies (PI) were included as a negative control. Rad50L1240F abundance was too low to rigorously determine whether complex formation was disrupted.

I n t a c t

Normal

No rescue

CPT sensitivity

E, a model of sensitivity to DNA-damaging agents such as irinotecan driven by the synthetic lethality between simultaneous genetic and pharmacologic perturbation of both axes (ATM and ATR) of the DDR by RAD50 hypomorphism and checkpoint inhibition, respectively.

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Figure 3. RAD50 hypomorphism attenuates ATM signaling, synergizing with checkpoint inhibition to confer chemotherapy sensitivity. A, although the Rad50L1240F protein level is reduced, the Mre11 complex is intact in rad50Δ cells as well as those harboring similar D-loop or adjacent mutations. The Mre11–Rad50 interaction was assessed by communoprecipitation with Rad50 or Mre11 antibodies (Rad50-IP or Mre11-IP) and Western blot analysis (anti-Rad50 or anti-Mre11) from yeast extracts of the indicated genotypes. Preimmune antibodies (PI) were included as a negative control. Rad50L1240F abundance was too low to rigorously determine whether complex formation was disrupted. B, Mec1 (yeast ortholog of human ATR) deficiency dramatically potentiates the DNA-damage sensitivity of rad50Δ cells. The Mre11 complex is intact in rad50Δ cells as well as those harboring similar D-loop or adjacent mutations. The Mre11–Rad50 interaction was assessed by communoprecipitation with Rad50 or Mre11 antibodies (Rad50-IP or Mre11-IP) and Western blot analysis (anti-Rad50 or anti-Mre11) from yeast extracts of the indicated genotypes. Preimmune antibodies (PI) were included as a negative control. Rad50L1240F abundance was too low to rigorously determine whether complex formation was disrupted.
As the Mre11 complex also regulates the DDR kinase ATM, we next assessed the functional status of Tel1 (the yeast ATM ortholog and Mec1 paralogue) in rad50 mutants. In mec1Δ sac2Δ mutants, cells that are only able to respond to DNA damage through Tel1 via a functional Mre11 complex (see Supplementary Data; refs. 10, 11), rad50ΔL1240F triple-mutant cells had a sensitivity to both camptothecin and the DNA-damaging agent methyl methanesulfonate equal to that of rad50-mutant mec1Δ alone, indicating defective activation of Tel1 in Rad50 D-loop–mutant cells (Fig. 3B and Supplementary Fig. S7). Next, we examined DNA damage–dependent activation of Rad53, which, as a downstream substrate of Tel1 analogous to human Chk2, can only be activated by Tel1 in the absence of Mec1. Although methyl methanesulfonate treatment induced Rad53 phosphorylation levels in wild-type cells, and some additional Rad53 stimulation is apparent upon Sac2 loss, sac2Δ cannot rescue Rad53 phosphorylation levels in any of the rad50 mutants tested (Fig. 3C and Supplementary Fig. S8). This attenuation of Rad53 phosphorylation levels in the triple mutants confirms that Tel1 (ATM) signaling is defective in the Rad50-mutant cells.

As Tel1 kinase activity is important for telomere maintenance, we assessed the impact of this molecular phenotype on telomere length in the rad50 mutants. As in previous studies that showed significantly shorter telomeres resulting from tel1Δ and Tel1 kinase-dead strains (12), we also witnessed shorter telomeres in the rad50-mutant cells (Supplementary Fig. S9). This observation, along with the defect in Rad53 phosphorylation in Mec1-deficient cells, suggests that ATM activation was compromised in the rad50ΔL1237F index responder. In sum, the results suggest that the marked sensitivity of the Rad50L1237F–mutant tumor to irinotecan was due, at least in part, to simultaneous inhibition of both the ATR (by AZD7762) and ATM (by RAD50L1237F) axes of the DDR.

We further recapitulated these findings in mammalian cells. We engineered mouse embryonic fibroblasts (MEF) in which the sole source of Rad53 was Rad50L1237F. Upon treatment with the Chk1 inhibitor and camptothecin, these cells had reduced phosphorylation of the substrate Kap1 at Ser824, an ATM-dependent site (Supplementary Fig. S10A). Consequently, these cells had reduced γH2AX formation following irradiation (Supplementary Fig. S10B), confirming the ATM signaling defect. Moreover, although colony formation was reduced significantly upon irinotecan treatment irrespective of genotype, this was greatest upon cotreatment with the Chk1 inhibitor in Rad50L1237F cells (Supplementary Fig. S10C).

**DISCUSSION**

In summary, we find that a hypomorphic mutation in RAD50 accompanied by LOH identified by WGS of an extreme outlier responder likely contributed to a complete and durable response to irinotecan in combination with a selective inhibitor of CHK1. The RAD50L1237F mutant was both clonal and arose early, suggesting that RAD50 dysfunction may have contributed to tumor initiation, perhaps in combination with mutant p53, by potentiating the profound structural remodeling of this patient’s tumor genome. Although our functional results indicate that RAD50L1237F confers dramatically enhanced sensitivity to the combination of irinotecan and CHK1 inhibition, additional factors may have contributed to the profound and durable response observed. For example, the clonal nature of this responder’s tumor, with 95.1% of all somatic mutations identified present in the dominant tumor clone (Supplementary Fig. S3), may have contributed to the depth and durability of the response. It has been suggested that extensive subclonal mutations in treatment-naïve patients are associated with a shorter time to relapse and a worse outcome (13). The limited subclonal structure of this patient’s tumor may, therefore, have resulted in a less-tolerant environment for the selection and outgrowth of a preexisting resistant clone. This may have been especially true given the dose-dense weekly cytotoxic treatment regimen used, which may not have allowed the tumor sufficient time to adapt a fitter and more resistant clone.

In addition to demonstrating the indispensability of the D-loop of RAD50 for proper ATM activation and downstream checkpoint signaling (Fig. 3D), the hypomorphic nature of the RAD50L1237F allele is noteworthy. Whereas the somatic mutation was defective, innocuous D-loop alanine substitutions (rad50ΔL1240F and rad50ΔL1241F) had only a very mild impact, despite these residues being so highly conserved. Thus, there is considerable plasticity in the D-loop sequence that produces a narrow solution space in which RAD50 hypomorphism can be achieved through somatic mutation. This illustrates the potential importance of functional rather than fully inactivating mutations of highly conserved components of essential cellular systems like the DDR to various malignant phenotypes, including treatment sensitivity.

Although D-loop mutations in RAD50 have been studied previously (5, 14), our phenotypic characterization of the somatic RAD50L1237F allele revealed new insights into RAD50 function that may be exploited therapeutically. Whereas RAD50 mutation produced a negligible DSBR repair defect, ATM activation was severely impaired. This resulted in marked synergy with inhibition of the ATR–CHK1 axis of the DDR in the setting of cotreatment with a DNA damage–inducing cytotoxic chemotherapy (Fig. 3E). These data suggest a tumor-specific combination therapy strategy in which checkpoint inhibition in combination with DNA-damaging chemotherapy is synthetically lethal in tumor cells but not in normal cells with somatic mutations impairing Mre11 complex function. Indeed, as we found Mre11 complex mutations along with those in ATM to be present in a significant minority of patients across diverse human cancer types (Supplementary Table S5), these data argue for the development of inhibitors of checkpoint control generally and also targeted inhibitors of the Mre11 complex specifically or its synthetic lethal partners (such as ATM). As suggested by prior studies, this combinatorial approach may prove particularly effective in p53-mutant patients, as was the case in the index patient described here (15). This synthetic lethality is thus analogous to the use of PARP inhibitors in patients with BRCA1/2 mutations and highlights the potential utility of targeting DNA repair pathways in combination with mutagenic chemotherapies in patients who have a tumor-restricted defect in DDR. Finally, this work highlights that the value of whole-genome analyses of extreme outlier phenotypes is not limited to targeted therapeutics or the
RESEARCH BRIEF

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discovery of biomarkers of clinical benefit. Rather, analyses of exceptional responses can reveal new facets of pathway biology that suggest rational polytherapy strategies to interdict in a manner that extends profound, life-altering activity to molecularly defined patient populations.

METHODS

Clinical Presentation and Phase I Trial

A 47-year-old woman presented with severe flank pain and gross hematuria. Computed tomography (CT) identified a lesion in the right ureter, which biopsy confirmed was an invasive poorly differ-
entiated carcinoma with small-cell features (Supplementary Fig. S1). She underwent a distal right ureterectomy that showed high-grade small-cell carcinoma with local invasion and lymph node metastasis (pT3N1). She was treated with six cycles of etoposide and cis-
platin chemotherapy, but 4 months later, CT indicated a recurrent infiltrative soft-tissue mass within her right kidney and increasing retroperitoneal lymphadenopathy. At that time, she underwent a right nephroureterectomy with retroperitoneal lymph node dissec-
tion from which a recurrent small-cell carcinoma was confirmed with invasion into the renal hilar fat and parenchyma with 2 of 16 posi-
tive retroperitoneal lymph nodes. Subsequent imaging indicated an enlarging retrocaval lymph node and a new left iliac bone metastasis. The patient was then enrolled in an open-label phase I multicenter dose-escalation study of AZD7762, an ATP-competitive checkpoint kinase inhibitor, and weekly irinotecan (ClinicalTrials.gov number NCT00473616; ref. 1). This combination therapy was based on preclinical evidence that AZD7762, a potent inhibitor of CHK1 and CHK2, abrogates the G2–M checkpoint induced by SN-38, the active metabolite of irinotecan, resulting in enhanced DNA damage and cancer cell death (15). Within 1 month of treatment initiation, CT indicated a greater than 50% reduction in lymph nodes and evolving sclerosis of bone metastasis, suggesting response. Within eight cycles of therapy, this evolved into a complete response. She continued on AZD7762 in combination with irinotecan until trial termination (December 2010) and irinotecan alone until June 2011. As she had remained without evidence of disease for 1.5 years, chemotherapy was discontinued. At present, the patient remains free of disease. This patient was the only one of 68 trial participants to achieve a complete response. Because of the limited activity seen in an unselected population of solid tumors, the combination therapy did not move forward to a phase II trial. Moreover, AZD7762 is not under active development due to toxicities with monotherapy.

Sample Preparation and Sequencing

Clinical information and tumor and normal tissues were obtained from patients with informed consent and in accordance with Institutional Review Board approval at Memorial Sloan Kettering Cancer Center (New York, NY; MSKCC IRB #89-076). For targeted capture and sequencing, DNA was isolated from frozen tumor tissue using the DNEasy Blood and Tis-

sae2 triple mutants were generated by standard yeast genetic manipulations. Yeast strains used in this study are provided in Supplementary Table S6. Cell viability analysis was performed as 5-fold serial cell dilutions (250,000 to 80 cells per spot) that were spotted on yeast extract peptone dextrose (YPD) plates with or without camptothecin and incubated for 2 to 3 days at 30°C. Yeast cell extracts were prepared and immunoprecipitations and Western blot analyses were performed as described previously (16). To assess Rad53 phosphorylation upon methyl methanesulfonate treatment, YPD overnight cultures were grown to 2 to 3 × 10^6 cells/mL. In total, 2 mL cells were transferred to tubes containing either 20 μL of 10% methyl methanesulfonate (final concentration, 0.1% methyl meth-
anesulfonate) or no methyl methanesulfonate. Following 60 to 90 minutes of incubation at 30°C, 1 mL 1% sodium thiosulfate was added to all cultures, and the cells were pelleted. Protein extracts were prepared by standard trichlororacetic acid (TCA) extraction and quantified using the RCDc kit from Bio-Rad. Proteins (10 μg) were separated on an 8% SDS-PAGE (14 cm × 16 cm, 12–14 hours at 80 V) and transferred to a nitrocellulose membrane. FLAG-Rad53 was detected by Western blotting with FLAG M2 mAb (Sigma) and anti-
mouse horseradish peroxidase (HRP; Pierce) antibodies and visualized by chemifluorescence using the ECL Prime Kit (Amersham). Finally, for the telomere Southern blot, genomic DNA was Xhol-
digested and probed with a telomere-specific probe as previously described (17). Sequencing by Sanger biochemistry was performed to validate the RAD50 L1237F mutation identified in the index patient by both whole-genome and targeted exon capture sequencing.

Mutant Rad50 Cultured Cells and Cellular Assays

Two mutant mRad50-expressing vectors under the control of a phos-
phoglycerate kinase (PGK) promoter (pmRad50 L1237F and pmRad50 D1241A) were established through mutagenesis by using the mRad50 expres-
sion vector containing the full-length cDNA of the mRad50 gene (18). Details of the pmRad50 L1237F and pmRad50 D1241A constructs are available upon request. Rad50Δ +/- WT, Rad50Δ +/- L1237F, and Rad50Δ +/- L1240, Q1262 cells were prepared by cotransfection of pmRad50, pmRad50 L1237F, or pmRad50 D1241A, with pPGK-Hyg into SV40-immortalized Rad50Δ +/- MEFs (18) and selected with hygromycin (0.4 μg/ mL). Cells were then treated with tamoxifen (500 nmol/L) for 48 hours to induce deletion of the Rad50Δ +/- allele and production of the Rad50Δ allele, and single-cell clones were isolated. For colony formation assays, cells were plated in triplicate and pretreated the next day with 500 nmol/L of the CHK1 inhibitor PF-477736 (Sigma-Aldrich) for 4 hours followed by treatment with irinotecan for 24 hours. Colonies were assessed 10 days later by staining with crystal violet. Western blot analyses were performed on 30 μg of protein extracted with SDS buffer.

Sequence Analysis

The alignment, processing, and variant detection analyses (point mutations, insertions and deletions, DNA CNAs, and structural rearrangements) were performed for the tumor and matched normal whole-genome and targeted sequences, all as previously described (2), and were supplemented with comprehensive mutational data in 7,494 human tumors assembled from published and public access sources (see Supplementary Data). Further details about the phe-
notype-to-genotype analysis of mutational data, mutation rate and clonality analyses, in silico analysis of the predicted functional signifi-
cance of mutations, and screening for Mre11–Rad50–Nbs1 complex mutations in cancer are available in Supplementary Data.
RAD50 IHC

IHC for RAD50 was performed on a 4-μm thick FFPE tissue section for the tumor from the salvage nephrectomy (same specimen undergoing WGS). A primary monoclonal anti-RAD50 antibody was used and diluted to 1:100, CC1 standard (ab89; Abcam). Staining was assessed with a Ventana Discovery XT Automated System with DAB Map kit detection system (Ventana Medical Systems).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H. Al-Ahmadi, G. Iyer, A. Inagaki, A.J. Hanrahan, S.N. Scott, P. Kim, A. Viale, G.K. Schwartz, V. Reuter, B.H. Bochner, M.F. Berger, J.H.J. Petrini, D.B. Solit


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Al-Ahmadi, G. Iyer, P. Kim, G.K. Schwartz, M.F. Berger, D.B. Solit, B.S. Taylor


Other (created yeast strains, performed yeast experiments, assisted with yeast data interpretations and writing of the yeast data experimental part): M. Hohl

Grant Support

This work was supported by NIH GM56888 (to J.H.J. Petrini), Cycle for Survival (to H. Al-Ahmadi and D.B. Solit), the Wiener Fund (to D.B. Solit), an American Society of Clinical Oncology Young Investigator Award (to G. Iyer), and a Prostate Cancer Foundation Young Investigator Award (to B.S. Taylor).

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Received April 10, 2014; revised June 4, 2014; accepted June 11, 2014; published OnlineFirst June 16, 2014.

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Synthetic Lethality in ATM-Deficient \textit{RAD50}-Mutant Tumors Underlies Outlier Response to Cancer Therapy

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\textit{Cancer Discovery} Published OnlineFirst June 16, 2014.