

Consent for publication

Not applicable.

Copyright

© The Author(s) 2019.

REFERENCES

1. Flohr C, Bürkle A, Radicella JP, Epe B. Poly (ADP-ribose) ation accelerates DNA repair in a pathway dependent on Cockayne syndrome B protein. *Nucleic Acids Res* 2003;31:5332-37.
2. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly (ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. *Proc Natl Acad Sci U S A* 2011;108:3406-11.
3. Couto CA, Wang HY, Green JC, Kiely R, Siddaway R, et al. PARP regulates nonhomologous end joining through retention of Ku at double-strand breaks. *J Cell Biol* 2011;194:367-75.
4. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discov* 2015;5:1137-54.
5. Sfeir A, Symington LS. Microhomology-mediated end joining: a back-up survival mechanism or dedicated pathway? *Trends Biochem Sci* 2015;40:701-14.
6. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. *Nature* 2005;434:913-7.
7. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434:917-21.
8. Durkacz BW, Omidiji O, Gray DA, Shall S. (ADP-ribose) n participates in DNA excision repair. *Nature* 1980;283:593-6.
9. Purnell MR, Whish WJ. Novel inhibitors of poly (ADP-ribose) synthetase. *Biochem J* 1980;185:775-7.
10. Calvert H, Azzariti A. The clinical development of inhibitors of poly (ADP-ribose) polymerase. *Ann Oncol* 2011;22(suppl_1):i53-9.
11. Calabrese CR, Batey MA, Thomas HD, Durkacz BW, Wang LZ, et al. Identification of potent nontoxic poly (ADP-Ribose) polymerase-I inhibitors: chemopotential and pharmacological studies. *Clin Cancer Res* 2003;9:2711-8.
12. Plummer R1, Jones C, Middleton M, Wilson R, Evans J, et al. Phase I study of the poly (ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. *Clin Cancer Res* 2008;14:7917-7923.
13. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci U S A* 2008;105:17079-84.
14. Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, et al. Poly (ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010;28:2512-9.
15. Kaye SB, Lubinski J, Matulonis U, Ang JE. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol* 2011;30:372-9.
16. Domchek SM, Aghajanian C, Shapira-Frommer R, Schmutzler RK, Audeh MW, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. *Gynecol Oncol* 2016;140:199-203.
17. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *The Lancet* 2010;376:245-51.
18. Kaufman B, R Shapira-Frommer, Schmutzler RK, Audeh MW, Friedlander M, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2014;33:244-50.
19. Kristeleit RS, Shapira-Frommer R, Oaknin A, Balmaña J, Ray-Coquard IL, et al. Clinical activity of the poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib in patients (pts) with high-grade ovarian carcinoma (HGOC) and a BRCA mutation (BRCAmut): Analysis of pooled data from Study 10 (parts 1, 2a, and 3) and ARIEL2 (parts 1 and 2). *Ann Oncol* 2016;27:8560.
20. Kristeleit R, Shapiro GI, Burris HA, Oza AM, LoRusso P, et al. A phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res* 2017;23:4095-106.
21. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75-87.
22. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382-92.
23. Mirza MR, Monk BJ, Herrstedt J, S DM, Oza AM, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016;375:2154-64.
24. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oza AM, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* 2017;390:1949-61.
25. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary

- peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30:2039-45.
26. Coleman RL, Brady MF, JHerzog T, Sabbatini P, ArmstrongColeman DK, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:779-791.
 27. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian Cancer. *N Engl J Med* 2018;379:2495-505.
 28. Spriggs DR, Longo DL. Progress in BRCA-Mutated Ovarian Cancer. *N Engl J Med* 2018;379:2567-68.
 29. Pujade-Lauraine E, Ledermann JA, Selle F, Gebbski V, Penson RT, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18:1274-84.
 30. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014;15:1207-14.
 31. Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Lancet Oncol* 2015;16:87-97.
 32. Konstantinopoulos PA, Waggoner SE, Vidal GA, Mita MM, Fleming GF, et al. TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib+ pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort. *J Clin Oncol* 2018;36:106.
 33. Robson M, Im SA, Senkus E, Xu B, Domchek SM, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017;377:523-33.
 34. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018;379:753-63.
 35. Pahuja S, Beumer JH, Appleman LJ, Tawbi HAH, Stoller RG, et al. A phase I study of veliparib (ABT-888) in combination with weekly carboplatin and paclitaxel in advanced solid malignancies and enriched for triple-negative breast cancer (TNBC). *J Clin Oncol* 2015;33:1015.
 36. Kummur S, Ji J, Morgan R, Lenz HJ, Puhalla SL, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res* 2012;18:1726-34.
 37. Coleman RL, Sill MW, Bell-McGuinn K, Aghajanian C, Gray HJ, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation—an NRG oncology/gynecologic oncology group study. *Gynecol Oncol* 2015;137:386-91.
 38. Murai J, Huang SY, Renaud A, Zhang Y, Ji J, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther* 2014;13:433-43.
 39. Plummer ER, Dua D, Cresti N, Suder A, Drew Y, et al. First-in-human phase I study of the PARP/tankyrase inhibitor 2X-121 (E7449) as monotherapy in patients with advanced solid tumors and validation of a novel drug response predictor (DRP) mRNA biomarker. *J Clin Oncol* 2018;36:2505.
 40. Plummer R, Stephens P, Aissat-Daudigny L, Cambois A, Moachon G, et al. Phase I dose-escalation study of the PARP inhibitor CEP-9722 as monotherapy or in combination with temozolomide in patients with solid tumors. *Cancer Chemoth Pharm* 2014;74:257-65.
 41. Awada A, Campone M, Varga A, Aftimos P, Frenel JS, et al. An open-label, dose-escalation study to evaluate the safety and pharmacokinetics of CEP-9722 (a PARP-1 and PARP-2 inhibitor) in combination with gemcitabine and cisplatin in patients with advanced solid tumors. *Anti-cancer Drugs* 2016;27:342-8.
 42. O'Shaughnessy J, Schwartzberg L, Danso MA, Miller KD, Rugo HS, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol* 2014;32:3840-7.
 43. Patel AG, De Lorenzo SB, Flatten KS, Poirier GG, Kaufmann SH. Failure of iniparib to inhibit poly(ADP-Ribose) polymerase in vitro. *Clin Cancer Res* 2012;18:1655-62.
 44. Gagné JP, Isabelle M, Lo KS, Bourassa S, Hendzel MJ, et al. Proteome-wide identification of poly(ADP-ribose) binding proteins and poly(ADP-ribose)-associated protein complexes. *Nucleic Acids Res* 2008;36:6959-76.
 45. El-Khamisy SF, Masutani M, Suzuki H, Caldecott KW. A requirement for PARP-1 for the assembly or stability of XRCC1 nuclear foci at sites of oxidative DNA damage. *Nucleic Acids Res* 2003;31:5526-33.
 46. Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, et al. Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair. *Nature* 2015;518:258-62.
 47. Mateos-Gomez PA, Gong F, Nair N, Miller KM, Lazzarini-Denchi E, et al. Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination. *Nature* 2015;518:254-7.
 48. Murai J, Huang SN, Das BB, Renaud A, Zhang Y, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res* 2012;72:5588-99.
 49. Caldecott KW. Protein ADP-ribosylation and the cellular response to DNA strand breaks. *DNA repair* 2014;19:108-113.
 50. Hopkins TA, Shi Y, Rodriguez LE, Solomon LR, Donawho CK, et al. Mechanistic Dissection of PARP1 Trapping and the Impact on In Vivo Tolerability and Efficacy of PARP Inhibitors. *Mol Cancer Res* 2015;13:1465-77.
 51. Hopkins TA, Ainsworth WB, Ellis PA, Donawho CK, DiGiannarino EL, et al. PARP1 Trapping by PARP Inhibitors Drives Cytotoxicity in Both Cancer Cells and Healthy Bone Marrow. *Mol Cancer Res* 2019;17:409-419.
 52. Grundy GJ, Polo LM, Zeng Z, Rulten SL, Hoch NC, et al. PARP3 is a sensor of nicked nucleosomes and monoribosylates histone

- H2B(Glu2). *Nat Commun* 2016;7:12404.
53. Knezevic CE, Wright G, Rix LLR, Kim W, Kuenzi BM, et al. Proteome-wide Profiling of Clinical PARP Inhibitors Reveals Compound-Specific Secondary Targets. *Cell Chem Biol* 2016;23:1490-1503.
 54. Puhalla S, Beumer JH, Pahuja S, Appleman LJ, Tawbi HAH, et al. Final results of a phase I study of single-agent veliparib (V) in patients (pts) with either BRCA1/2-mutated cancer (BRCA+), platinum-refractory ovarian, or basal-like breast cancer (BRCA-wt). *J Clin Oncol* 2014;32:2570.
 55. Li J, Kim S, Sha X, Wiegand R, Wu J, et al. Complex disease-, gene-, and drug-drug interactions: impacts of renal function, CYP2D6 phenotype, and OCT2 activity on veliparib pharmacokinetics. *Clin Cancer Res* 2014;20:3931-44.
 56. Norquist B, Wurz KA, Pennil CC, Garcia R, Gross J, et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. *J Clin Oncol* 2011;29:3008-15.
 57. Barber LJ, Sandhu S, Chen L, Campbell J, Kozarewa I, et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J Pathol* 2013;229:422-9.
 58. Kondrashova O, Nguyen M, Shield-Artin K, Tinker AV, Teng NHH, et al. Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-grade ovarian carcinoma. *Cancer Discov* 2017;7:984-998.
 59. Goodall J, Mateo J, Yuan W, Mossop H, Porta N, et al. Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. *Cancer Discov* 2017;7:1006-17.
 60. Quigley D, Alumkal JJ, Wyatt AW, Kothari V, Foye A, et al. Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors. *Cancer Discov* 2017;7:999-1005.
 61. Isono M, Niimi A, Oike T, Hagiwara Y, Sato H, et al. BRCA1 Directs the Repair Pathway to Homologous Recombination by Promoting 53BP1 Dephosphorylation. *Cell Rep* 2017;18:520-32.
 62. Bunting SF, Callén E, Wong N, Chen HT, Polato F, et al. 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. *Cell* 2010;141:243-54.
 63. Hurley RM, Wahner Hendrickson AE, Visscher DW, Ansell P, Harrell MI, et al. 53BP1 as a potential predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. *Gynecol Oncol* 2019;153:127-134.
 64. Xu G, Chapman JR, Brandsma I, Yuan J, Mistrik M, et al. REV7 counteracts DNA double-strand break resection and affects PARP inhibition. *Nature* 2015;521:541-4.
 65. Chaudhuri AR, Callen E, Ding X, Gogola E, Duarte AA, et al. Replication fork stability confers chemoresistance in BRCA-deficient cells. *Nature* 2016;535:382-7.
 66. Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, et al. Prediction of DNA Repair Inhibitor Response in Short-Term Patient-Derived Ovarian Cancer Organoids. *Cancer Discov* 2018;8:1404-21.
 67. Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, et al. Selective Loss of PARG Restores PARylation and Counteracts PARP Inhibitor-Mediated Synthetic Lethality. *Cancer Cell* 2019;35:950-952.
 68. Godoy H, Mhawech-Fauceglia P, Beck A, Miller A, Lele S, et al. Expression of poly (adenosine diphosphate-ribose) polymerase and p53 in epithelial ovarian cancer and their role in prognosis and disease outcome. *Int J Gynecol Pathol* 2011;30:139-44.
 69. Mazzotta A, Partipilo G, De Summa S, Giotta F, Simone G, et al. Nuclear PARP1 expression and its prognostic significance in breast cancer patients. *Tumour Biol* 2016;37:6143-53.
 70. Bitler BG, Watson ZL, Wheeler LJ, Behbakht K. PARP inhibitors: Clinical utility and possibilities of overcoming resistance. *Gynecol Oncol* 2017;147:695-704.
 71. Kondrashova O, Topp M, Nestic K, Lieschke E, Ho GY, et al. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. *Nat Commun* 2018;9:3970.
 72. Neijenhuis S, Bajrami I, Miller R, Lord CJ, Ashworth A. Identification of miRNA modulators to PARP inhibitor response. *DNA Repair* 2013;12:394-402.
 73. Do K, Wilsker D, Ji J, Zlott J, Freshwater T, et al. Phase I study of single-agent AZD1775 (MK-1775), a Wee1 kinase inhibitor, in patients with refractory solid tumors. *J Clin Oncol* 2015; 33:3409-15.
 74. Moore KN, Secord AA, Geller MA, Miller DS, Cloven NG, et al. QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) who have received ≥ 3 prior chemotherapy regimens. *J Clin Oncol* 2018;36:5514.
 75. Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. *Clin Cancer Res* 2017;23:3711-20.
 76. Vinayak S, Tolaney SM, Schwartzberg LS, Mita MM, McCann GAL, et al. TOPACIO/Keynote-162: Niraparib+ pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC), a phase 2 trial. *J Clin Oncol* 2018;36:1011.
 77. Teo MY, Seier K, Ostrovnaya I, Regazzi AM, Kania BE, et al. Alterations in DNA damage response and repair genes as potential marker of clinical benefit from PD-1/PD-L1 blockade in advanced urothelial cancers. *J Clin Oncol* 2018;36:1685-94.
 78. Nolan E, Savas P, Policheni AN, Darcy PK, Vaillant F, et al. Combined immune checkpoint blockade as a therapeutic strategy for BRCA1-mutated breast cancer. *Sci Transl Med* 2017;9:eaal4922.
 79. Turner NC, Balmaña J, Fasching PA, Hurvitz SA, Telli ML, et al. A phase 2 study (2-stage, 2-cohort) of the oral PARP inhibitor talazoparib (BMN 673) in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer (ABRAZO). *J Clin Oncol* 2015;33:TPS1108.
 80. Somlo G, Frankel PH, Arun BK, Ma CX, Garcia AA, et al. Efficacy of the PARP inhibitor veliparib with carboplatin or as a single agent in patients with germline BRCA1- or BRCA2-associated metastatic brea. *Clin Cancer Res* 2017;23:4066-76.