Exploiting DNA repair defects in colorectal cancer

(Article begins on next page)

07 July 2024

Exploiting DNA repair defects in colorectal cancer

Nicole M. Reilly[1], Luca Novara[2], Federica Di Nicolantonio[2,3], and Alberto Bardelli[2,3*]

[1]Fondazione Piemontese per la Ricerca sul Cancro ONLUS, Candiolo, TO, Italy

[2]Candiolo Cancer Institute, FPO-IRCCS, Candiolo, TO, Italy

[3]Department of Oncology, University of Torino, SP 142 km 3.95, 10060 Candiolo, TO, Italy

*To whom correspondence should be addressed:

Alberto Bardelli

Department of Oncology, University of Torino, SP 142 km 3.95, 10060 Candiolo, TO, Italy

Candiolo Cancer Institute, FPO-IRCCS, 10060 Candiolo, TO, Italy

Tel: +39 011 993 3235. Fax: +39 011 993 3225

Email address: alberto.bardelli@unito.it

Running title: The role of DNA repair in colorectal cancer

Abstract

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide. Therapies that take advantage of defects in DNA repair pathways have been explored in the context of breast, ovarian, and other tumor types, but not yet systematically in CRC. At present, only immune checkpoint blockade therapies have been FDA approved for use in mismatch repair deficient colorectal tumors. Here, we discuss how systematic identification of alterations in DNA repair genes could provide new therapeutic opportunities for CRCs. Analysis of The Cancer Genome Atlas Colon Adenocarcinoma (TCGA-COAD) and Rectal Adenocarcinoma (TCGA-READ) PanCancer Atlas datasets identified 141 (out of 528) cases with putative driver mutations in 29 genes associated with DNA damage response and repair, including the mismatch repair and homologous recombination pathways. Genetic defects in these pathways might confer repair-deficient characteristics, such as genomic instability in the absence of homologous recombination, which can be exploited. For example, inhibitors of poly(ADP)-ribose polymerase are effectively used to treat cancers that carry mutations in *BRCA1* and/or *BRCA2*, and have shown promising results in CRC pre-clinical studies. HR deficiency can also occur in cells with no detectable BRCA1/BRCA2 mutations but exhibiting *BRCA-like* phenotypes. DNA repair-targeting therapies, such as ATR and CHK1 inhibitors (which are most effective against cancers carrying *ATM* mutations), can be used in combination with current genotoxic chemotherapies in CRCs to

further improve therapy response. Finally, therapies that target alternative DNA repair mechanisms, such as thiopurines, also have the potential to confer increased sensitivity to current chemotherapy regimens, thus expanding the spectrum of therapy options and potentially improving clinical outcomes for CRC patients.

1 Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer related deaths (Bray, Ferlay et al. 2018). In Europe, CRC accounts for the second highest number of cancer cases and deaths (Malvezzi, Carioli et al. 2018), and in North America CRC has the fourth highest rate of incidence and the second highest number of cancer-related deaths (Jemal, Ward et al. 2017). While CRC death rates are slowly declining in the United States and Europe (Jemal, Ward et al. 2017, Malvezzi, Carioli et al. 2018), the five-year overall survival for patients with metastatic CRC (mCRC) remains poor (approximately 14.0% (NCI 2017)). The standard chemotherapeutic regimen for mCRC is 5-fluorouracil (5-FU) in combination with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) (Cremolini, Schirripa et al. 2015). These chemotherapy agents induce genotoxic damage in tumor cells that is recognized and repaired by DNA repair proteins (Helleday, Petermann et al. 2008).

In 2012, The Cancer Genome Atlas (TCGA) conducted a comprehensive characterization of CRC tumors, including exome sequences, DNA copy numbers, and RNA expression levels (Network 2012). Of the cases analyzed, 16% were classified as hypermutated (greater than 12 mutations per 10^6 bases) and exhibited mutation enrichment in microsatellite regions indicating microsatellite instability (MSI) phenotype. The other 84% of cases were classified as microsatellite stable (MSS), and exhibited a higher frequency of somatic copy number alterations, suggesting chromosomal and sub-chromosomal defects (Network 2012). The most frequently identified gene mutations in CRC tumors occur in *APC*, *TP53*, and *KRAS* (Huang, Sun et al. 2018, Wolff, Hoffman et al. 2018, Yaeger, Chatila et al. 2018). Recent analysis of TCGA data identified mutations associated with DNA damage

response genes and found that cases in the colon adenocarcinoma (COAD) and rectal adenocarcinoma (READ) datasets carried mutations in several DNA damage response and repair (DDR) genes (Knijnenburg, Wang et al. 2018).

Acquisition of mutations is a critical step for tumor development (Hanahan and Weinberg 2011), and mutations that occur in DNA repair genes impair cells' ability to restore damaged DNA and can lead to cell death or genome instability (Aguilera and Gomez-Gonzalez 2008). Mutations in MMR genes are observed in 2 – 3% of CRC patients (Lorans, Dow et al. 2018), while approximately 10% of CRC patients exhibit hypermethylation of *MLH1* (Pearlman, Frankel et al. 2017, AlDubayan, Giannakis et al. 2018), contributing to a MMR-deficient (MMRd) phenotype. The remaining CRC patient population can be classified as MMR-proficient (MMRp). Defects in the MMR pathway are commonly used to classify CRCs, while mutations in HR and FA genes have been historically linked with breast and ovarian cancers (Knijnenburg, Wang et al. , Hoang and Gilks 2018). The TCGA-COAD and -READ PanCancer Atlas cohort (Cerami, Gao et al. 2012, Gao, Aksoy et al. 2013, Liu, Lichtenberg et al. 2018) includes mutational data for 528 patient tumor samples, and analysis of these samples identified 141 cases that carried mutations in at least one of 420 DNA repair genes. The majority of mutations identified were classified as "putative passenger." While these mutations are not currently known to drive carcinogenesis, it is possible that the presence of these mutations will cause the cells to be DNA repair-deficient. Using criteria that excluded likely passenger mutations, putative driver mutations were identified in 29 DNA damage response and repair genes (Table 1).

Epigenetic modulation of gene expression can also lead to a repair-defective phenotype. For example, hypermethylation of the *MLH1* promoter has been associated with the MSI phenotype in sporadic endometrial and hereditary nonpolyposis colorectal cancers (Esteller, Levine et al. 1998, Planck, Ericson et al. 2003, Niv 2007). Epigenetic down-regulation of MMR genes has also been linked with resistance to alkylating chemotherapy agents in CRC tumor models (Planck, Ericson et al. 2003), and studies have demonstrated that preventing down-regulation of MMR genes can restore cellular sensitivity to these

agents (Francia, Green et al. 2005). Methylation data was not available for the PanCancer Atlas dataset; however, analysis of the TCGA-COADREAD Provisional dataset (Cerami, Gao et al. 2012, Gao, Aksoy et al. 2013) determined that 10.3% of cases (37 out of 358) exhibited hypermethylation of *MLH1*. The presence of mutations or hypermethylation of promoter regions in one or more DNA repair genes in a CRC cell may contribute to a DNA repair defective phenotype that can be used to classify tumor sub-types and to choose an appropriate therapy regimen.

2 DNA repair-defective phenotypes in colorectal cancers

2.1 Mismatch repair

The MMR pathway recognizes and removes DNA base pair mismatches that occur due to replication errors (Iyer, Pluciennik et al. 2006, Modrich 2006) (Figure 1; left panel). First, the mismatch is recognized by MutSα (MSH2/MSH6) and MutLβ (MLH1/PMS1) or MutSβ (MSH2/MSH3) and MutLα (MLH1/PMS2) heterodimer complexes that bind the DNA surrounding the mismatch. Downstream, the exonuclease EXO1 interacts with proliferating cell nuclear antigen (PCNA), initiating DNA resection in a 5′ to 3′ manner. Finally, polymerase δ replicates across the excised region and the DNA is ligated by DNA ligase I. Inactivating mutations in any of these genes decreases recognition of base pair mismatches, leading to increased mutational burden, particularly in microsatellite regions of the genome (Popat, Hubner et al. 2005, Hause, Pritchard et al. 2016, Cortes-Ciriano, Lee et al. 2017). One of the phenotypes exhibited in MMRd cells is MSI (Zeinalian, Hashemzadeh-Chaleshtori et al. 2018), and several studies have shown that MSI corresponds with favorable prognosis and better survival (Thibodeau, Bren et al. 1993, Popat, Hubner et al. 2005).

2.1.1 Microsatellite instability

A phenotype of cells that carry defects in mismatch repair is microsatellite instability (MSI), defined as high mutational burden in sequences along the genome that contain repetitive, short-tandem sequences containing 1–6 nucleotide units up to 100 times, known as microsatellites (Zeinalian, Hashemzadeh-Chaleshtori et al. 2018). The National Institutes of Health has defined five biomarkers that contain mono- or dinucleotide repeats in specific regions of the genome to be used for clinical determination of MSI status (Boland, Thibodeau et al. 1998). PCR amplification of biomarker regions is performed, and the product size in tumor cells is compared with matched normal cells to determine if mutations are present (Zeinalian, Hashemzadeh-Chaleshtori et al. 2018). New advents in sequencing technology has allowed for the detection of MSI using whole-exome sequencing (WES) data from tumor samples and normal tissue isolated from the same patient (Hause, Pritchard et al. 2016). A comprehensive analysis of microsatellite stability in 5,930 exome samples demonstrated that these strategies are capable of distinguishing MSI cancer from MSS cancers, and these analyses identified genomic 'hot spots' that exhibit higher frequencies of MSI across cancer sub-types (Hause, Pritchard et al. 2016). Immunohistochemistry using antibodies against MLH1, MSH2, MSH6, and PMS2 is another effective technique that is used to assess MMR status (Yuan, Chi et al. 2015, Zeinalian, Hashemzadeh-Chaleshtori et al. 2018).

Generation of neoantigens is another phenotype of MMRd cells that has been well-characterized in CRC (Scarpa, Ruffolo et al. 2015, Germano, Lamba et al. 2017, Le, Durham et al. 2017). The defects in MMR machinery lead to frameshifts and indels that produce novel peptides within a cell. Once translated, these peptides can be exposed to the outside of the cell by the HLA proteins and activate immune surveillance of the tumor cells, thus making MMRd cells more susceptible to immune surveillance (Nakayama 2014).

2.2 *Homologous recombination*

The HR pathway is essential for preserving genome integrity in the event of DNA double strand breaks (DSBs) (Ranjha, Howard et al. 2018) (Figure 1; right panel). If left unrepaired, this type of damage can lead to deletions, frameshifts, chromosome aberrations, and aneuploidy (Jackson and Bartek 2009). During S phase, a DSB is first recognized by poly(ADP-ribose) polymerase 1 (PARP1), a protein that scans the genome and detects DSB lesions (Ciccia and Elledge 2010). PARP1 marks the damage site by attaching ADP-ribose molecules to chromatin-bound proteins surrounding the break (Haince, McDonald et al. 2008). The ADP-ribose units are essential for recruitment of meiotic recombination 11 (MRE11), RAD50, and Nijmegen Breakage Syndrome (NBS1) proteins, which form the MRN complex. The exonuclease activity of this complex produces single strand DNA (ssDNA) surrounding the break (Haince, McDonald et al. 2008, Dodson, Limbo et al. 2010, Huen, Sy et al. 2010, You and Bailis 2010), and localization of MRN triggers ATM-mediated signaling of downstream repair factors. Following MRN-mediated resection, the single strand binding protein replication protein A (RPA) stabilizes the newly produced ssDNA overhangs (Marechal and Zou 2015). Recruitment of BRCA1 and BRCA2, along with BRIP1, PALB2, and the RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex, promotes RAD51 binding to the ssDNA overhangs (Jensen, Ozes et al. 2013, Candelli, Holthausen et al. 2014, Short, Liu et al. 2016, Xu, Zhao et al. 2017). Finally, RAD51 mediates strand invasion of the ssDNA overhang into a homologous DNA region, usually a sister chromatid, enabling repair to be completed (Qi, Redding et al. 2015).

2.2.1 *Genome instability*

In the context of distinct cancers types, such as breast and ovarian, 'genome instability' is typically attributed to defects in HR DNA repair genes (Janssen, van der Burg et al. 2011, Burrell, McClelland et al. 2013, Chien, Sicotte et al. 2015, Vanderstichele, Busschaert et al. 2017). Hanahan and Weinberg classified 'genome instability' as an enabling characteristic of cancer and described how defects in DNA repair lead to loss of chromosomes, particularly at

the telomere region (Hanahan and Weinberg 2011). Genome instability is identified by structural alterations that include copy number variations and loss-of-heterozygosity, often observed in CRC cells (Druliner, Ruan et al. 2018), and chromosomal rearrangements (Aguilera and Gomez-Gonzalez 2008). These elements are characteristic of HR defective cells, and specific genomic signatures have been identified in breast and ovarian cancer cells (Davies, Glodzik et al. 2017, Vanderstichele, Busschaert et al. 2017, Hillman, Chisholm et al. 2018). The detection of genomic rearrangements by whole-genome sequencing in BRCA1/BRCA2 deficient samples lead to identification of six distinct mutational signatures that correlated with BRCA status (Davies, Glodzik et al. 2017). Notably, the so-called *BRCA-ness* signature was also identified in cells that did not have detectable BRCA1/BRCA2 mutations, connecting genomic rearrangements with functional HR-deficiency, and suggesting that additional molecular alterations might underline *BRCA-like* phenotypes (Davies, Glodzik et al. 2017). *BRCA-ness* mutational signatures in CRC tumors might be used as predictive biomarkers for HR-deficiency regardless of BRCA status.

2.2.2 Telomere defects

In addition to genomic rearrangements, telomere length is a measurement of genome instability (Hackett, Feldser et al. 2001). HR repair proteins function to protect telomere regions from damage (Tarsounas, Munoz et al. 2004, Claussin and Chang 2015), and telomere defects are often observed in genome unstable cells (Venkatesan, Natarajan et al. 2015). A recent study investigating telomere length in CRC determined that *KRAS* mutated cells exhibited extensive telomere shortening compared with control cells. In contrast, cells that carried *BRAF* mutations or were classified as MSI did not exhibit telomere defects (Balc'h, Grandin et al. 2017). Another independent study analyzed telomere length in precursor colorectal lesions and observed that telomere shortening was associated with mitochondrial microsatellite instability in the tumor tissue samples, and with *KRAS* and *BRAF* mutations in the normal tissues (Park, Bae et al. 2017). Studies have also demonstrated that *KRAS* mutated CRC cells can become dependent on RAD51-mediated

repair (Kalimutho, Bain et al. 2017), a key protein in the HR pathway that is essential for maintaining telomere integrity (Le, Moore et al. 1999, Signon, Malkova et al. 2001, Badie, Escandell et al. 2010, Lu, Pal et al. 2014). Together, these data suggest that telomere shortening is indicative of DNA repair defects and may be a biomarker of early CRC carcinogenesis.

3 Targeting DNA repair in colorectal cancer

Current medical regimens for CRC patients include combination therapies with oxaliplatin, irinotecan, and 5-FU (Cremolini, Schirripa et al. 2015). These 'genotoxic' drugs directly or indirectly induce DNA damage that is recognized by specific repair pathways (Figure 2). Oxaliplatin is a platinum-based compound that can induce cell death through several mechanisms, such as inducing ribosome biogenesis stress (Bruno, Liu et al. 2017). The genotoxic activity of this drug is attributed to its ability to bind the N7 of guanine nucleotides in DNA, generating inter-strand crosslinks that can inhibit replication during S phase (Ray, Gupta et al. 2018). Irinotecan, a camptothecin analog, binds to topoisomerase I and DNA, preventing dissociation of topoisomerase I during S phase and ultimately leading to DNA DSBs (Li, Jiang et al. 2017). These two types of DNA damage are recognized and repaired by the FA/HR pathways (Ceccaldi, Sarangi et al. 2016). 5-FU is an antimetabolite that inhibits thymidylate synthase, an enzyme involved in nucleotide synthesis, and is thought to inhibit DNA replication thus leading to abasic sites that are repaired by base excision repair (BER) proteins (Huehls, Huntoon et al. 2016). 5-FU can also be incorporated into DNA, resulting in DNA mismatches that are recognized and repaired by the MMR pathway (Iwaizumi, Tseng-Rogenski et al. 2011). An alternative nucleotide analog, TAS-102, has been approved by the FDA as a treatment option for mCRC patients (Marcus, Lemery et al. 2017). TAS-102 inhibits nucleoside synthesis in a similar mechanism of action to the standard therapy 5-FU, and is effective in treating patients that are refractory to 5-FU therapy (Lenz, Stintzing et al. 2015). Recent studies have linked mutations in DNA repair

genes, specifically those associated with HR, as predictive markers of the efficacy of TAS-102 in patients (Suenaga, Schirripa et al. 2017).

These compounds are most effective in cells with defects in the respective repair pathways, and CRC patients that carry mutations in repair-associated genes can be predicted to respond well to these types of therapies.

3.1. Immune checkpoint blockade

CRC tumors that have increased neoantigen production due to MMR-deficiency also have higher levels of tumor infiltrating lymphocytes (TILs) and increased programmed death ligand-1 (PDL-1) protein expression (Llosa, Cruise et al. 2015, Kim, Park et al. 2016, Germano, Amirouchene-Angelozzi et al. 2018). Recent studies have shown that MSI tumor cells are responsive to PD-1 and CTLA-4 immune blockade (McGranahan, Furness et al. 2016, Germano, Lamba et al. 2017, Le, Durham et al. 2017, Luksza, Riaz et al. 2017). In one study, patients with higher TILs and PD-L1 expression responded to checkpoint blockade better compared with patients with lower PD-L1 expression, suggesting that this phenotype can be used as a predictor of therapy response (Wang, Gong et al. 2018). A 2017 Phase II clinical trial of nivolumab, a PD-L1 immune checkpoint inhibitor, in patients with MMRd and MSI-H CRC who had received at least three rounds of prior therapy and were no longer responsive to first-line treatments found that this therapy provided durable response and disease control in these patients. Of the 74 patients enrolled, 31% achieved objective response and 51% achieved disease control (Overman, Lonardi et al. 2018). Based on these data, nivolumab was given FDA approval for the treatment of mCRC with MSI-H or MMRd tumors (Sarshekeh, Overman et al. 2018). In addition to CRC, studies have demonstrated that solid tumors of multiple tissue types exhibiting MSI show durable response to PD-L1 blockade, and based on this evidence, the FDA approved these agents for use in any cancers that histologically exhibit MSI (Lemery, Keegan et al. 2017).

MMRd tumors have increased mutational burden (TMB), a phenotype that can also be observed in a small subset of tumors that are MSS. One study analyzed over 6,000 CRC cases, 95% of which were classified as MSS, and observed that 2.9% of MSS tumors exhibited high TMB and, within this subset of tumors, 54% responded to anti PD-L1 immunotherapy (Fabrizio, George et al. 2018). The results of this study suggest that in MMRd tumors that do not exhibit MSI, TMB can be used as a predictor for therapy response to tumor checkpoint inhibition.

3.2 PARP inhibitors

In the presence of directly induced DNA breaks, PARP1 poly(ADP-ribosyl)ates chromatin surrounding the damage to initiate activity of downstream HR proteins (Haince, McDonald et al. 2008). Additionally, PARP functions to regulate replication fork progression and maintain fork stability. Chemical inhibition of PARP activity can interfere with either of these activities, leading to replication fork collapse or accelerated fork progression that generates DNA single and double strand breaks (D'Andrea 2018, Maya-Mendoza, Moudry et al. 2018). Poly-(ADP) ribose polymerase inhibitors (PARPi) have been used as anticancer agents since the early 2000's (McCabe, Turner et al. 2006), and the first PARPi, olaparib, was approved for *BRCA* mutated ovarian cancer in 2014 (Kim, Ison et al. 2015). Approval of these drugs was first given for the treatment of breast and ovarian cancers, and studies found that this therapy regimen was most effective in cells that carry functional defects in DNA DSB pathways, most notably in *BRCA* mutated cells (Lin, Ratner et al. 2014, Ghiringhelli, Richard et al. 2016, Lord and Ashworth 2017, Cortesi, Toss et al. 2018, Mittica, Ghisoni et al. 2018, Sunada, Nakanishi et al. 2018). Recent studies ascribed this synthetic lethality phenotype to the loss of PARP activity at replication forks, suggesting that PARP inhibition promotes rapid fork progression, leading to increased genome instability that the cell cannot overcome when HR defects are also present (Maya-Mendoza, Moudry et al. 2018).

Early investigations into the use of PARPi for the treatment of CRC began with the inhibitor ABT-888, later known as veliparib. Prior studies had demonstrated that ABT-888 was effective in *BRCA*-deficient cells compared with proficient counterparts, and that response to PARPi was further increased when combined with platinum-based genotoxic compounds (Clark, Weitzel et al. 2012). Following on the premise that PARPi will increase sensitivity to genotoxic compounds in cancer cells, the effect of ABT-888 in combination with irinotecan in CRC cells was investigated (Davidson, Wang et al. 2013). This study observed a synergistic response to irinotecan or oxaliplatin in combination with ABT-888 in CRC cells (Davidson, Wang et al. 2013). Another study demonstrated that addition of ABT-888 increased sensitivity of CRC cells to radiation (Shelton, Waxweiler et al. 2013), further supporting the hypothesis that PARPi are a viable option to improve response to current therapy regimens in CRC. A recent Phase II open label study evaluated the efficacy of the veliparib PARPi in combination with temozolomide in mCRC patients that were refractory to standard therapies. Fifty patients were enrolled in the trial, and 24% exhibited disease control response and 4% showed partial response to the combination therapy (Pishvaian, Slack et al. 2018).

Synthetic lethality has been clearly demonstrated in cells that harbor defects in DNA DSB repair pathways, specifically *BRCA* mutated cells (McCabe, Turner et al. 2006, Lord and Ashworth 2017). For this reason, it can be predicted that CRC cells that respond well to PARPi most likely carry defects in DSB repair proteins. One study found that CRC cells carrying inactivating mutations in *ATM* have increased sensitivity to the PARPi olaparib (Wang, Jette et al. 2017). These data correlate well with earlier studies in gastric and lung cancers that found that loss of ATM protein expression increased cellular sensitivity to PARP inhibition (Kubota, Williamson et al. 2014, Schmitt, Knittel et al. 2017). However, due to the limited number of preclinical models studied, these results should be confirmed in larger cohorts.

In addition to exploiting DSB repair defects in CRC cells, it has been postulated that cells that exhibit MSI may also be susceptible to PARP inhibition. In 2014, a study demonstrated that loss of MRE11 in MSI CRC cells increased cellular sensitivity to ABT-888 (Vilar, Bartnik et al. 2011). One proposed explanation is the MSI induces mutations within DNA repair genes, conferring a repair deficient phenotype and making the cells more susceptible to the effects of PARP inhibition. This hypothesis has been supported in models of myeloid malignancies (Gaymes, Mohamedali et al. 2013). More recently, a Phase II clinical trial investigated off-label of use of PARPi in MSS and MSI CRCs to determine if microsatellite status was a predictive marker of PARPi response. The results of this study suggested that PARPi alone did not affect patient outcomes regardless of microsatellite status (Leichman, Groshen et al. 2016). While PARPi have been approved for the treatment of other cancer types that exhibit HR deficiency, PARPi are not currently used for CRC patients.

As discussed above, HR deficiency can also occur in cells with no detectable BRCA1/BRCA2 mutations but showing *BRCA-like* phenotypes. Accordingly, it will be of interest to assess whether the *BRCA-ness* mutational signatures might be used as predictive biomarkers for sensitivity to PARP inhibitors and oxaliplatin.

3.2.1 DNA repair-mediated resistance mechanisms to PARP inhibition

DNA repair associated resistance mechanisms to PARP inhibition have been well characterized in breast and ovarian cancers (D'Andrea 2018), and it is reasonable to predict that similar mechanisms may promote resistance in CRC patients following PARP blockade. One mechanism is re-activation of HR activity, either through acquired mutations in DNA repair genes or through increased activity of effector proteins that promote HR activity. Acquired mutations have also been described in HR genes that restore the reading frame and expression of the protein following exposure to PARPi (Quigley, Alumkal et al. 2017). Restoration of BRCA1 expression reverses HR-mediated repair deficiency and allows the cells to repair the damage induced through PARP inhibition (D'Andrea 2018), and mutations

that restore activity of other HR proteins have also been observed in PARPi resistant cancer cells. A study of 12 pre-treatment and post-progression patient samples observed the acquisition of mutations in the *RAD51D* and *RAD51C* genes that restored protein expression and promoted resistance to rucaparib (Kondrashova, Nguyen et al. 2017), and an independent study identified a point mutation in the *XRCC2* DNA repair gene that decreased sensitivity of CRC cells to olaparib (Xu, Song et al. 2014). In addition to mutations that restore gene expression, epigenetic regulation of gene expression can predict response and resistance to PARPi. In a study of 12 high grade serous ovarian cancer (HGSOC) patient-derived xenografts and 21 patient samples (ARIEL2 trial), response and resistance to rucaparib was correlated with methylation status of *BRCA1*. Methylation-mediated silencing of all *BRCA1* copies predicted response to rucaparib, while heterozygous methylation was associated with resistance to therapy (Kondrashova, Topp et al. 2018).

HR activity can also be increased through regulatory effector proteins, such as the demethylase JMJD1C. This enzymes targets MDC1 for demethylation at Lys45 to promote its interaction with RNF8 and its function in the HR signalling cascade (Watanabe, Watanabe et al. 2013). Overexpression of JMJD1C has been detected in colon cancer tissues compared with normal tissues (Chen, Aihemaiti et al. 2018). Furthermore, depletion of JMJD1C in cells induces cellular resistance to ionizing radiation (IR) and PARPi (Watanabe, Watanabe et al. 2013). These data suggest that resistance mechanisms can arise from regulatory proteins in DNA repair pathways and further show that a comprehensive understanding of repair efficiency is necessary to properly predict therapy response.

A second mechanism of PARPi resistance described in *BRCA* mutated cancers is increased activity of alternative DNA repair pathways. In the absence of BRCA1, activity of non-homologous end joining (NHEJ), an alternative DNA DSB repair pathway, is increased specifically through loss of p53 binding protein 1 (53BP1) expression (Bouwman, Aly et al. 2010, Jaspers, Kersbergen et al. 2013). 53BP1 regulates pathway choice in response to DNA DSBs and promotes NHEJ activity through inhibition of BRCA1 recruitment during early DSB repair (Bakr, Kocher et al. 2016). Somatic loss of 53BP1 expression in *BRCA1*-mutated

cancers lead to partial restoration of HR-mediated DSB repair and contributed to resistance to PARPi (Jaspers, Kersbergen et al. 2013). A recent study observed that cancer cells carrying mutations that lead to expression of a truncated BRCA1 protein, which maintained the ability to interact with PALB2, still developed PARPi resistance even in the absence of 53BP1. In contrast, loss of the interaction between BRCA1 and PALB2 did not confer PARPi resistance when 53BP1 expression was decreased, suggesting that this protein interaction is required for any measurable HR activity (Nacson, Krais et al. 2018).

Increased activity of NHEJ in the absence of BRCA1 can also be attributed to expression of REV7, the non-catalytic subunit of DNA polymerase ζ, which functions to promote translesion synthesis in the presence of DNA damage (Lee, Gregory et al. 2014). In response to DSBs, REV7 interacts with 53BP1 to prevent DNA-end resection at the break site. This activity promotes end-ligation mediated by NHEJ proteins and contributes to DSB repair following PARP inhibition (Xu, Chapman et al. 2015). REV7 also functions as part of the Shieldin complex that promotes 53BP1 mediated NHEJ in *Brca1*-deficient cells (Ghezraoui, Oliveira et al. 2018), a function that could potentially contribute to PARP inhibitor resistance. These activities in the presence of DSBs induced through PARP inhibition provide mechanisms to overcome the damage, leading to resistance to PARP targeting therapies.

A third mechanism of resistance to PARPi, specifically in HR-deficient cancer cells, is restoration of replication fork stability. One study demonstrated that reduced recruitment of the exonuclease MRE11 in BRCA1-deficient cells prevented end resection at these sites and promoted fork stability (Ray Chaudhuri, Callen et al. 2016). Reduced recruitment of another DNA exonuclease, MUS81, has also been shown to promote stability of replication forks in BRCA2-deficient cancers that develop resistance to PARP inhibition (Rondinelli, Gogola et al. 2017). Finally, it has been reported that maintenance of replication forks can be regulated at the transcriptional level. One study observed that BRCA2-deficient cells treated with PARPi overcome therapeutic pressure by down-regulating expression of the transcription repressor E2F7. One of the genes under the control of E2F7 is RAD51, and loss of E2F7

expression increases expression of RAD51, enhancing HR activity even in the absence of BRCA2 (Clements, Thakar et al. 2018).

Resistance to PARP inhibition can also arise from altered activity of PARP and PARP-associated proteins. One example is loss of poly(ADP-ribose) glycohydrolase (PARG) that has been shown to be a major resistance mechanism to PARP inhibition in *Brca2*-mutated cells (Gogola, Duarte et al. 2018). Under unperturbed cellular conditions, PARG functions to remove poly(ADP-ribose) chains generated by PARP1 at the site of DNA damage. PARP inhibitors can either trap PARP1 on the chromatin, leading to stalled replication forks and DSBs, or can inhibit the enzymatic activity and prevent generation of poly(ADP-ribose) polymers that signal HR-mediated DSB repair (Dziadkowiec, Gasiorowska et al. 2016). In the case of the former, PARPi are most effective when PARG is still active in order to remove the poly(ADP-ribose) polymers and inhibit HR signaling. When PARG activity is lost, the polymers are still present and HR-mediated repair is still functional. This residual HR activity can counteract the effect of the PARPi and lead to resistance (Gogola, Duarte et al. 2018).

Together, these studies describe mechanisms of resistance associated with re-activation of HR activity and provide evidence describing how activity of multiple repair pathways can contribute to resistance to DNA repair targeted therapies.

4 Alternative DNA repair targeting therapies for use in colorectal cancer

The most common chemotherapy agents used for the treatment of CRC induce DNA damage that is recognized and repaired by DNA repair pathways. Inherent defects in these pathways make CRC cells more sensitive to these treatments, and for tumors that do not harbor mutations in DNA repair associated genes, these pathways can be targeted to induce a repair defective phenotype. The therapies described in the previous section either target or exploit characteristics of DNA repair-deficient CRC cells. However, there are still other alternative therapies that target DNA repair mechanisms that have not been studied in the context of CRC (Gavande, VanderVere-Carozza et al. 2016). In this section, we will describe

alternative, and potentially novel, treatment regimens that can either take advantage of repair defects in CRC cells or induce repair deficiency in CRC tumors and thus make those cells more responsive to current chemotherapy agents.

4.1 ATR inhibitors

Colorectal adenomas exhibit endogenous replication stress (Bartkova, Horejsi et al. 2005), a phenotype that can be exploited through therapies that target replication stress signaling proteins (Halazonetis, Gorgoulis et al. 2008). One target under investigation is the ataxia telangiectasia and Rad3 related (ATR) protein. ATR functions at the sites of replication forks and is essential for signaling repair proteins when a cell experiences stress due to DNA damage that blocks replication progression. ATR directly interacts with RPA that coats single strand DNA generated during replication, and this ability allows ATR to sense stalled replication forks and corresponding DNA damage (Zou and Elledge 2003). Additionally, ATR functions in conjunction with ATM in response to IR and is required for promoting accurate repair of DNA DSB damage (Marechal and Zou 2013). Defects in replication fork protection are correlated with sensitivity to ATR inhibitiors (ATRi), and patients who do not exhibit defects in HR but have unstable replication forks may benefit from ATRi therapies (Hill, Decker et al. 2018). Furthermore, ATRi is also a viable option to target BRCA-deficient cancer cells that have acquired resistance to PARPi, by inhibiting the "rewired" HR pathway that is promotes resistance to PARP inhibition (Yazinski, Comaills et al. 2017, Haynes, Murai et al. 2018). For these reasons, ATR is an attractive target to disrupt DNA repair in cancer cells.

Early investigations into ATRi were performed in breast and ovarian cancer cells. Several studies have identified a synthetic lethality with ATRi and ATM- or p53-deficiency (Reaper, Griffiths et al. 2011, Toledo, Murga et al. 2011), and this effect is further increased when cells are also treated with genotoxic agents (Reaper, Griffiths et al. 2011, Shi, Shen et al. 2018). One study reported that the ATRi NU6027 sensitized cells to cisplatin in wild-type p53 and functional MMR expressing cells, while mutant p53 cells with functional MMR were

most sensitive to temozolomide in combination with NU6027 (Peasland, Wang et al. 2011). In addition, ATR inhibition was synthetic lethal in combination with PARPi or in cells that had defective HR (through loss of XRCC1) (Peasland, Wang et al. 2011, Sultana, Abdel-Fatah et al. 2013). Interestingly, one study reported that inhibition of ATR in BRCA1-depleted cells further sensitized the cells to damage induced by cisplatin and veliparib, suggesting that ATR inhibition functions independently of BRCA status (Huntoon, Flatten et al. 2013). More recent studies have shown that pancreatic ductal adenocarcinoma (PDAC) and various gastrointestinal cancer cells that exhibit loss of ATM were more sensitive to ATRi (Min, Im et al. 2017, Perkhofer, Schmitt et al. 2017). One study demonstrated that the ATR inhibitor AZD6738 induces a synthetic lethal phenotype in ATM-deficient, but not ATM-proficient, gastric cancer cells, and *in vivo* tumor growth of ATM-deficient gastric cell xenografts was effectively controlled by treatment with AZD6738 compared with control (Min, Im et al. 2017).

Recently, DNA DSB repair has been implicated in regulating the expression of PD-L1 in cancer cells (Sato, Niimi et al. 2017), and the effect of ATR inhibition on PD-L1 expression, and consequently on immune surveillance of tumor cells, has been investigated (Sun, Yang et al. 2018, Vendetti, Karukonda et al. 2018). A siRNA-mediated screen of DSB repair genes found that loss of BRCA2 enhanced expression of PD-L1, specifically in response to DSBs induced by IR or PARPi. Furthermore, loss of genes associated with the error-prone NHEJ pathway, such as Ku80, substantially enhanced PD-L1 expression in response to IR (Sato, Niimi et al. 2017). It was observed that treatment with IR and cisplatin significantly increased expression of PD-L1, and that this effect was abrogated when cells were also treated with pharmacological inhibitors of ATR. Additionally, decreased PD-L1 expression in the presence of ATRi led to increased immune surveillance of tumor cells, and controlled tumor growth. These data suggest that ATRi would be effective in MMRp cells that have increased PD-L1 expression as a mechanism of overcoming immune evasion and re-activating the immunogenicity of these tumor cells (Sun, Yang et al. 2018).

Together, these data suggest that ATR inhibition is most effective when combined with genotoxic agents and support the hypothesis that DNA repair defective CRC cells may also experience synthetic lethality when treated with ATRi. It would be interesting to test ATRi in MMRd preclinical models of mCRCs that are able to evade immune surveillance despite high levels of neoantigens.

4.2 CHK1 Inhibitors

Another key player in the DNA damage response signaling cascade is checkpoint kinase 1 (CHK1) that directly interacts with ATR in the presence of replication stress during S phase and promotes replication fork stabilization (Chen and Poon 2008). Following the same principle as ATRi, inhibitors targeting CHK1 (CHK1i) have been developed to inhibit replication stress signaling in cancer cells that already exhibit DNA repair defects.

Prexasertib is one CHK1i that has been thoroughly investigated in patients with squamous cell carcinomas (Hong, Moore et al. 2018), non-small cell lung carcinomas (Sen, Tong et al. 2017), and high grade serous ovarian carcinomas (Brill, Yokoyama et al. 2017, Lee, Nair et al. 2018), often in combination with other therapies. Early studies demonstrated that prexasertib (LY2606368) induced replication catastrophe and DNA damage while concomitantly disabling cell cycle checkpoints, ultimately leading to apoptosis. This effect was observed *in vitro* and *in vivo* in models of acute lymphoblastic leukemia and squamous cell carcinoma (King, Diaz et al. 2015, Ghelli Luserna Di Rora, Iacobucci et al. 2016).

In the context of CRC, one study investigated the effect of CHK1 inhibition on CRC stem cells (Manic, Signore et al. 2018). The authors observed that treatment with prexasertib, both *in vitro* and *in vivo*, inhibited replication and disabled cell cycle checkpoints, causing the cells to enter mitosis prematurely, ultimately leading to apoptosis. Interestingly, this effect was observed in cells that harbored *KRAS* mutations, a subset of CRCs particularly difficult to target and treat (Manic, Signore et al. 2018). An independent study also observed efficacy of CHK1 inhibition in *KRAS* mutated lung and colon adenocarcinoma cells, especially when combined with MK2 inhibitors (Dietlein, Kalb et al. 2015). MK2

functions in a pathway parallel to CHK1 and is responsible for maintaining cell cycle checkpoints in response to stress (Reinhardt, Hasskamp et al. 2010). *KRAS* mutated cells exhibit intrinsic genotoxic stress that leads to constant activation of CHK1 and MK2, and inhibition of these proteins induced mitotic catastrophe *in vitro*, in murine cancer models, and in patient derived cells (Dietlein, Kalb et al. 2015). CHK1 inhibitors might be tested in *KRAS*-mutated CRC, a subset that currently has limited therapy options.

4.3 Thiopurines

Thiopurines are a class of nucleotide analogs that have been used successfully for the treatment of childhood leukemias (Karran 2006). Thiopurines are incorporated into DNA during replication, leading to DNA base pair mismatches that are removed by MMR proteins (Coulthard and Hogarth 2005, Karran 2006, Munshi, Lubin et al. 2014). The effect of the thiopurine analog 6-thioguanine (6TG) on cell growth has been tested in CRC cell models. MMRd CRC cell lines are resistant to 6TG compared with MMRp counterparts (Carethers, Hawn et al. 1996, Yan, Berry et al. 2003). 6TG induces reactive oxygen species (Brem and Karran 2012) can trigger activity of BER proteins, suggesting that BER-deficient cells may have increased cellular sensitivity to thiopurines. Further studies have also demonstrated that HR and FA proteins function to repair thiopurine induced damage (Brem and Karran 2012), and that cells deficient for HR proteins, such as RAD51D, have increased sensitivity to thiopurines (Rajesh, Litvinchuk et al. 2011). These data suggest that this class of compounds might be effective in CRC tumors that are MMRp but carry mutations in genes associated with HR and BER.

5 Clinical trials of DNA repair inhibitors in colorectal cancer

Targeting DNA repair in CRC has the potential to further increase the efficacy of current therapies, and, as described above, there have been multiple pre-clinical studies investigating DNA repair targeting therapies in CRC. None of these therapies have been approved by the FDA for use in CRC patients; however, several trials are on-going (Table 2).

To date, six clinical trials investigating the efficacy of PARPi in CRC are on-going or have been completed. Of the five completed trials, only NCT00912743 has reported results (Leichman, Groshen et al. 2016). In this study, the efficacy of olaparib was investigated in 33 CRC patients stratified by microsatellite status. Thirteen MSI-H and 20 non-MSI-H patients were enrolled and treated with olaparib 400mg twice a day. The median of progression free survival (PFS) was 61 days for the MSI-H cohort and 55 for the non-MSI-H cohort. Overall survival (OS) was reported to be 248 days for the MSI-H cohort and 209.5 days for the non-MSI-H. There was no statistical significance in the median PFS or OS for non-MSI-H cohort. The results of this study suggest that olaparib alone is ineffective in CRC patients regardless of microsatellite status, and the authors recommend that further studies investigate the use of olaparib in combination with DNA damaging agents for this patient cohort (Leichman, Groshen et al. 2016). Importantly, this study was conducted in CRC patients that were not enriched for HR deficiency status.

Multiple clinical trials investigating the efficacy of the ATRi AZD6738 have been initiated, and most of these include gastrointestinal malignancies other than CRC. NCT01955668 is the only trial that has been completed thus far, and the results of this study have not been reported in full. Currently, the majority of clinical trials for AZD6738 focus on assessing the efficacy and safety of the drug in patients. As yet, there have not been any trials initiated to further elucidate sensitivity of specific cancer subtypes, such as *ATM-deficient* tumors, in the clinical setting. In addition to analyzing the efficacy of AZD6738 alone, several studies are investigating the efficacy of this drug in combination with the PARPi olaparib, particularly in patients who were refractory to primary therapies. Once completed, these studies have the potential to describe novel therapy regimens can be used to treat CRC patients.

Multiple clinical trials with CHK1 inhibitors are on-going. One trial (NCT02203513) has reported results from a cohort of *BRCA* wild-type high grade serous ovarian cancer patients treated with the CHK1 inhibitor prexasertib (Lee, Nair et al. 2018). In this cohort, 80% of the patients were platinum-resistant or refractory at the start of the trial. Sixteen

patients (out of 28) exhibited partial response during the treatment time and one patient died during the study due to tumor progression (Lee, Nair et al. 2018). Pre-clinical data that led to another ongoing trial (NCT02555644) investigated the efficacy of CHK1 inhibitors in combination with EGFR targeted therapies and/or radiotherapy (Zeng, Beggs et al. 2017). In this study, prexasertib combined with EGFR targeting therapies significantly decreased cell proliferation and delayed tumor growth in both HPV-positive and –negative head and neck squamous cell carcinoma mouse models (Zeng, Beggs et al. 2017). These promising results provided rationale to test CHK1 inhibitors in combination with both genotoxic and non-genotoxic therapy regimens for cancer treatment.

6 Concluding remarks

Standard clinical testing of CRC includes identifying mutations in oncogenes such as *KRAS* and *BRAF*, as well as characterization of the microsatellite status. Currently, the status of DNA repair genes is not investigated in CRCs. However, MSS CRCs carry a higher proportion of mutations in HR genes, and defects in this pathway have been associated with genomic instability. Whole-genome sequencing analysis of breast cancer samples can identify tumors that exhibit genomic rearrangements due to functional deficiencies in homologous recombination even *BRCA* wild-type cells, and these characteristics can be used to predict therapy response to PARP inhibitors. We propose that, in addition to genetic screening for mutations in known DNA repair genes, identification of gene alterations and genomic rearrangements indicative of a repair-defective phenotype should be performed systematically in CRC patients. Characterizations based on functional repair deficiency, rather than analyses based primarily on genetic alterations, are likely to better predict therapy response to inhibitors of DNA repair pathways in CRC patient cohorts.

Acknowledgements

Author contributions

N.M.R. wrote the manuscript. L.N. performed bioinformatics analysis of The Cancer Genome Atlas datasets. F.D.N. and A.B. contributed to manuscript preparation.

Conflicts of interest

The authors declare no conflicts of interest.

References:

Aguilera, A. and B. Gomez-Gonzalez (2008). "Genome instability: a mechanistic view of its causes and consequences." Nat Rev Genet **9**(3): 204-217.

AlDubayan, S. H., M. Giannakis, N. D. Moore, G. C. Han, B. Reardon, T. Hamada, X. J. Mu, R. Nishihara, Z. Qian, L. Liu, M. B. Yurgelun, S. Syngal, L. A. Garraway, S. Ogino, C. S. Fuchs and E. M. Van Allen (2018). "Inherited DNA-Repair Defects in Colorectal Cancer." Am J Hum Genet **102**(3): 401-414.

Badie, S., J. M. Escandell, P. Bouwman, A. R. Carlos, M. Thanasoula, M. M. Gallardo, A. Suram, I. Jaco, J. Benitez, U. Herbig, M. A. Blasco, J. Jonkers and M. Tarsounas (2010). "BRCA2 acts as a RAD51 loader to facilitate telomere replication and capping." Nat Struct Mol Biol **17**(12): 1461-1469.

Bakr, A., S. Kocher, J. Volquardsen, R. Reimer, K. Borgmann, E. Dikomey, K. Rothkamm and W. Y. Mansour (2016). "Functional crosstalk between DNA damage response proteins 53BP1 and BRCA1 regulates double strand break repair choice." Radiother Oncol **119**(2): 276-281.

Balc'h, E. L., N. Grandin, M. V. Demattei, S. Guyetant, A. Tallet, J. C. Pages, M. Ouaissi, T. Lecomte and M. Charbonneau (2017). "Measurement of Telomere Length in Colorectal Cancers for Improved Molecular Diagnosis." Int J Mol Sci **18**(9).

Bartkova, J., Z. Horejsi, K. Koed, A. Kramer, F. Tort, K. Zieger, P. Guldberg, M. Sehested, J. M. Nesland, C. Lukas, T. Orntoft, J. Lukas and J. Bartek (2005). "DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis." Nature **434**(7035): 864-870.

Berlin, J., R. K. Ramanathan, J. H. Strickler, D. S. Subramaniam, J. Marshall, Y. K. Kang, R. Hetman, M. W. Dudley, J. Zeng, C. Nickner, H. Xiong, P. Komarnitsky, S. P. Shepherd, H. Hurwitz and H. J. Lenz (2018). "A phase 1 dose-escalation study of veliparib with bimonthly FOLFIRI in patients with advanced solid tumours." Br J Cancer **118**(7): 938-946.

Boland, C. R., S. N. Thibodeau, S. R. Hamilton, D. Sidransky, J. R. Eshleman, R. W. Burt, S. J. Meltzer, M. A. Rodriguez-Bigas, R. Fodde, G. N. Ranzani and S. Srivastava (1998). "A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer." Cancer Res **58**(22): 5248-5257.

Bouwman, P., A. Aly, J. M. Escandell, M. Pieterse, J. Bartkova, H. van der Gulden, S. Hiddingh, M. Thanasoula, A. Kulkarni, Q. Yang, B. G. Haffty, J. Tommiska, C. Blomqvist, R. Drapkin, D. J. Adams, H. Nevanlinna, J. Bartek, M. Tarsounas, S. Ganesan and J. Jonkers (2010). "53BP1 loss rescues BRCA1 deficiency and is associated with triple-negative and BRCA-mutated breast cancers." Nat Struct Mol Biol **17**(6): 688-695.

Bray, F., J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre and A. Jemal (2018). "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." CA Cancer J Clin **68**(6): 394-424.

Brem, R. and P. Karran (2012). "Oxidation-mediated DNA cross-linking contributes to the toxicity of 6-thioguanine in human cells." Cancer Res **72**(18): 4787-4795.

Brill, E., T. Yokoyama, J. Nair, M. Yu, Y. R. Ahn and J. M. Lee (2017). "Prexasertib, a cell cycle checkpoint kinases 1 and 2 inhibitor, increases in vitro toxicity of PARP inhibition by preventing Rad51 foci formation in BRCA wild type high-grade serous ovarian cancer." Oncotarget **8**(67): 111026-111040.

Bruno, P. M., Y. Liu, G. Y. Park, J. Murai, C. E. Koch, T. J. Eisen, J. R. Pritchard, Y. Pommier, S. J. Lippard and M. T. Hemann (2017). "A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress." Nat Med **23**(4): 461-471.

Burrell, R. A., S. E. McClelland, D. Endesfelder, P. Groth, M. C. Weller, N. Shaikh, E. Domingo, N. Kanu, S. M. Dewhurst, E. Gronroos, S. K. Chew, A. J. Rowan, A. Schenk, M. Sheffer, M. Howell, M. Kschischo, A. Behrens, T. Helleday, J. Bartek, I. P. Tomlinson and C. Swanton (2013). "Replication stress links structural and numerical cancer chromosomal instability." Nature **494**(7438): 492-496.

Candelli, A., J. T. Holthausen, M. Depken, I. Brouwer, M. A. Franker, M. Marchetti, I. Heller, S. Bernard, E. B. Garcin, M. Modesti, C. Wyman, G. J. Wuite and E. J. Peterman (2014). "Visualization

and quantification of nascent RAD51 filament formation at single-monomer resolution." Proc Natl Acad Sci U S A **111**(42): 15090-15095.

Carethers, J. M., M. T. Hawn, D. P. Chauhan, M. C. Luce, G. Marra, M. Koi and C. R. Boland (1996). "Competency in mismatch repair prohibits clonal expansion of cancer cells treated with N-methyl-N'-nitro-N-nitrosoguanidine." J Clin Invest **98**(1): 199-206.

Ceccaldi, R., P. Sarangi and A. D. D'Andrea (2016). "The Fanconi anaemia pathway: new players and new functions." Nat Rev Mol Cell Biol **17**(6): 337-349.

Cerami, E., J. Gao, U. Dogrusoz, B. E. Gross, S. O. Sumer, B. A. Aksoy, A. Jacobsen, C. J. Byrne, M. L. Heuer, E. Larsson, Y. Antipin, B. Reva, A. P. Goldberg, C. Sander and N. Schultz (2012). "The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data." Cancer Discov **2**(5): 401-404.

Chen, C., M. Aihemaiti, X. Zhang, H. Qu, Q. L. Sun, Q. S. He and W. B. Yu (2018). "Downregulation of histone demethylase JMJD1C inhibits colorectal cancer metastasis through targeting ATF2." Am J Cancer Res **8**(5): 852-865.

Chen, Y. and R. Y. Poon (2008). "The multiple checkpoint functions of CHK1 and CHK2 in maintenance of genome stability." Front Biosci **13**: 5016-5029.

Chien, J., H. Sicotte, J. B. Fan, S. Humphray, J. M. Cunningham, K. R. Kalli, A. L. Oberg, S. N. Hart, Y. Li, J. I. Davila, S. Baheti, C. Wang, S. Dietmann, E. J. Atkinson, Y. W. Asmann, D. A. Bell, T. Ota, Y. Tarabishy, R. Kuang, M. Bibikova, R. K. Cheetham, R. J. Grocock, E. M. Swisher, J. Peden, D. Bentley, J. P. Kocher, S. H. Kaufmann, L. C. Hartmann, V. Shridhar and E. L. Goode (2015). "TP53 mutations, tetraploidy and homologous recombination repair defects in early stage high-grade serous ovarian cancer." Nucleic Acids Res **43**(14): 6945-6958.

Ciccia, A. and S. J. Elledge (2010). "The DNA damage response: making it safe to play with knives." Mol Cell **40**(2): 179-204.

Clark, C. C., J. N. Weitzel and T. R. O'Connor (2012). "Enhancement of synthetic lethality via combinations of ABT-888, a PARP inhibitor, and carboplatin in vitro and in vivo using BRCA1 and BRCA2 isogenic models." Mol Cancer Ther **11**(9): 1948-1958.

Claussin, C. and M. Chang (2015). "The many facets of homologous recombination at telomeres." Microb Cell **2**(9): 308-321.

Clements, K. E., T. Thakar, C. M. Nicolae, X. Liang, H. G. Wang and G. L. Moldovan (2018). "Loss of E2F7 confers resistance to poly-ADP-ribose polymerase (PARP) inhibitors in BRCA2-deficient cells." Nucleic Acids Res **46**(17): 8898-8907.

Cortes-Ciriano, I., S. Lee, W. Y. Park, T. M. Kim and P. J. Park (2017). "A molecular portrait of microsatellite instability across multiple cancers." Nat Commun **8**: 15180.

Cortesi, L., A. Toss and I. Cucinotto (2018). "Parp Inhibitors for the Treatment of Ovarian Cancer." Curr Cancer Drug Targets.

Coulthard, S. and L. Hogarth (2005). "The thiopurines: an update." Invest New Drugs **23**(6): 523-532.

Cremolini, C., M. Schirripa, C. Antoniotti, R. Moretto, L. Salvatore, G. Masi, A. Falcone and F. Loupakis (2015). "First-line chemotherapy for mCRC-a review and evidence-based algorithm." Nat Rev Clin Oncol **12**(10): 607-619.

Czito, B. G., D. A. Deming, G. S. Jameson, M. F. Mulcahy, H. Vaghefi, M. W. Dudley, K. D. Holen, A. DeLuca, R. K. Mittapalli, W. Munasinghe, L. He, J. R. Zalcberg, S. Y. Ngan, P. Komarnitsky and M. Michael (2017). "Safety and tolerability of veliparib combined with capecitabine plus radiotherapy in patients with locally advanced rectal cancer: a phase 1b study." Lancet Gastroenterol Hepatol **2**(6): 418-426.

D'Andrea, A. D. (2018). "Mechanisms of PARP inhibitor sensitivity and resistance." DNA Repair (Amst).

Davidson, D., Y. Wang, R. Aloyz and L. Panasci (2013). "The PARP inhibitor ABT-888 synergizes irinotecan treatment of colon cancer cell lines." Invest New Drugs **31**(2): 461-468.

Davies, H., D. Glodzik, S. Morganella, L. R. Yates, J. Staaf, X. Zou, M. Ramakrishna, S. Martin, S. Boyault, A. M. Sieuwerts, P. T. Simpson, T. A. King, K. Raine, J. E. Eyfjord, G. Kong, A. Borg, E. Birney,

H. G. Stunnenberg, M. J. van de Vijver, A. L. Borresen-Dale, J. W. Martens, P. N. Span, S. R. Lakhani, A. Vincent-Salomon, C. Sotiriou, A. Tutt, A. M. Thompson, S. Van Laere, A. L. Richardson, A. Viari, P. J. Campbell, M. R. Stratton and S. Nik-Zainal (2017). "HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures." Nat Med **23**(4): 517-525.

Dietlein, F., B. Kalb, M. Jokic, E. M. Noll, A. Strong, L. Tharun, L. Ozretic, H. Kunstlinger, K. Kambartel, W. J. Randerath, C. Jungst, A. Schmitt, A. Torgovnick, A. Richters, D. Rauh, F. Siedek, T. Persigehl, C. Mauch, J. Bartkova, A. Bradley, M. R. Sprick, A. Trumpp, R. Rad, D. Saur, J. Bartek, J. Wolf, R. Buttner, R. K. Thomas and H. C. Reinhardt (2015). "A Synergistic Interaction between Chk1- and MK2 Inhibitors in KRAS-Mutant Cancer." Cell **162**(1): 146-159.

Dodson, G. E., O. Limbo, D. Nieto and P. Russell (2010). "Phosphorylation-regulated binding of Ctp1 to Nbs1 is critical for repair of DNA double-strand breaks." Cell Cycle **9**(8): 1516-1522.

Druliner, B. R., X. Ruan, H. Sicotte, D. O'Brien, H. Liu, J. A. Kocher and L. Boardman (2018). "Early genetic aberrations in patients with sporadic colorectal cancer." Mol Carcinog **57**(1): 114-124.

Dziadkowiec, K. N., E. Gasiorowska, E. Nowak-Markwitz and A. Jankowska (2016). "PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting." Prz Menopauzalny **15**(4): 215-219.

Esteller, M., R. Levine, S. B. Baylin, L. H. Ellenson and J. G. Herman (1998). "MLH1 promoter hypermethylation is associated with the microsatellite instability phenotype in sporadic endometrial carcinomas." Oncogene **17**(18): 2413-2417.

Fabrizio, D. A., T. J. George, Jr., R. F. Dunne, G. Frampton, J. Sun, K. Gowen, M. Kennedy, J. Greenbowe, A. B. Schrock, A. F. Hezel, J. S. Ross, P. J. Stephens, S. M. Ali, V. A. Miller, M. Fakih and S. J. Klempner (2018). "Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition." J Gastrointest Oncol **9**(4): 610-617.

Francia, G., S. K. Green, G. Bocci, S. Man, U. Ernmenegger, J. M. L. Ebos, A. Weinerman, Y. Shaked and R. S. Kerbel (2005). "Down-regulation of DNA mismatch repair proteins in human and murine tumor spheroids: implications for multicellular resistance to alkylating agents." Molecular Cancer Therapeutics **4**(10): 1484-1494.

Gao, J., B. A. Aksoy, U. Dogrusoz, G. Dresdner, B. Gross, S. O. Sumer, Y. Sun, A. Jacobsen, R. Sinha, E. Larsson, E. Cerami, C. Sander and N. Schultz (2013). "Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal." Sci Signal **6**(269): pl1.

Gavande, N. S., P. S. VanderVere-Carozza, H. D. Hinshaw, S. I. Jalal, C. R. Sears, K. S. Pawelczak and J. J. Turchi (2016). "DNA repair targeted therapy: The past or future of cancer treatment?" Pharmacol Ther **160**: 65-83.

Gaymes, T. J., A. M. Mohamedali, M. Patterson, N. Matto, A. Smith, A. Kulasekararaj, R. Chelliah, N. Curtin, F. Farzaneh, S. Shall and G. J. Mufti (2013). "Microsatellite instability induced mutations in DNA repair genes CtIP and MRE11 confer hypersensitivity to poly (ADP-ribose) polymerase inhibitors in myeloid malignancies." Haematologica **98**(9): 1397-1406.

Germano, G., N. Amirouchene-Angelozzi, G. Rospo and A. Bardelli (2018). "The Clinical Impact of the Genomic Landscape of Mismatch Repair-Deficient Cancers." Cancer Discov **8**(12): 1518-1528.

Germano, G., S. Lamba, G. Rospo, L. Barault, A. Magri, F. Maione, M. Russo, G. Crisafulli, A. Bartolini, G. Lerda, G. Siravegna, B. Mussolin, R. Frapolli, M. Montone, F. Morano, F. de Braud, N. Amirouchene-Angelozzi, S. Marsoni, M. D'Incalci, A. Orlandi, E. Giraudo, A. Sartore-Bianchi, S. Siena, F. Pietrantonio, F. Di Nicolantonio and A. Bardelli (2017). "Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth." Nature **552**(7683): 116-120.

Ghelli Luserna Di Rora, A., I. Iacobucci, E. Imbrogno, C. Papayannidis, E. Derenzini, A. Ferrari, V. Guadagnuolo, V. Robustelli, S. Parisi, C. Sartor, M. C. Abbenante, S. Paolini and G. Martinelli (2016). "Prexasertib, a Chk1/Chk2 inhibitor, increases the effectiveness of conventional therapy in B-/T- cell progenitor acute lymphoblastic leukemia." Oncotarget **7**(33): 53377-53391.

Ghezraoui, H., C. Oliveira, J. R. Becker, K. Bilham, D. Moralli, C. Anzilotti, R. Fischer, M. Deobagkar-Lele, M. Sanchiz-Calvo, E. Fueyo-Marcos, S. Bonham, B. M. Kessler, S. Rottenberg, R. J. Cornall, C. M.

Green and J. R. Chapman (2018). "53BP1 cooperation with the REV7-shieldin complex underpins DNA structure-specific NHEJ." Nature **560**(7716): 122-127.

Ghiringhelli, F., C. Richard, S. Chevrier, F. Vegran and R. Boidot (2016). "Efficiency of olaparib in colorectal cancer patients with an alteration of the homologous repair protein." World J Gastroenterol **22**(48): 10680-10686.

Gogola, E., A. A. Duarte, J. R. de Ruiter, W. W. Wiegant, J. A. Schmid, R. de Bruijn, D. I. James, S. Guerrero Llobet, D. J. Vis, S. Annunziato, B. van den Broek, M. Barazas, A. Kersbergen, M. van de Ven, M. Tarsounas, D. J. Ogilvie, M. van Vugt, L. F. A. Wessels, J. Bartkova, I. Gromova, M. Andujar-Sanchez, J. Bartek, M. Lopes, H. van Attikum, P. Borst, J. Jonkers and S. Rottenberg (2018). "Selective Loss of PARG Restores PARylation and Counteracts PARP Inhibitor-Mediated Synthetic Lethality." Cancer Cell **33**(6): 1078-1093.e1012.

Gorbunova, V., J. T. Beck, R. D. Hofheinz, P. Garcia-Alfonso, M. Nechaeva, A. Cubillo Gracian, L. Mangel, E. Elez Fernandez, D. A. Deming, R. K. Ramanathan, A. H. Torres, D. Sullivan, Y. Luo and J. D. Berlin (2018). "A phase 2 randomised study of veliparib plus FOLFIRI+/-bevacizumab versus placebo plus FOLFIRI+/-bevacizumab in metastatic colorectal cancer." Br J Cancer.

Hackett, J. A., D. M. Feldser and C. W. Greider (2001). "Telomere dysfunction increases mutation rate and genomic instability." Cell **106**(3): 275-286.

Haince, J. F., D. McDonald, A. Rodrigue, U. Dery, J. Y. Masson, M. J. Hendzel and G. G. Poirier (2008). "PARP1-dependent kinetics of recruitment of MRE11 and NBS1 proteins to multiple DNA damage sites." J Biol Chem **283**(2): 1197-1208.

Halazonetis, T. D., V. G. Gorgoulis and J. Bartek (2008). "An oncogene-induced DNA damage model for cancer development." Science **319**(5868): 1352-1355.

Hanahan, D. and R. A. Weinberg (2011). "Hallmarks of cancer: the next generation." Cell **144**(5): 646-674.

Hause, R. J., C. C. Pritchard, J. Shendure and S. J. Salipante (2016). "Classification and characterization of microsatellite instability across 18 cancer types." Nat Med **22**(11): 1342-1350.

Haynes, B., J. Murai and J. M. Lee (2018). "Restored replication fork stabilization, a mechanism of PARP inhibitor resistance, can be overcome by cell cycle checkpoint inhibition." Cancer Treat Rev **71**: 1-7.

Helleday, T., E. Petermann, C. Lundin, B. Hodgson and R. A. Sharma (2008). "DNA repair pathways as targets for cancer therapy." Nat Rev Cancer **8**(3): 193-204.

Hill, S. J., B. Decker, E. A. Roberts, N. S. Horowitz, M. G. Muto, M. J. Worley, C. M. Feltmate, M. R. Nucci, E. M. Swisher, H. Nguyen, C. Yang, R. Morizane, B. S. Kochupurakkal, K. T. Do, P. A. Konstantinopoulos, J. F. Liu, J. V. Bonventre, U. A. Matulonis, G. I. Shapiro, R. S. Berkowitz, C. P. Crum and A. D. D'Andrea (2018). "Prediction of DNA Repair Inhibitor Response in Short Term Patient-Derived Ovarian Cancer Organoids." Cancer Discov.

Hillman, R. T., G. B. Chisholm, K. H. Lu and P. A. Futreal (2018). "Genomic Rearrangement Signatures and Clinical Outcomes in High-Grade Serous Ovarian Cancer." J Natl Cancer Inst **110**(3).

Hoang, L. N. and B. C. Gilks (2018). "Hereditary Breast and Ovarian Cancer Syndrome: Moving Beyond BRCA1 and BRCA2." Adv Anat Pathol **25**(2): 85-95.

Hong, D. S., K. Moore, M. Patel, S. C. Grant, H. A. Burris, 3rd, W. N. William, Jr., S. Jones, F. Meric-Bernstam, J. Infante, L. Golden, W. Zhang, R. Martinez, S. Wijayawardana, R. Beckmann, A. B. Lin, C. Eng and J. Bendell (2018). "Evaluation of Prexasertib, a Checkpoint Kinase 1 Inhibitor, in a Phase Ib Study of Patients with Squamous Cell Carcinoma." Clin Cancer Res **24**(14): 3263-3272.

Huang, D., W. Sun, Y. Zhou, P. Li, F. Chen, H. Chen, D. Xia, E. Xu, M. Lai, Y. Wu and H. Zhang (2018). "Mutations of key driver genes in colorectal cancer progression and metastasis." Cancer Metastasis Rev **37**(1): 173-187.

Huehls, A. M., C. J. Huntoon, P. M. Joshi, C. A. Baehr, J. M. Wagner, X. Wang, M. Y. Lee and L. M. Karnitz (2016). "Genomically Incorporated 5-Fluorouracil that Escapes UNG-Initiated Base Excision Repair Blocks DNA Replication and Activates Homologous Recombination." Mol Pharmacol **89**(1): 53-62.

Huen, M. S., S. M. Sy and J. Chen (2010). "BRCA1 and its toolbox for the maintenance of genome integrity." Nat Rev Mol Cell Biol **11**(2): 138-148.

Huntoon, C. J., K. S. Flatten, A. E. Wahner Hendrickson, A. M. Huehls, S. L. Sutor, S. H. Kaufmann and L. M. Karnitz (2013). "ATR inhibition broadly sensitizes ovarian cancer cells to chemotherapy independent of BRCA status." Cancer Res **73**(12): 3683-3691.

Iwaizumi, M., S. Tseng-Rogenski and J. M. Carethers (2011). "DNA mismatch repair proficiency executing 5-fluorouracil cytotoxicity in colorectal cancer cells." Cancer Biol Ther **12**(8): 756-764.

Iyer, R. R., A. Pluciennik, V. Burdett and P. L. Modrich (2006). "DNA mismatch repair: functions and mechanisms." Chem Rev **106**(2): 302-323.

Jackson, S. P. and J. Bartek (2009). "The DNA-damage response in human biology and disease." Nature **461**(7267): 1071-1078.

Janssen, A., M. van der Burg, K. Szuhai, G. J. Kops and R. H. Medema (2011). "Chromosome segregation errors as a cause of DNA damage and structural chromosome aberrations." Science **333**(6051): 1895-1898.

Jaspers, J. E., A. Kersbergen, U. Boon, W. Sol, L. van Deemter, S. A. Zander, R. Drost, E. Wientjens, J. Ji, A. Aly, J. H. Doroshow, A. Cranston, N. M. Martin, A. Lau, M. J. O'Connor, S. Ganesan, P. Borst, J. Jonkers and S. Rottenberg (2013). "Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors." Cancer Discov **3**(1): 68-81.

Jemal, A., E. M. Ward, C. J. Johnson, K. A. Cronin, J. Ma, B. Ryerson, A. Mariotto, A. J. Lake, R. Wilson, R. L. Sherman, R. N. Anderson, S. J. Henley, B. A. Kohler, L. Penberthy, E. J. Feuer and H. K. Weir (2017). "Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival." J Natl Cancer Inst **109**(9).

Jensen, R. B., A. Ozes, T. Kim, A. Estep and S. C. Kowalczykowski (2013). "BRCA2 is epistatic to the RAD51 paralogs in response to DNA damage." DNA Repair (Amst) **12**(4): 306-311.

Kalimutho, M., A. L. Bain, B. Mukherjee, P. Nag, D. M. Nanayakkara, S. K. Harten, J. L. Harris, G. N. Subramanian, D. Sinha, S. Shirasawa, S. Srihari, S. Burma and K. K. Khanna (2017). "Enhanced dependency of KRAS-mutant colorectal cancer cells on RAD51-dependent homologous recombination repair identified from genetic interactions in Saccharomyces cerevisiae." Mol Oncol **11**(5): 470-490.

Karran, P. (2006). "Thiopurines, DNA damage, DNA repair and therapy-related cancer." Br Med Bull **79-80**: 153-170.

Kim, G., G. Ison, A. E. McKee, H. Zhang, S. Tang, T. Gwise, R. Sridhara, E. Lee, A. Tzou, R. Philip, H. J. Chiu, T. K. Ricks, T. Palmby, A. M. Russell, G. Ladouceur, E. Pfuma, H. Li, L. Zhao, Q. Liu, R. Venugopal, A. Ibrahim and R. Pazdur (2015). "FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy." Clin Cancer Res **21**(19): 4257-4261.

Kim, J. H., H. E. Park, N. Y. Cho, H. S. Lee and G. H. Kang (2016). "Characterisation of PD-L1-positive subsets of microsatellite-unstable colorectal cancers." Br J Cancer **115**(4): 490-496.

King, C., H. B. Diaz, S. McNeely, D. Barnard, J. Dempsey, W. Blosser, R. Beckmann, D. Barda and M. S. Marshall (2015). "LY2606368 Causes Replication Catastrophe and Antitumor Effects through CHK1-Dependent Mechanisms." Mol Cancer Ther **14**(9): 2004-2013.

Knijnenburg, T. A., L. Wang, M. T. Zimmermann, N. Chambwe, G. F. Gao, A. D. Cherniack, H. Fan, H. Shen, G. P. Way, C. S. Greene, Y. Liu, R. Akbani, B. Feng, L. A. Donehower, C. Miller, Y. Shen, M. Karimi, H. Chen, P. Kim, P. Jia, E. Shinbrot, S. Zhang, J. Liu, H. Hu, M. H. Bailey, C. Yau, D. Wolf, Z. Zhao, J. N. Weinstein, L. Li, L. Ding, G. B. Mills, P. W. Laird, D. A. Wheeler, I. Shmulevich, S. J. Caesar-Johnson, J. A. Demchok, I. Felau, M. Kasapi, M. L. Ferguson, C. M. Hutter, H. J. Sofia, R. Tarnuzzer, Z. Wang, L. Yang, J. C. Zenklusen, J. Zhang, S. Chudamani, J. Liu, L. Lolla, R. Naresh, T. Pihl, Q. Sun, Y. Wan, Y. Wu, J. Cho, T. DeFreitas, S. Frazer, N. Gehlenborg, G. Getz, D. I. Heiman, J. Kim, M. S. Lawrence, P. Lin, S. Meier, M. S. Noble, G. Saksena, D. Voet, H. Zhang, B. Bernard, V. Dhankani, T. Knijnenburg, R. Kramer, K. Leinonen, M. Miller, S. Reynolds, V. Thorsson, W. Zhang, B. M. Broom, A. M. Hegde, Z. Ju, R. S. Kanchi, A. Korkut, J. Li, H. Liang, S. Ling, W. Liu, Y. Lu, K.-S. Ng, A. Rao, M. Ryan,

J. Wang, J. Zhang, A. Abeshouse, J. Armenia, D. Chakravarty, W. K. Chatila, I. de Bruijn, J. Gao, B. E. Gross, Z. J. Heins, R. Kundra, K. La, M. Ladanyi, A. Luna, M. G. Nissan, A. Ochoa, S. M. Phillips, E. Reznik, F. Sanchez-Vega, C. Sander, N. Schultz, R. Sheridan, S. O. Sumer, Y. Sun, B. S. Taylor, J. Wang, H. Zhang, P. Anur, M. Peto, P. Spellman, C. Benz, J. M. Stuart, C. K. Wong, D. N. Hayes, J. S. Parker, M. D. Wilkerson, A. Ally, M. Balasundaram, R. Bowlby, D. Brooks, R. Carlsen, E. Chuah, N. Dhalla, R. Holt, S. J. M. Jones, K. Kasaian, D. Lee, Y. Ma, M. A. Marra, M. Mayo, R. A. Moore, A. J. Mungall, K. Mungall, A. G. Robertson, S. Sadeghi, J. E. Schein, P. Sipahimalani, A. Tam, N. Thiessen, K. Tse, T. Wong, A. C. Berger, R. Beroukhim, C. Cibulskis, S. B. Gabriel, G. Ha, M. Meyerson, S. E. Schumacher, J. Shih, M. H. Kucherlapati, R. S. Kucherlapati, S. Baylin, L. Cope, L. Danilova, M. S. Bootwalla, P. H. Lai, D. T. Maglinte, D. J. Van Den Berg, D. J. Weisenberger, J. T. Auman, S. Balu, T. Bodenheimer, C. Fan, K. A. Hoadley, A. P. Hoyle, S. R. Jefferys, C. D. Jones, S. Meng, P. A. Mieczkowski, L. E. Mose, A. H. Perou, C. M. Perou, J. Roach, Y. Shi, J. V. Simons, T. Skelly, M. G. Soloway, D. Tan, U. Veluvolu, T. Hinoue, W. Zhou, M. Bellair, K. Chang, K. Covington, C. J. Creighton, H. Dinh, H. Doddapaneni, J. Drummond, R. A. Gibbs, R. Glenn, W. Hale, Y. Han, J. Hu, V. Korchina, S. Lee, L. Lewis, W. Li, X. Liu, M. Morgan, D. Morton, D. Muzny, J. Santibanez, M. Sheth, M. Wang, L. Xi, F. Zhao, J. Hess, E. L. Appelbaum, M. Bailey, M. G. Cordes, C. C. Fronick, L. A. Fulton, R. S. Fulton, C. Kandoth, E. R. Mardis, M. D. McLellan, C. A. Miller, H. K. Schmidt, R. K. Wilson, D. Crain, E. Curley, J. Gardner, K. Lau, D. Mallery, S. Morris, J. Paulauskis, R. Penny, C. Shelton, T. Shelton, M. Sherman, E. Thompson, P. Yena, J. Bowen, J. M. Gastier-Foster, M. Gerken, K. M. Leraas, T. M. Lichtenberg, N. C. Ramirez, L. Wise, E. Zmuda, N. Corcoran, T. Costello, C. Hovens, A. L. Carvalho, A. C. de Carvalho, J. H. Fregnani, A. Longatto-Filho, R. M. Reis, C. Scapulatempo-Neto, H. C. S. Silveira, D. O. Vidal, A. Burnette, J. Eschbacher, B. Hermes, A. Noss, R. Singh, M. L. Anderson, P. D. Castro, M. Ittmann, D. Huntsman, B. Kohl, X. Le, R. Thorp, C. Andry, E. R. Duffy, V. Lyadov, O. Paklina, G. Setdikova, A. Shabunin, M. Tavobilov, C. McPherson, R. Warnick, R. Berkowitz, D. Cramer, C. Feltmate, N. Horowitz, A. Kibel, M. Muto, C. P. Raut, A. Malykh, J. S. Barnholtz-Sloan, W. Barrett, K. Devine, J. Fulop, Q. T. Ostrom, K. Shimmel, Y. Wolinsky, A. E. Sloan, A. De Rose, F. Giuliante, M. Goodman, B. Y. Karlan, C. H. Hagedorn, J. Eckman, J. Harr, J. Myers, K. Tucker, L. A. Zach, B. Deyarmin, L. Kvecher, C. Larson, R. J. Mural, S. Somiari, A. Vicha, T. Zelinka, J. Bennett, M. Iacocca, B. Rabeno, P. Swanson, M. Latour, L. Lacombe, B. Têtu, A. Bergeron, M. McGraw, S. M. Staugaitis, J. Chabot, H. Hibshoosh, A. Sepulveda, T. Su, T. Wang, O. Potapova, O. Voronina, L. Desjardins, O. Mariani, S. Roman-Roman, X. Sastre, M.-H. Stern, F. Cheng, S. Signoretti, A. Berchuck, D. Bigner, E. Lipp, J. Marks, S. McCall, R. McLendon, A. Secord, A. Sharp, M. Behera, D. J. Brat, A. Chen, K. Delman, S. Force, F. Khuri, K. Magliocca, S. Maithel, J. J. Olson, T. Owonikoko, A. Pickens, S. Ramalingam, D. M. Shin, G. Sica, E. G. Van Meir, H. Zhang, W. Eijckenboom, A. Gillis, E. Korpershoek, L. Looijenga, W. Oosterhuis, H. Stoop, K. E. van Kessel, E. C. Zwarthoff, C. Calatozzolo, L. Cuppini, S. Cuzzubbo, F. DiMeco, G. Finocchiaro, L. Mattei, A. Perin, B. Pollo, C. Chen, J. Houck, P. Lohavanichbutr, A. Hartmann, C. Stoehr, R. Stoehr, H. Taubert, S. Wach, B. Wullich, W. Kycler, D. Murawa, M. Wiznerowicz, K. Chung, W. J. Edenfield, J. Martin, E. Baudin, G. Bubley, R. Bueno, A. De Rienzo, W. G. Richards, S. Kalkanis, T. Mikkelsen, H. Noushmehr, L. Scarpace, N. Girard, M. Aymerich, E. Campo, E. Giné, A. L. Guillermo, N. Van Bang, P. T. Hanh, B. D. Phu, Y. Tang, H. Colman, K. Evason, P. R. Dottino, J. A. Martignetti, H. Gabra, H. Juhl, T. Akeredolu, S. Stepa, D. Hoon, K. Ahn, K. J. Kang, F. Beuschlein, A. Breggia, M. Birrer, D. Bell, M. Borad, A. H. Bryce, E. Castle, V. Chandan, J. Cheville, J. A. Copland, M. Farnell, T. Flotte, N. Giama, T. Ho, M. Kendrick, J.-P. Kocher, K. Kopp, C. Moser, D. Nagorney, D. O'Brien, B. P. O'Neill, T. Patel, G. Petersen, F. Que, M. Rivera, L. Roberts, R. Smallridge, T. Smyrk, M. Stanton, R. H. Thompson, M. Torbenson, J. D. Yang, L. Zhang, F. Brimo, J. A. Ajani, A. M. A. Gonzalez, C. Behrens, J. Bondaruk, R. Broaddus, B. Czerniak, B. Esmaeli, J. Fujimoto, J. Gershenwald, C. Guo, A. J. Lazar, C. Logothetis, F. Meric-Bernstam, C. Moran, L. Ramondetta, D. Rice, A. Sood, P. Tamboli, T. Thompson, P. Troncoso, A. Tsao, I. Wistuba, C. Carter, L. Haydu, P. Hersey, V. Jakrot, H. Kakavand, R. Kefford, K. Lee, G. Long, G. Mann, M. Quinn, R. Saw, R. Scolyer, K. Shannon, A. Spillane, J. Stretch, M. Synott, J. Thompson, J. Wilmott, H. Al-Ahmadie, T. A. Chan, R. Ghossein, A. Gopalan, D. A. Levine, V. Reuter, S. Singer, B. Singh, N. V. Tien, T. Broudy, C. Mirsaidi, P. Nair, P. Drwiega, J. Miller, J. Smith, H. Zaren, J.-W. Park, N. P. Hung, E. Kebebew, W. M.

Linehan, A. R. Metwalli, K. Pacak, P. A. Pinto, M. Schiffman, L. S. Schmidt, C. D. Vocke, N. Wentzensen, R. Worrell, H. Yang, M. Moncrieff, C. Goparaju, J. Melamed, H. Pass, N. Botnariuc, I. Caraman, M. Cernat, I. Chemencedji, A. Clipca, S. Doruc, G. Gorincioi, S. Mura, M. Pirtac, I. Stancul, D. Tcaciuc, M. Albert, I. Alexopoulou, A. Arnaout, J. Bartlett, J. Engel, S. Gilbert, J. Parfitt, H. Sekhon, G. Thomas, D. M. Rassl, R. C. Rintoul, C. Bifulco, R. Tamakawa, W. Urba, N. Hayward, H. Timmers, A. Antenucci, F. Facciolo, G. Grazi, M. Marino, R. Merola, R. de Krijger, A.-P. Gimenez-Roqueplo, A. Piché, S. Chevalier, G. McKercher, K. Birsoy, G. Barnett, C. Brewer, C. Farver, T. Naska, N. A. Pennell, D. Raymond, C. Schilero, K. Smolenski, F. Williams, C. Morrison, J. A. Borgia, M. J. Liptay, M. Pool, C. W. Seder, K. Junker, L. Omberg, M. Dinkin, G. Manikhas, D. Alvaro, M. C. Bragazzi, V. Cardinale, G. Carpino, E. Gaudio, D. Chesla, S. Cottingham, M. Dubina, F. Moiseenko, R. Dhanasekaran, K.-F. Becker, K.-P. Janssen, J. Slotta-Huspenina, M. H. Abdel-Rahman, D. Aziz, S. Bell, C. M. Cebulla, A. Davis, R. Duell, J. B. Elder, J. Hilty, B. Kumar, J. Lang, N. L. Lehman, R. Mandt, P. Nguyen, R. Pilarski, K. Rai, L. Schoenfield, K. Senecal, P. Wakely, P. Hansen, R. Lechan, J. Powers, A. Tischler, W. E. Grizzle, K. C. Sexton, A. Kastl, J. Henderson, S. Porten, J. Waldmann, M. Fassnacht, S. L. Asa, D. Schadendorf, M. Couce, M. Graefen, H. Huland, G. Sauter, T. Schlomm, R. Simon, P. Tennstedt, O. Olabode, M. Nelson, O. Bathe, P. R. Carroll, J. M. Chan, P. Disaia, P. Glenn, R. K. Kelley, C. N. Landen, J. Phillips, M. Prados, J. Simko, K. Smith-McCune, S. VandenBerg, K. Roggin, A. Fehrenbach, A. Kendler, S. Sifri, R. Steele, A. Jimeno, F. Carey, I. Forgie, M. Mannelli, M. Carney, B. Hernandez, B. Campos, C. Herold-Mende, C. Jungk, A. Unterberg, A. von Deimling, A. Bossler, J. Galbraith, L. Jacobus, M. Knudson, T. Knutson, D. Ma, M. Milhem, R. Sigmund, A. K. Godwin, R. Madan, H. G. Rosenthal, C. Adebamowo, S. N. Adebamowo, A. Boussioutas, D. Beer, T. Giordano, A.-M. Mes-Masson, F. Saad, T. Bocklage, L. Landrum, R. Mannel, K. Moore, K. Moxley, R. Postier, J. Walker, R. Zuna, M. Feldman, F. Valdivieso, R. Dhir, J. Luketich, E. M. M. Pinero, M. Quintero-Aguilo, C. G. Carlotti, Jr., J. S. Dos Santos, R. Kemp, A. Sankarankuty, D. Tirapelli, J. Catto, K. Agnew, E. Swisher, J. Creaney, B. Robinson, C. S. Shelley, E. M. Godwin, S. Kendall, C. Shipman, C. Bradford, T. Carey, A. Haddad, J. Moyer, L. Peterson, M. Prince, L. Rozek, G. Wolf, R. Bowman, K. M. Fong, I. Yang, R. Korst, W. K. Rathmell, J. L. Fantacone-Campbell, J. A. Hooke, A. J. Kovatich, C. D. Shriver, J. DiPersio, B. Drake, R. Govindan, S. Heath, T. Ley, B. Van Tine, P. Westervelt, M. A. Rubin, J. I. Lee, N. D. Aredes, A. Mariamidze, R. J. Monnat, Jr., Y. Xiao and C. Wang "Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas." Cell Reports **23**(1): 239-254.e236.

Knijnenburg, T. A., L. Wang, M. T. Zimmermann, N. Chambwe, G. F. Gao, A. D. Cherniack, H. Fan, H. Shen, G. P. Way, C. S. Greene, Y. Liu, R. Akbani, B. Feng, L. A. Donehower, C. Miller, Y. Shen, M. Karimi, H. Chen, P. Kim, P. Jia, E. Shinbrot, S. Zhang, J. Liu, H. Hu, M. H. Bailey, C. Yau, D. Wolf, Z. Zhao, J. N. Weinstein, L. Li, L. Ding, G. B. Mills, P. W. Laird, D. A. Wheeler, I. Shmulevich, R. J. Monnat, Jr., Y. Xiao and C. Wang (2018). "Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas." Cell Rep **23**(1): 239-254.e236.

Kondrashova, O., M. Nguyen, K. Shield-Artin, A. V. Tinker, N. N. H. Teng, M. I. Harrell, M. J. Kuiper, G. Y. Ho, H. Barker, M. Jasin, R. Prakash, E. M. Kass, M. R. Sullivan, G. J. Brunette, K. A. Bernstein, R. L. Coleman, A. Floquet, M. Friedlander, G. Kichenadasse, D. M. O'Malley, A. Oza, J. Sun, L. Robillard, L. Maloney, D. Bowtell, H. Giordano, M. J. Wakefield, S. H. Kaufmann, A. D. Simmons, T. C. Harding, M. Raponi, I. A. McNeish, E. M. Swisher, K. K. Lin and C. L. Scott (2017). "Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma." Cancer Discov **7**(9): 984-998.

Kondrashova, O., M. Topp, K. Nesic, E. Lieschke, G. Y. Ho, M. I. Harrell, G. V. Zapparoli, A. Hadley, R. Holian, E. Boehm, V. Heong, E. Sanij, R. B. Pearson, J. J. Krais, N. Johnson, O. McNally, S. Ananda, K. Alsop, K. J. Hutt, S. H. Kaufmann, K. K. Lin, T. C. Harding, N. Traficante, A. deFazio, I. A. McNeish, D. D. Bowtell, E. M. Swisher, A. Dobrovic, M. J. Wakefield and C. L. Scott (2018). "Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma." Nat Commun **9**(1): 3970.

Kubota, E., C. T. Williamson, R. Ye, A. Elegbede, L. Peterson, S. P. Lees-Miller and D. G. Bebb (2014). "Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines." Cell Cycle **13**(13): 2129-2137.

Le, D. T., J. N. Durham, K. N. Smith, H. Wang, B. R. Bartlett, L. K. Aulakh, S. Lu, H. Kemberling, C. Wilt, B. S. Luber, F. Wong, N. S. Azad, A. A. Rucki, D. Laheru, R. Donehower, A. Zaheer, G. A. Fisher, T. S. Crocenzi, J. J. Lee, T. F. Greten, A. G. Duffy, K. K. Ciombor, A. D. Eyring, B. H. Lam, A. Joe, S. P. Kang, M. Holdhoff, L. Danilova, L. Cope, C. Meyer, S. Zhou, R. M. Goldberg, D. K. Armstrong, K. M. Bever, A. N. Fader, J. Taube, F. Housseau, D. Spetzler, N. Xiao, D. M. Pardoll, N. Papadopoulos, K. W. Kinzler, J. R. Eshleman, B. Vogelstein, R. A. Anders and L. A. Diaz, Jr. (2017). "Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade." Science **357**(6349): 409-413.

Le, S., J. K. Moore, J. E. Haber and C. W. Greider (1999). "RAD50 and RAD51 define two pathways that collaborate to maintain telomeres in the absence of telomerase." Genetics **152**(1): 143-152.

Lee, J. M., J. Nair, A. Zimmer, S. Lipkowitz, C. M. Annunziata, M. J. Merino, E. M. Swisher, M. I. Harrell, J. B. Trepel, M. J. Lee, M. H. Bagheri, D. A. Botesteanu, S. M. Steinberg, L. Minasian, I. Ekwede and E. C. Kohn (2018). "Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study." Lancet Oncol **19**(2): 207-215.

Lee, Y. S., M. T. Gregory and W. Yang (2014). "Human Pol zeta purified with accessory subunits is active in translesion DNA synthesis and complements Pol eta in cisplatin bypass." Proc Natl Acad Sci U S A **111**(8): 2954-2959.

Leichman, L., S. Groshen, B. H. O'Neil, W. Messersmith, J. Berlin, E. Chan, C. G. Leichman, S. J. Cohen, D. Cohen, H. J. Lenz, P. Gold, B. Boman, A. Fielding, G. Locker, R. C. Cason, S. R. Hamilton and H. S. Hochster (2016). "Phase II Study of Olaparib (AZD-2281) After Standard Systemic Therapies for Disseminated Colorectal Cancer." Oncologist **21**(2): 172-177.

Lemery, S., P. Keegan and R. Pazdur (2017). "First FDA Approval Agnostic of Cancer Site - When a Biomarker Defines the Indication." N Engl J Med **377**(15): 1409-1412.

Lenz, H. J., S. Stintzing and F. Loupakis (2015). "TAS-102, a novel antitumor agent: a review of the mechanism of action." Cancer Treat Rev **41**(9): 777-783.

Li, F., T. Jiang, Q. Li and X. Ling (2017). "Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer?" Am J Cancer Res **7**(12): 2350-2394.

Lin, Z. P., E. S. Ratner, M. E. Whicker, Y. Lee and A. C. Sartorelli (2014). "Triapine disrupts CtIP-mediated homologous recombination repair and sensitizes ovarian cancer cells to PARP and topoisomerase inhibitors." Mol Cancer Res **12**(3): 381-393.

Liu, J., T. Lichtenberg, K. A. Hoadley, L. M. Poisson, A. J. Lazar, A. D. Cherniack, A. J. Kovatich, C. C. Benz, D. A. Levine, A. V. Lee, L. Omberg, D. M. Wolf, C. D. Shriver, V. Thorsson and H. Hu (2018). "An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics." Cell **173**(2): 400-416.e411.

Llosa, N. J., M. Cruise, A. Tam, E. C. Wicks, E. M. Hechenbleikner, J. M. Taube, R. L. Blosser, H. Fan, H. Wang, B. S. Luber, M. Zhang, N. Papadopoulos, K. W. Kinzler, B. Vogelstein, C. L. Sears, R. A. Anders, D. M. Pardoll and F. Housseau (2015). "The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints." Cancer Discov **5**(1): 43-51.

Lorans, M., E. Dow, F. A. Macrae, I. M. Winship and D. D. Buchanan (2018). "Update on Hereditary Colorectal Cancer: Improving the Clinical Utility of Multigene Panel Testing." Clin Colorectal Cancer.

Lord, C. J. and A. Ashworth (2017). "PARP inhibitors: Synthetic lethality in the clinic." Science **355**(6330): 1152-1158.

Lu, R., J. Pal, L. Buon, P. Nanjappa, J. Shi, M. Fulciniti, Y. T. Tai, L. Guo, M. Yu, S. Gryaznov, N. C. Munshi and M. A. Shammas (2014). "Targeting homologous recombination and telomerase in Barrett's adenocarcinoma: impact on telomere maintenance, genomic instability and tumor growth." Oncogene **33**(12): 1495-1505.

Luksza, M., N. Riaz, V. Makarov, V. P. Balachandran, M. D. Hellmann, A. Solovyov, N. A. Rizvi, T. Merghoub, A. J. Levine, T. A. Chan, J. D. Wolchok and B. D. Greenbaum (2017). "A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy." Nature **551**(7681): 517-520.

Malvezzi, M., G. Carioli, P. Bertuccio, P. Boffetta, F. Levi, C. La Vecchia and E. Negri (2018). "European cancer mortality predictions for the year 2018 with focus on colorectal cancer." Ann Oncol.

Manic, G., M. Signore, A. Sistigu, G. Russo, F. Corradi, S. Siteni, M. Musella, S. Vitale, M. L. De Angelis, M. Pallocca, C. A. Amoreo, F. Sperati, S. Di Franco, S. Barresi, E. Policicchio, G. De Luca, F. De Nicola, M. Mottolese, A. Zeuner, M. Fanciulli, G. Stassi, M. Maugeri-Sacca, M. Baiocchi, M. Tartaglia, I. Vitale and R. De Maria (2018). "CHK1-targeted therapy to deplete DNA replication-stressed, p53-deficient, hyperdiploid colorectal cancer stem cells." Gut **67**(5): 903-917.

Marcus, L., S. J. Lemery, S. Khasar, E. Wearne, W. S. Helms, W. Yuan, K. He, X. Cao, J. Yu, H. Zhao, Y. Wang, O. Stephens, E. Englund, R. Agarwal, P. Keegan and R. Pazdur (2017). "FDA Approval Summary: TAS-102." Clin Cancer Res **23**(12): 2924-2927.

Marechal, A. and L. Zou (2013). "DNA damage sensing by the ATM and ATR kinases." Cold Spring Harb Perspect Biol **5**(9).

Marechal, A. and L. Zou (2015). "RPA-coated single-stranded DNA as a platform for post-translational modifications in the DNA damage response." Cell Res **25**(1): 9-23.

Maya-Mendoza, A., P. Moudry, J. M. Merchut-Maya, M. Lee, R. Strauss and J. Bartek (2018). "High speed of fork progression induces DNA replication stress and genomic instability." Nature **559**(7713): 279-284.

McCabe, N., N. C. Turner, C. J. Lord, K. Kluzek, A. Bialkowska, S. Swift, S. Giavara, M. J. O'Connor, A. N. Tutt, M. Z. Zdzienicka, G. C. Smith and A. Ashworth (2006). "Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition." Cancer Res **66**(16): 8109-8115.

McGranahan, N., A. J. Furness, R. Rosenthal, S. Ramskov, R. Lyngaa, S. K. Saini, M. Jamal-Hanjani, G. A. Wilson, N. J. Birkbak, C. T. Hiley, T. B. Watkins, S. Shafi, N. Murugaesu, R. Mitter, A. U. Akarca, J. Linares, T. Marafioti, J. Y. Henry, E. M. Van Allen, D. Miao, B. Schilling, D. Schadendorf, L. A. Garraway, V. Makarov, N. A. Rizvi, A. Snyder, M. D. Hellmann, T. Merghoub, J. D. Wolchok, S. A. Shukla, C. J. Wu, K. S. Peggs, T. A. Chan, S. R. Hadrup, S. A. Quezada and C. Swanton (2016). "Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade." Science **351**(6280): 1463-1469.

Min, A., S. A. Im, H. Jang, S. Kim, M. Lee, D. K. Kim, Y. Yang, H. J. Kim, K. H. Lee, J. W. Kim, T. Y. Kim, D. Y. Oh, J. Brown, A. Lau, M. J. O'Connor and Y. J. Bang (2017). "AZD6738, A Novel Oral Inhibitor of ATR, Induces Synthetic Lethality with ATM Deficiency in Gastric Cancer Cells." Mol Cancer Ther **16**(4): 566-577.

Mittica, G., E. Ghisoni, G. Giannone, S. Genta, M. Aglietta, A. Sapino and G. Valabrega (2018). "PARP Inhibitors in Ovarian Cancer." Recent Pat Anticancer Drug Discov.

Modrich, P. (2006). "Mechanisms in eukaryotic mismatch repair." J Biol Chem **281**(41): 30305-30309.

Munshi, P. N., M. Lubin and J. R. Bertino (2014). "6-thioguanine: a drug with unrealized potential for cancer therapy." Oncologist **19**(7): 760-765.

Nacson, J., J. J. Krais, A. J. Bernhardy, E. Clausen, W. Feng, Y. Wang, E. Nicolas, K. Q. Cai, R. Tricarico, X. Hua, D. DiMarcantonio, E. Martinez, D. Zong, E. A. Handorf, A. Bellacosa, J. R. Testa, A. Nussenzweig, G. P. Gupta, S. M. Sykes and N. Johnson (2018). "BRCA1 Mutation-Specific Responses to 53BP1 Loss-Induced Homologous Recombination and PARP Inhibitor Resistance." Cell Rep **24**(13): 3513-3527.e3517.

Nakayama, M. (2014). "Antigen Presentation by MHC-Dressed Cells." Front Immunol **5**: 672.

NCI. (2017). "Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2016)." Retrieved April 1, 2018, from www.seer.cancer.gov/popdata.

Network, C. G. A. (2012). "Comprehensive molecular characterization of human colon and rectal cancer." Nature **487**(7407): 330-337.

Niv, Y. (2007). "Microsatellite instability and MLH1 promoter hypermethylation in colorectal cancer." World J Gastroenterol **13**(12): 1767-1769.

Overman, M. J., S. Lonardi, K. Y. M. Wong, H. J. Lenz, F. Gelsomino, M. Aglietta, M. A. Morse, E. Van Cutsem, R. McDermott, A. Hill, M. B. Sawyer, A. Hendlisz, B. Neyns, M. Svrcek, R. A. Moss, J. M. Ledeine, Z. A. Cao, S. Kamble, S. Kopetz and T. Andre (2018). "Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer." J Clin Oncol **36**(8): 773-779.

Park, W. J., S. U. Bae, Y. R. Heo, S. J. Jung and J. H. Lee (2017). "Telomere shortening in non-tumorous and tumor mucosa is independently related to colorectal carcinogenesis in precancerous lesions." Int J Mol Epidemiol Genet **8**(5): 53-58.

Pearlman, R., W. L. Frankel, B. Swanson, W. Zhao, A. Yilmaz, K. Miller, J. Bacher, C. Bigley, L. Nelsen, P. J. Goodfellow, R. M. Goldberg, E. Paskett, P. G. Shields, J. L. Freudenheim, P. P. Stanich, I. Lattimer, M. Arnold, S. Liyanarachchi, M. Kalady, B. Heald, C. Greenwood, I. Paquette, M. Prues, D. J. Draper, C. Lindeman, J. P. Kuebler, K. Reynolds, J. M. Brell, A. A. Shaper, S. Mahesh, N. Buie, K. Weeman, K. Shine, M. Haut, J. Edwards, S. Bastola, K. Wickham, K. S. Khanduja, R. Zacks, C. C. Pritchard, B. H. Shirts, A. Jacobson, B. Allen, A. de la Chapelle and H. Hampel (2017). "Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer." JAMA Oncol **3**(4): 464-471.

Peasland, A., L. Z. Wang, E. Rowling, S. Kyle, T. Chen, A. Hopkins, W. A. Cliby, J. Sarkaria, G. Beale, R. J. Edmondson and N. J. Curtin (2011). "Identification and evaluation of a potent novel ATR inhibitor, NU6027, in breast and ovarian cancer cell lines." Br J Cancer **105**(3): 372-381.

Perkhofer, L., A. Schmitt, M. C. Romero Carrasco, M. Ihle, S. Hampp, D. A. Ruess, E. Hessmann, R. Russell, A. Lechel, N. Azoitei, Q. Lin, S. Liebau, M. Hohwieler, H. Bohnenberger, M. Lesina, H. Algul, L. Gieldon, E. Schrock, J. Gaedcke, M. Wagner, L. Wiesmuller, B. Sipos, T. Seufferlein, H. C. Reinhardt, P. O. Frappart and A. Kleger (2017). "ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage." Cancer Res **77**(20): 5576-5590.

Pishvaian, M. J., R. S. Slack, W. Jiang, A. R. He, J. J. Hwang, A. Hankin, K. Dorsch-Vogel, D. Kukadiya, L. M. Weiner, J. L. Marshall and J. R. Brody (2018). "A phase 2 study of the PARP inhibitor veliparib plus temozolomide in patients with heavily pretreated metastatic colorectal cancer." Cancer **124**(11): 2337-2346.

Pishvaian, M. J., R. S. Slack, W. Jiang, A. R. He, J. J. Hwang, A. Hankin, K. Dorsch-Vogel, D. Kukadiya, L. M. Weiner, J. L. Marshall and J. R. Brody (2018). "A phase 2 study of the PARP inhibitor veliparib plus temozolomide in patients with heavily pretreated metastatic colorectal cancer." Cancer.

Planck, M., K. Ericson, Z. Piotrowska, B. Halvarsson, E. Rambech and M. Nilbert (2003). "Microsatellite instability and expression of MLH1 and MSH2 in carcinomas of the small intestine." Cancer **97**(6): 1551-1557.

Popat, S., R. Hubner and R. S. Houlston (2005). "Systematic review of microsatellite instability and colorectal cancer prognosis." J Clin Oncol **23**(3): 609-618.

Qi, Z., S. Redding, J. Y. Lee, B. Gibb, Y. Kwon, H. Niu, W. A. Gaines, P. Sung and E. C. Greene (2015). "DNA sequence alignment by microhomology sampling during homologous recombination." Cell **160**(5): 856-869.

Quigley, D., J. J. Alumkal, A. W. Wyatt, V. Kothari, A. Foye, P. Lloyd, R. Aggarwal, W. Kim, E. Lu, J. Schwartzman, K. Beja, M. Annala, R. Das, M. Diolaiti, C. Pritchard, G. Thomas, S. Tomlins, K. Knudsen, C. J. Lord, C. Ryan, J. Youngren, T. M. Beer, A. Ashworth, E. J. Small and F. Y. Feng (2017). "Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors." Cancer Discov **7**(9): 999-1005.

Rajesh, P., A. V. Litvinchuk, D. L. Pittman and M. D. Wyatt (2011). "The homologous recombination protein RAD51D mediates the processing of 6-thioguanine lesions downstream of mismatch repair." Mol Cancer Res **9**(2): 206-214.

Ranjha, L., S. M. Howard and P. Cejka (2018). "Main steps in DNA double-strand break repair: an introduction to homologous recombination and related processes." Chromosoma.

Ray, B., B. Gupta and R. Mehrotra (2018). "Binding of Platinum Derivative, Oxaliplatin to Deoxyribonucleic Acid: Structural Insight into Antitumor Action." J Biomol Struct Dyn: 1-24.

Ray Chaudhuri, A., E. Callen, X. Ding, E. Gogola, A. A. Duarte, J. E. Lee, N. Wong, V. Lafarga, J. A. Calvo, N. J. Panzarino, S. John, A. Day, A. V. Crespo, B. Shen, L. M. Starnes, J. R. de Ruiter, J. A. Daniel, P. A. Konstantinopoulos, D. Cortez, S. B. Cantor, O. Fernandez-Capetillo, K. Ge, J. Jonkers, S. Rottenberg, S. K. Sharan and A. Nussenzweig (2016). "Replication fork stability confers chemoresistance in BRCA-deficient cells." Nature **535**(7612): 382-387.

Reaper, P. M., M. R. Griffiths, J. M. Long, J. D. Charrier, S. Maccormick, P. A. Charlton, J. M. Golec and J. R. Pollard (2011). "Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR." Nat Chem Biol **7**(7): 428-430.

Reinhardt, H. C., P. Hasskamp, I. Schmedding, S. Morandell, M. A. van Vugt, X. Wang, R. Linding, S. E. Ong, D. Weaver, S. A. Carr and M. B. Yaffe (2010). "DNA damage activates a spatially distinct late cytoplasmic cell-cycle checkpoint network controlled by MK2-mediated RNA stabilization." Mol Cell **40**(1): 34-49.

Rondinelli, B., E. Gogola, H. Yucel, A. A. Duarte, M. van de Ven, R. van der Sluijs, P. A. Konstantinopoulos, J. Jonkers, R. Ceccaldi, S. Rottenberg and A. D. D'Andrea (2017). "EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation." Nat Cell Biol **19**(11): 1371-1378.

Sarshekeh, A. M., M. J. Overman and S. Kopetz (2018). "Nivolumab in the treatment of microsatellite instability high metastatic colorectal cancer." Future Oncol **14**(18): 1869-1874.

Sato, H., A. Niimi, T. Yasuhara, T. B. M. Permata, Y. Hagiwara, M. Isono, E. Nuryadi, R. Sekine, T. Oike, S. Kakoti, Y. Yoshimoto, K. D. Held, Y. Suzuki, K. Kono, K. Miyagawa, T. Nakano and A. Shibata (2017). "DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells." Nat Commun **8**(1): 1751.

Scarpa, M., C. Ruffolo, F. Canal, S. Basato, F. Erroi, A. Fiorot, L. Dall'Agnese, A. Pozza, A. Porzionato, I. Castagliuolo, A. P. Dei Tos, N. Bassi and C. Castoro (2015). "Mismatch repair gene defects in sporadic colorectal cancer enhance immune surveillance." Oncotarget **6**(41): 43472-43482.

Schmitt, A., G. Knittel, D. Welcker, T. P. Yang, J. George, M. Nowak, U. Leeser, R. Buttner, S. Perner, M. Peifer and H. C. Reinhardt (2017). "ATM Deficiency Is Associated with Sensitivity to PARP1- and ATR Inhibitors in Lung Adenocarcinoma." Cancer Res **77**(11): 3040-3056.

Sen, T., P. Tong, C. A. Stewart, S. Cristea, A. Valliani, D. S. Shames, A. B. Redwood, Y. H. Fan, L. Li, B. S. Glisson, J. D. Minna, J. Sage, D. L. Gibbons, H. Piwnica-Worms, J. V. Heymach, J. Wang and L. A. Byers (2017). "CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib." Cancer Res **77**(14): 3870-3884.

Shelton, J. W., T. V. Waxweiler, J. Landry, H. Gao, Y. Xu, L. Wang, B. El-Rayes and H. K. Shu (2013). "In vitro and in vivo enhancement of chemoradiation using the oral PARP inhibitor ABT-888 in colorectal cancer cells." Int J Radiat Oncol Biol Phys **86**(3): 469-476.

Shi, Q., L. Y. Shen, B. Dong, H. Fu, X. Z. Kang, Y. B. Yang, L. Dai, W. P. Yan, H. C. Xiong, Z. Liang and K. N. Chen (2018). "The identification of the ATR inhibitor VE-822 as a therapeutic strategy for enhancing cisplatin chemosensivity in esophageal squamous cell carcinoma." Cancer Lett **432**: 56-68.

Short, J. M., Y. Liu, S. Chen, N. Soni, M. S. Madhusudhan, M. K. Shivji and A. R. Venkitaraman (2016). "High-resolution structure of the presynaptic RAD51 filament on single-stranded DNA by electron cryo-microscopy." Nucleic Acids Res **44**(19): 9017-9030.

Signon, L., A. Malkova, M. L. Naylor, H. Klein and J. E. Haber (2001). "Genetic requirements for RAD51- and RAD54-independent break-induced replication repair of a chromosomal double-strand break." Mol Cell Biol **21**(6): 2048-2056.

Suenaga, M., M. Schirripa, S. Cao, W. Zhang, D. Yang, S. Murgioni, D. Rossini, F. Marmorino, A. Mennitto, Y. Ning, S. Okazaki, M. D. Berger, Y. Miyamoto, R. Gopez, Jr., A. Barzi, T. Yamaguchi, F. Loupakis and H. J. Lenz (2017). "Genetic variants of DNA repair-related genes predict efficacy of TAS-102 in patients with refractory metastatic colorectal cancer." Ann Oncol **28**(5): 1015-1022.

Sultana, R., T. Abdel-Fatah, C. Perry, P. Moseley, N. Albarakti, V. Mohan, C. Seedhouse, S. Chan and S. Madhusudan (2013). "Ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase inhibition is synthetically lethal in XRCC1 deficient ovarian cancer cells." PLoS One **8**(2): e57098.

Sun, L. L., R. Y. Yang, C. W. Li, M. K. Chen, B. Shao, J. M. Hsu, L. C. Chan, Y. Yang, J. L. Hsu, Y. J. Lai and M. C. Hung (2018). "Inhibition of ATR downregulates PD-L1 and sensitizes tumor cells to T cell-mediated killing." Am J Cancer Res **8**(7): 1307-1316.

Sunada, S., A. Nakanishi and Y. Miki (2018). "Crosstalk of DNA double-strand break repair pathways in poly(ADP-ribose) polymerase inhibitor treatment of breast cancer susceptibility gene 1/2-mutated cancer." Cancer Sci.

Tarsounas, M., P. Munoz, A. Claas, P. G. Smiraldo, D. L. Pittman, M. A. Blasco and S. C. West (2004). "Telomere maintenance requires the RAD51D recombination/repair protein." Cell **117**(3): 337-347.

Thibodeau, S. N., G. Bren and D. Schaid (1993). "Microsatellite instability in cancer of the proximal colon." Science **260**(5109): 816-819.

Toledo, L. I., M. Murga, R. Zur, R. Soria, A. Rodriguez, S. Martinez, J. Oyarzabal, J. Pastor, J. R. Bischoff and O. Fernandez-Capetillo (2011). "A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations." Nat Struct Mol Biol **18**(6): 721-727.

Vanderstichele, A., P. Busschaert, S. Olbrecht, D. Lambrechts and I. Vergote (2017). "Genomic signatures as predictive biomarkers of homologous recombination deficiency in ovarian cancer." Eur J Cancer **86**: 5-14.

Vendetti, F. P., P. Karukonda, D. A. Clump, T. Teo, R. Lalonde, K. Nugent, M. Ballew, B. F. Kiesel, J. H. Beumer, S. N. Sarkar, T. P. Conrads, M. J. O'Connor, R. L. Ferris, P. T. Tran, G. M. Delgoffe and C. J. Bakkenist (2018). "ATR kinase inhibitor AZD6738 potentiates CD8+ T cell-dependent antitumor activity following radiation." J Clin Invest **128**(9): 3926-3940.

Venkatesan, S., A. T. Natarajan and M. P. Hande (2015). "Chromosomal instability--mechanisms and consequences." Mutat Res Genet Toxicol Environ Mutagen **793**: 176-184.

Vilar, E., C. M. Bartnik, S. L. Stenzel, L. Raskin, J. Ahn, V. Moreno, B. Mukherjee, M. D. Iniesta, M. A. Morgan, G. Rennert and S. B. Gruber (2011). "MRE11 deficiency increases sensitivity to poly(ADP-ribose) polymerase inhibition in microsatellite unstable colorectal cancers." Cancer Res **71**(7): 2632-2642.

Wang, C., J. Gong, T. Y. Tu, P. P. Lee and M. Fakih (2018). "Immune profiling of microsatellite instability-high and polymerase epsilon (POLE)-mutated metastatic colorectal tumors identifies predictors of response to anti-PD-1 therapy." J Gastrointest Oncol **9**(3): 404-415.

Wang, C., N. Jette, D. Moussienko, D. G. Bebb and S. P. Lees-Miller (2017). "ATM-Deficient Colorectal Cancer Cells Are Sensitive to the PARP Inhibitor Olaparib." Transl Oncol **10**(2): 190-196.

Watanabe, S., K. Watanabe, V. Akimov, J. Bartkova, B. Blagoev, J. Lukas and J. Bartek (2013). "JMJD1C demethylates MDC1 to regulate the RNF8 and BRCA1-mediated chromatin response to DNA breaks." Nat Struct Mol Biol **20**(12): 1425-1433.

Wolff, R. K., M. D. Hoffman, E. C. Wolff, J. S. Herrick, L. C. Sakoda, W. S. Samowitz and M. L. Slattery (2018). "Mutation analysis of adenomas and carcinomas of the colon: Early and late drivers." Genes Chromosomes Cancer.

Xu, G., J. R. Chapman, I. Brandsma, J. Yuan, M. Mistrik, P. Bouwman, J. Bartkova, E. Gogola, D. Warmerdam, M. Barazas, J. E. Jaspers, K. Watanabe, M. Pieterse, A. Kersbergen, W. Sol, P. H. N. Celie, P. C. Schouten, B. van den Broek, A. Salman, M. Nieuwland, I. de Rink, J. de Ronde, K. Jalink, S. J. Boulton, J. Chen, D. C. van Gent, J. Bartek, J. Jonkers, P. Borst and S. Rottenberg (2015). "REV7 counteracts DNA double-strand break resection and affects PARP inhibition." Nature **521**(7553): 541-544.

Xu, J., L. Zhao, Y. Xu, W. Zhao, P. Sung and H. W. Wang (2017). "Cryo-EM structures of human RAD51 recombinase filaments during catalysis of DNA-strand exchange." Nat Struct Mol Biol **24**(1): 40-46.

Xu, K., X. Song, Z. Chen, C. Qin and Y. He (2014). "XRCC2 rs3218536 polymorphism decreases the sensitivity of colorectal cancer cells to poly(ADP-ribose) polymerase 1 inhibitor." Oncol Lett **8**(3): 1222-1228.

Yaeger, R., W. K. Chatila, M. D. Lipsyc, J. F. Hechtman, A. Cercek, F. Sanchez-Vega, G. Jayakumaran, S. Middha, A. Zehir, M. T. A. Donoghue, D. You, A. Viale, N. Kemeny, N. H. Segal, Z. K. Stadler, A. M. Varghese, R. Kundra, J. Gao, A. Syed, D. M. Hyman, E. Vakiani, N. Rosen, B. S. Taylor, M. Ladanyi, M. F. Berger, D. B. Solit, J. Shia, L. Saltz and N. Schultz (2018). "Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer." Cancer Cell **33**(1): 125-136.e123.

Yan, T., S. E. Berry, A. B. Desai and T. J. Kinsella (2003). "DNA mismatch repair (MMR) mediates 6-thioguanine genotoxicity by introducing single-strand breaks to signal a G2-M arrest in MMR-proficient RKO cells." Clin Cancer Res **9**(6): 2327-2334.

Yazinski, S. A., V. Comaills, R. Buisson, M. M. Genois, H. D. Nguyen, C. K. Ho, T. Todorova Kwan, R. Morris, S. Lauffer, A. Nussenzweig, S. Ramaswamy, C. H. Benes, D. A. Haber, S. Maheswaran, M. J. Birrer and L. Zou (2017). "ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells." Genes Dev **31**(3): 318-332.

You, Z. and J. M. Bailis (2010). "DNA damage and decisions: CtIP coordinates DNA repair and cell cycle checkpoints." Trends Cell Biol **20**(7): 402-409.

Yuan, L., Y. Chi, W. Chen, X. Chen, P. Wei, W. Sheng, X. Zhou and D. Shi (2015). "Immunohistochemistry and microsatellite instability analysis in molecular subtyping of colorectal carcinoma based on mismatch repair competency." Int J Clin Exp Med **8**(11): 20988-21000.

Zeinalian, M., M. Hashemzadeh-Chaleshtori, R. Salehi and M. H. Emami (2018). "Clinical Aspects of Microsatellite Instability Testing in Colorectal Cancer." Adv Biomed Res **7**: 28.

Zeng, L., R. R. Beggs, T. S. Cooper, A. N. Weaver and E. S. Yang (2017). "Combining Chk1/2 Inhibition with Cetuximab and Radiation Enhances In Vitro and In Vivo Cytotoxicity in Head and Neck Squamous Cell Carcinoma." Mol Cancer Ther **16**(4): 591-600.

Zou, L. and S. J. Elledge (2003). "Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes." Science **300**(5625): 1542-1548.

Figure Legends:

Figure 1. DNA repair pathways with mutated genes highlighted. Left panel: DNA mismatch repair pathway recognizes and removes incorrect DNA base pairs generated during replication. Right panel: homologous recombination proteins recognize and repair DNA double strand breaks. Key proteins in each pathway are shown and the percent of cases that carried mutations in these genes are listed (see Table 1 for details).

Figure 2. Therapies targeting cancer specific DNA repair defects. Current chemotherapy agents (black) used to treat mCRC. Oxaliplatin induces DNA interstrand crosslinks that are repaired by nucleotide excision repair proteins during G1 and by Fanconi Anemia and HR proteins during S phase. Irinotecan (SN38) is a topoisomerase inhibitor that induces single (SSB) and double strand breaks (DSBs) that are repaired by HR and BER proteins. 5-fluorouracil is an anti-metabolite that can lead to DNA base pair mismatches repaired by the MMR pathway. Alternative therapies (red) that can be used in combination with current chemotherapy agents. PARPi and ATRi induce stalled replication forks and DSBs that are lethal in cells carrying mutations in HR genes, and CHKi block cell cycle arrest in the presence of replication stress. Chemosensitivity can be further induced in cells treated with genotoxic agents in combination with targeted therapies. Thiopurines induce DNA base pair mismatches that can lead to increased mutational and neoantigen burdens. Anti-PD-1 and CTLA-4 immunotherapies target MMRd CRC tumors and are most effective against tumors with high neoantigen burdens.

Table 1. Missense, truncating, and frameshift mutations (putative driver) in DNA damage response and repair genes identified in 528 colorectal cancer cases reported in The Cancer Genome Atlas Colon Adenocarcinoma (COAD) and Rectal Adenocarcinoma (READ) PanCancer Atlas datasets (Liu, Lichtenberg et al. 2018). Asterisk (*) indicates methylation data acquired from the TCGA-COADREAD Provisional dataset.
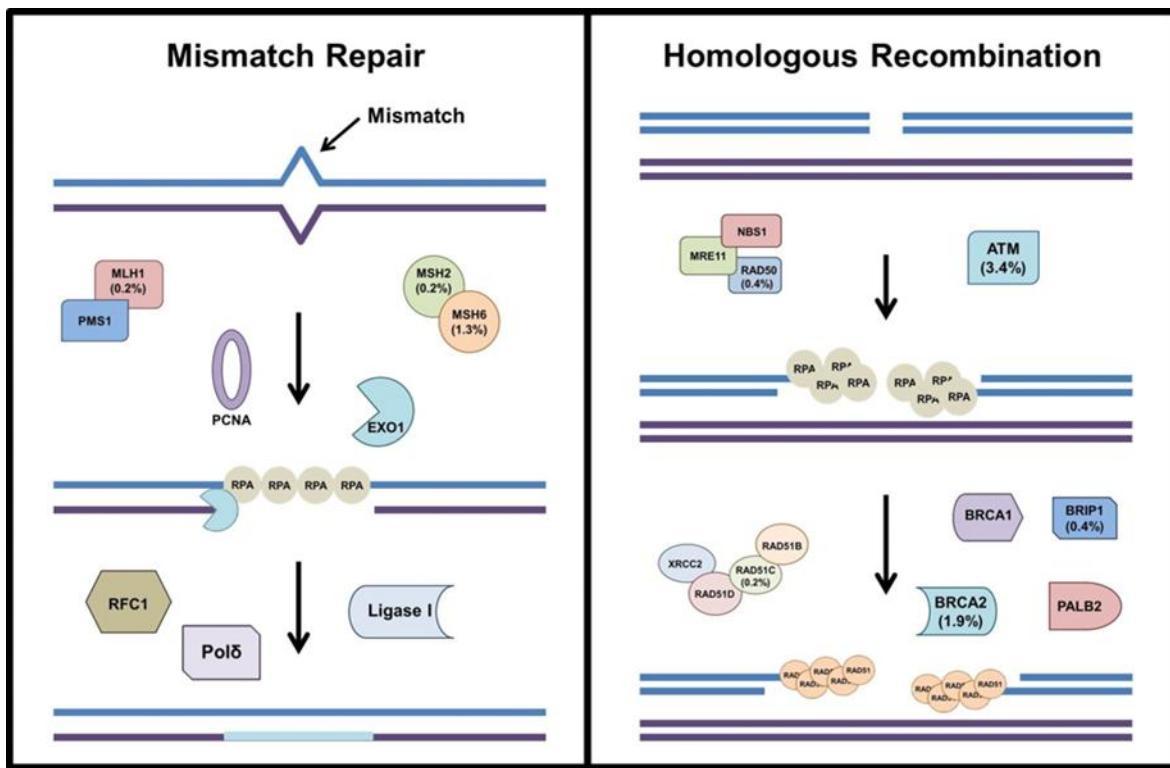
Gene	Cases Affected
TRP53	92 (17.4%)
ATM	18 (3.4%)
BRCA2	10 (1.9%)
TP53BP1	9 (1.7%)
MSH6	7 (1.3%)
ATR	7 (1.3%)
MTOR	5 (0.9%)
SMARCB1	4 (0.8%)
ATRX	3 (0.6%)
BARD1	3 (0.6%)
BLM	3 (0.6%)
MSH3	3 (0.6%)
BRIP1	2 (0.4%)
FANCA	2 (0.4%)
RAD50	2 (0.4%)
EPC2	1 (0.2%)
ERCC4	1 (0.2%)
MLH1	1 (0.2%) 37 (10.3%)*
MSH2	1 (0.2%)
PMS2	1 (0.2%)
RAD21	1 (0.2%)
RAD21L1	1 (0.2%)
RAD51C	1 (0.2%)
SMC1A	1 (0.2%)
XRCC2	1 (0.2%)
XRCC3	1 (0.2%)

Table 2. Clinical trials of PARP, ATR, and CHK1 inhibitors reported to the U.S. National Library of Medicine. (https://clinicaltrials.gov/ct2/home).

Clinical Trials in Colorectal Cancer			
Trial Identifier	**Therapy**	**Disease(s)**	**Status**
NCT00912743	Olaparib	Chemorefractory Metastatic Colorectal Cancer	Completed Results Available (Leichman, Groshen et al. 2016)
NCT02484404	Olaparib Cediranib MEDI4736	Ovarian, Triple Negative Breast, Lung, Prostate, Colorectal Cancers	Recruiting
NCT02305758	FOLFIRI Bevacizumab Veliparib	Untreated Metastatic Colorectal Cancer	Completed (Gorbunova, Beck et al. 2018)
NCT01051596	Temozolomide ABT-888	Colorectal Cancer	Completed (Pishvaian, Slack et al. 2018)
NCT01589419	Veliparib Capecitabine Radiation	Locally Advanced Rectal Cancer	Completed (Czito, Deming et al. 2017)
NCT02033551	Veliparib Carboplatin Paclitaxel FOLFIRI	Metastatic and chemorefractory Breast Cancer, Ovarian Cancer, Colon Cancer, Lung Cancer, Gastric Cancer, Solid Tumors	Completed (Berlin, Ramanathan et al. 2018)

Clinical Trials in Other Cancers			
Trial Identifier	**Therapy**	**Disease(s)**	**Status**
NCT03669601	AZD6738 Gemcitabine	Cancer	Not yet recruiting
NCT03682289	AZD6738 Olaparib	Clear Cell Renal Cell Carcinoma, Pancreatic Ductal Adenocarcinoma, Renal Cell Carcinoma Cancers	Not yet recruiting
NCT03428607	AZD6738 Olaparib	SCLC	Not yet recruiting
NCT02630199	AZD6738 Paclitaxel	Refractory Cancers	Recruiting
NCT03462342	AZD6738 Olaparib	High Grade Serous Carcinoma	Recruiting
NCT02223923	AZD6738	Solid Tumor Refractory to Conventional Therapy	Suspended
NCT01955668	AZD6738	Chronic Lymphocytic Leukemia, Prolymphocytic Leukemia, B Cell Leukemia	Completed
NCT02264678	AZD6738 Carboplatin Olaparib MEDI4736	Advanced Solid Malignancies - H&N SCC, ATM Pro / Def NSCLC, Gastric & Breast Cancer	Recruiting
NCT03328273	AZD6738 Acalabrutinib	Chronic Lymphocytic Leukemia	Recruiting

NCT03330847	AZD6738 Olaparib	Metastatic Triple Negative Breast Cancer	Recruiting
NCT03022409	AZD6738 Olaparib	Head and Neck Squamous Cell Carcinoma	Recruiting
NCT02576444	AZD6738	Cancer	Recruiting
NCT03527147	AZD6738	NHL, DLBCL, Non-Hodgkin's Lymphoma, Diffuse Large B Cell Lymphoma	Recruiting
NCT03334617	AZD6738	Non-Small Cell Lung Cancer	Recruiting
NCT02937818	AZD6738 Olaparib	Platinum Refractory Extensive-Stage Small Cell Lung Carcinoma	Recruiting
NCT02203513	LY2606368	Breast, Ovarian, Prostate	Recruiting (Lee, Nair et al. 2018)
NCT01870596	SCH900776	Acute Myeloid Leukemia	Completed
NCT03495323	LY3300054 Prexasertib	Cancer	Recruiting
NCT02808650	Prexasertib	Childhood Solid Neoplasm, Recurrent Central Nervous System Neoplasm, Recurrent Malignant Solid Neoplasm, Refractory Central Nervous System Neoplasm, Refractory Malignant Solid Neoplasm	Recruiting
NCT02797964	SRA737	Advanced Solid Tumors or Non-Hodgkin's Lymphoma	Recruiting
NCT02797977	SRA737 Gemcitabine Cisplatin	Advanced Solid Tumors	Recruiting
NCT02873975	LY2606368	Advanced Cancers	Recruiting
NCT03057145	LY2606368 Olaparib	Solid Tumor	Recruiting
NCT01115790	Prexasertib	Advanced Cancer, Squamous Cell Carcinoma, Carcinoma, Squamous Cell of Head and Neck, Lung Squamous Cell Carcinoma, Anal Squamous Cell Carcinoma, Carcinoma, Non-Small Cell Lung	Completed
NCT01139775	LY2603618 Pemetrexed Cisplatin	Non-Small Cell Lung Cancer	Completed
NCT02735980	Prexasertib	Small Cell Lung Cancer	Completed
NCT02514603	Prexasertib	Neoplasm	Completed
NCT03735446	Prexasertib Mitoxantrone Etoposide Cytarabine	Acute Myeloid Leukemia, Myelodysplastic Syndromes	Not yet recruiting
NCT03377556	Talozoparib	Sqamous Cell Lung Cancer	Recruiting