

## Targeting DNA damage in SCLC

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## Abstract

SCLC accounts for 15% of lung cancer worldwide. Characterised by early dissemination and rapid development of chemo-resistant disease, less than 5% of patients survive 5 years. Despite 3 decades of clinical trials there has been no change to the standard platinum and etoposide regimen for first line treatment developed in the 1970's.

The exceptionally high number of genomic aberrations observed in SCLC combined with the characteristic rapid cellular proliferation results in accumulation of DNA damage and genomic instability. To flourish in this precarious genomic context, SCLC cells are reliant on functional DNA damage repair pathways and cell cycle checkpoints.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair mechanisms in order to increase treatment efficacy.

This review will summarise the rationale to target DNA damage response in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

## 1. Introduction

The incidence of lung cancer continues to rise, with small cell lung cancer (SCLC) currently accounting for ~15% of cases. The highest incidence is in Central and Eastern Europe [1] reflecting the direct link between SCLC and cigarette smoking [2]. Biologically, SCLC is characterised by a rapid cancer cell doubling time and early metastatic dissemination; two thirds of patients present with metastatic (extensive) disease (ED) [3]. Drug treatment has changed little in the past 30 years and very few patients survive beyond 5 years [4]. A platinum drug and etoposide (PE), with or without the addition of thoracic and prophylactic cranial radiation, is the universal frontline standard of care [4]. The aggressive nature of the disease leads to extremely rapid deterioration and median survival of only 3-4 months without chemotherapy [5] yet long term survival and cure can occasionally be achieved in patients with limited stage disease (LD) [6]. In patients with ED treatment is palliative with typical response rates of approximately 70%, median progression free survival (PFS) and overall survival (OS) of approximately 6 and 9 months, respectively and 1 year survival rate of approximately 30% [7]. Unfortunately SCLC recurs in the vast majority of patients. The only drug approved by the United States Food and Drug Administration for treatment of relapsed SCLC in the second line setting is topotecan [5] for which response rates are low between 7-24%, progression free survival approximately 3-4 months and overall survival approximately 6-8 months [8]. Agents such as irinotecan, temozolomide (TMZ), amrubicin and anthracycline based regimens have also shown similar activity to topotecan in the second line setting [9, 10].

SCLC is hallmarked by rapid development of acquired chemoresistance despite initial chemo and radiosensitivity (Figure 1), with recurrence after initial therapy almost inevitable, usually within one year of treatment. Around 30% of patients have primary chemoresistant or refractory tumours and the probability of response to second-line chemotherapy can be predicted according to response to first-line treatment and the time to progression after completing it [11-14]. Patients with SCLC that relapse during first line platinum combination therapy or who have a treatment free interval of 60 to 90 days or less after the end of first-line therapy (resistant/refractory disease) have a worse outcome compared to those relapsing more than 90 days after completion of first-line therapy (sensitive disease) [11, 13, 15]. Due to the increasing tumour resistance to second line treatment and often rapid clinical deterioration during or following second line treatment, very few patients receive a third line of therapy. For these reasons earlier study enrolment into trials of maintenance or first line combination studies have become more common.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy [16]. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair (DDR) mechanisms in order to enhance sensitivity and/or overcome resistance to conventional DNA damaging treatments [2]. The DDR network is highly complex and dynamic with at least 450 proteins integral to DNA repair [17]. Different DDR proteins and pathways have the ability to compensate in the absence of integrity of the optimal pathway [16]. Five major DNA repair pathways are known: base excision repair (BER) to repair single-strand breaks (SSBs); homologous recombination repair (HRR) and non-homologous end-joining (NHEJ) to repair double-strand breaks (DSBs);

mismatch repair (MMR) to repair replication errors, and nucleotide excision repair (NER) to repair bulky adducts caused by platinum salts and UV radiation, for example [16]. An armamentarium of novel DDR inhibitors, designed to inhibit distinct proteins critical for the integrity of these pathways are in various stages of preclinical and clinical development (see [16] for comprehensive review). Here we focus on the rationale to target DDR in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

## **2. Rationale to evaluate DDR inhibitors in SCLC**

In the setting of tobacco-related carcinogenesis the SCLC genome is highly damaged as evidenced by an exceptionally high mutation burden, with approximately 8.88 mutations per megabyte [3, 18]. The tumour suppressor genes *TP53* and *RB1* are the most commonly mutated, with *TP53* virtually universally mutated in SCLC. The oncogenic transcription factors *MYC* and *SOX2* are amplified in 27% of cases, and histone modifiers such as *CREBBP1* and *EP300* are mutated in 15% and 13% of cases, respectively [3, 19-21] (*Table 1. genomic alterations in SCLC*). The majority of mutations have little significance for the SCLC pathogenesis and are described as passenger mutations. The challenge is to find driver mutations in a heterogeneous disease between patients and then being able to use them as actionable targets for treatments. Performing whole genome sequencing to identify therapeutically targetable oncogenic driver mutations, George *et al.* detected *BRAF*, *KIT*, and *PIK3CA* mutations in 4 out of 110 tumours analysed [3, 19-21]. Although discrete, druggable subsets akin to those observed for non-small cell lung cancer (NSCLC) have not been identified, these results indicate that some patients might

benefit from genotyping and subsequent targeted therapy [3, 19-21]. The net consequence of the genomic aberrations in SCLC is rapid cellular proliferation in the context of accumulating DNA damage due to replication stress [22] and genomic instability. Replicative stress is the accumulation of errors during endogenous DNA replication. DNA repair pathways can maintain genomic integrity in times of replicative stress but defects in regulators, checkpoints or DNA repair pathways can result in genomic instability [23]. For instance, aberrant activation of the oncogene *MYC* in an *RB1* and *TP53* mutant background results in rapid proliferation and ultimately replication stress in SCLC [2]. To flourish in this precarious genomic context, SCLC cells are reliant on functional DDR pathways and cell cycle checkpoints. However, defects in the DDR mechanisms can be present and be compatible with tumour survival. These aberrations create potential 'Achilles heels' and opportunities to selectively increase the therapeutic effect of DNA-damaging agents on cancer cells by inhibition of the remaining intact DDR. Aberrations in DDR proteins or pathways have also been implicated in resistance to conventional DNA damaging agents [24].

Although little is known about the molecular mechanisms in SCLC that confer resistance to chemotherapy, three main mechanisms of platinum resistance have been described. The first two concern drug handling; reduced intracellular drug accumulation and increased inactivation of the drug, the third concerns increased capability for repair of DNA damage [25] (*Figure 2*). Platinum compounds damage DNA by causing DNA replication barriers from the intercalation of platinum adducts into DNA [26]. Upon uptake into cells, cisplatin is hydrolysed in the cytoplasm and the chloride atoms are displaced by water molecules [26]. Consequently, cisplatin acts as an electrophile that can react with nitrogen on nucleic acids and sulfhydryl

groups on proteins [26]. In the majority of cases, cisplatin causes 1,2-intrastrand cross-links of purine bases and thereby hinders cell division, causing DNA damage and leading ultimately to apoptosis [26, 27]. DNA damage seems to contribute most to cisplatin toxicity, which is underlined by the fact that cells with deficient DNA repair are hypersensitive to cisplatin [28]. The bulky adducts generated by cisplatin are repaired by nucleotide excision repair (NER) pathway [29] and cell death depends on the balance of DNA damage and repair [30].

In clinical studies of patients with SCLC a low expression level of excision repair cross complementation group 1 (ERCC1), a endonuclease part of the NER, correlates with clinical outcome. Low ERCC1 expression in tumours is associated with a higher response rate and longer survival of SCLC patients with limited disease (LD) [31, 32]. With respect to mechanisms of resistance to other cytotoxics, etoposide and topotecan inhibit the topoisomerase enzymes II and I respectively, culminating in DNA DSBs. Studies by Dingemans *et al.* and Karachaliou *et al.* demonstrate a correlation between the survival of SCLC patients and the expression of DNA Topoisomerase I and II [32, 33]. High expression of *TOPI*, *TOPIIA*, and *TOPIIB* is associated with a shorter PFS in LD patients, whereas high expression of *TOP2B* is associated with low response rates [32, 33]. Although circumstantial, these findings implicate a role for DDR mechanisms in chemoresistance.

A further rationale to target DDR mechanisms comes from knowledge that cancer cells often harbour defects and/or dysregulation of DDR proteins and pathways [34, 35]. While there is a paucity of data specific to SCLC, Byers *et al.* [36] conducted an elegant study that identified the DNA repair protein, poly (ADP-ribose) polymerase 1 (PARP 1) as a therapeutic target. A total of 34 SCLC cell lines were profiled for the expression of 193 total and phosphoproteins. PARP1 was found to be highly

expressed at both the mRNA and protein levels. Preclinical SCLC models were sensitive to PARP inhibition alone and the efficacy of chemotherapy was also enhanced by the addition of a PARP inhibitor [36]. Interestingly, SCLC cell lines revealed comparable or higher chemosensitivity than two breast cancer cell lines with *BRCA1* or *PTEN* mutations, and PARP inhibitor sensitivity correlated with PARP levels [36]. Clinical studies testing several PARP inhibitors are currently ongoing and are discussed below.

Simplistically, DDR inhibitors may have efficacy in patients with SCLC in two ways:

- a) A DDR inhibitor may be synergistic when combined with a conventional cytotoxic(s) through prevention of usual repair / treatment resistance.
- b) Or, a DDR inhibitor may have monotherapy activity in a genomic context that causes vulnerability in one or more DDR pathways. This is the concept of so-called 'synthetic lethality' for which the paradigm is the well evidenced efficacy of PARP inhibition in cells with defective homologous recombination repair of DNA DSBs due to *BRCA1* or *BRCA2* deficiency [37].

*Current clinical trials of DDR inhibitors in SCLC (Table 2)*

### **3. PARP Inhibitors**

The family of PARP enzymes are highly abundant nuclear proteins that mediate BER and HRR, and alternative end joining (a-EJ). PARP1 is crucial for the repair of SSBs and is activated by stalled replication forks. PARP1 mediates the attachment of ADP-ribose units to multiple proteins to restart replication forks after DNA damage repair [2]. First, PARP1 inhibitors mediate their cytotoxic effect by trapping the enzyme to the SSB by preventing the utilization of  $\text{NAD}^+$  [38]. Second, PARP1 inhibitors inhibit



PARylation and therefore binding of PARP to DNA [38]. The resulting PARP-DNA complexes lead to collapsing and stalling of replication forks and ultimately to the conversion of SSBs to DSBs leading to apoptosis [38]. The development of PARP inhibitors (PARPi) has been largely driven by the concept of synthetic lethality, in which a combination of two deficiencies (in DDR) results in cell death but cells with only one deficiency present remain viable. PARP inhibition is 1000 times more potent in *BRCA*-deficient cells in comparison to *BRCA* wild-type cells [37, 39]. Olaparib is the most extensively investigated PARPi and is approved by the US FDA for use in pretreated advanced germline *BRCA* mutated ovarian cancer [40]. As already indicated, SCLC exhibits high levels of PARP1 expression and there are preclinical data to support PARP1 inhibition for clinical evaluation as a monotherapy and in combination with DNA damaging agents [36, 41, 42]. In tumour models PARP inhibitors synergise with agents that increase the prevalence of SSBs such as temozolomide [43, 44]. In addition, in preclinical SCLC xenografts Byers *et al.* demonstrated single agent activity of olaparib, which was further increased when combined with cisplatin and etoposide or irinotecan [45]. The precise mechanism of action of PARP inhibition in SCLC is not well understood. However, non-HRR dependent mechanisms of PARP inhibitor sensitivity have recently been recognised and to date candidate biomarkers for PARPi sensitivity in SCLC identified have included a 17 DNA repair protein score [42] and SLFN11 expression [44]. Several PARP inhibitors have now entered clinical testing in patients with SCLC.

### 3.1. **Olaparib:**

In the first line setting single agent olaparib was tested as maintenance treatment in a randomised, placebo-controlled phase II, 3 arm study conducted in the United Kingdom [46]. Patients were allocated to one of two doses of olaparib (300mg twice

daily (bd) or 200mg three times daily (tds)) or placebo. Eligible patients had pathologically confirmed LD/ED-SCLC with response to first line chemotherapy or chemo-radiotherapy. Patients were stratified by metastasis-status and prior radiotherapy. In 220 patients randomised to placebo, olaparib bd or olaparib tds the median PFS was 2.6 (90% CI 1.8, 3.7), 3.6 (90% CI 3.1, 6.0) and 3.6 (90%CI 3.1, 4.7) months and the median OS was 8.9 (90% CI 7.0, 11.9), 9.9 (90% CI 7.6, 12.9) and 9.0 (90% CI 6.6, 11.8) months respectively. There was no significant difference in PFS or OS between olaparib and placebo for either the bd or the tds arm. There were more treatment discontinuations for olaparib (26 in olaparib BD, 25 olaparib TDS, 17 placebo group) and the most common toxicities were fatigue, nausea, anaemia, vomiting and anorexia.

In the setting of SCLC after platinum based chemotherapy (platinum sensitive and resistant disease), an objective response rate (ORR) of 46% was observed in a phase 1/2 study of olaparib in combination with temozolomide. An expansion to 20 patients at the recommended phase 2 dose (RP2D) is now underway [47]. In an attempt to identify predictive biomarkers, this is an innovatively designed study with inclusion of baseline and serial tumour biopsies and blood samples to establish patient derived and circulating tumour derived xenograft/explant models [48-50]. Various other trials of olaparib are ongoing (see Table 2) including strategies to combine olaparib with other DDR inhibitors rather than conventional cytotoxics (discussed later) and as 2nd or 3rd line monotherapy in a biomarker selected population with relapsed SCLC harbouring somatic BRCA 1/2 mutations, ATM deficiency or MRE11A mutations (NCT03009682). The latter study will be particularly

interesting with respect to the frequencies of these genomic aberrations in a trial eligible population of patients.

### **3.2.Veliparib:**

Veliparib is a potent PARP 1/2 inhibitor that was evaluated in combination with cisplatin and etoposide in a small phase I trial in the first line setting if ED-SCLC. This demonstrated the ability to safely deliver the combination of veliparib for 7 days of the 21 day cycle and resulted in an ORR of 71% (5/7 patients, 1 complete response (CR)). Although comparable to historical responses from chemotherapy alone the result proved that a PARP inhibitor could be tolerated in combination with chemotherapy [51]. The subsequent ECOG-ACRIN 2511 study (NCT01642251) of veliparib added to cisplatin and etoposide versus chemotherapy alone in the same 1st line setting was recently reported in abstract form [52]. A total of 128 patients with ED SCLC were randomised to receive a maximum of 4 cycles of cisplatin and etoposide with veliparib 100 mg twice daily on days 1 to 7 or matching placebo. The ORR had a mild and not statistically significant increase from 65.6% to 71.9% with the addition of veliparib ( $p=0.57$ ). The median PFS was 6.1 months for patients receiving veliparib which was statistically significantly better than for patients receiving placebo (PFS 5.5 months, HR 0.63,  $p = 0.01$ ). The median OS was 10.3 months for patients on veliparib and 8.9 months for patients on placebo which was not statistically significant (HR=0.83,  $p=0.17$ ). The veliparib and chemotherapy combination was less well tolerated with increased haematological toxicity, including neutropenia (9/9), leucopenia (9/9) and anaemia (8/9). Although statistically significant the 0.6 month difference in median PFS had questionable meaningful clinical benefit and highlights the unmet need for predictive biomarkers to select and enrich for patients most likely to benefit. The results from a randomised study of

veliparib or placebo in combination with temozolomide as a second or third line therapy in patients with relapsed platinum sensitive or refractory SCLC have also been reported [53]. The ORR was significantly better for the combination (39%) compared with that for temozolomide and placebo (14%,  $p$  value = 0.016). Disappointingly the 4 month PFS, median PFS and OS did not differ between the arms. Also, haematological toxicity was greater for the combination (Grades 3 and 4 thrombocytopenia 50% in the combination arm vs 9% in TMZ arm, G3/4 neutropenia 31% vs 7% respectively). In this study tissue samples from approximately half of the patients enrolled were available for immunohistochemical (IHC) analysis of PARP1 and SLFN11 expression. There was no correlation between either biomarker with response although a trend to high SLFN11 expression and better overall survival was observed. SLFN11 is actively recruited to sites of DNA damage, inhibiting HR [54] and activating a cellular replication-stress response [55, 56]. SLFN11 suppression has been associated with chemoresistance in SCLC models [57] and identified as a biomarker of PARP inhibitor response in SCLC PDX [44]. Circulating tumour cell enumeration was undertaken at baseline and after 1 cycle of chemotherapy. A count of <5CTCs at baseline and after one cycle was observed to be prognostic for better outcome, independent of treatment received.

### **3.3.Talazoparib:**

Talazoparib is a novel and potent PARP inhibitor with a dual effect on PARP catalytic activity and PARP trapping [58]. In a phase 1 study of 100 patients with advanced solid tumours with DNA repair pathway defects, responses were observed in patients with *BRCA* mutated breast cancer, ovarian cancer and patients with SCLC. In a subsequent expansion cohort a clinical benefit rate (partial response (PR) + stable disease (SD) >6 weeks) of 26% (6/23) was demonstrated for talazoparib

monotherapy among patients with platinum sensitive ED SCLC. Talazoparib was well tolerated with 4% grade III-IV toxicities, most commonly haematological suppression [59].

*(Table 3)*

#### **4. Mitotic inhibitors (aurora kinase and checkpoint inhibitors)**

Aurora kinases play an important role in cell proliferation, controlling chromatin segregation, dispensing genetic material to the new cell during mitosis. Aurora kinase A promote mitosis through activation of CHK1 and aurora kinase B is functionally important in cytokinesis [60].

CHK1 prevents entry into mitosis by activating the S and G2/M checkpoint and is involved in the co-ordination of HRR [61, 62].

The tyrosine kinase Wee1 negatively regulates entry into mitosis, arresting the cell at G2/M to enable DNA repair. Inhibition of Wee1 prevents G2/M arrest with the consequence that unchecked cells enter mitosis resulting in cell death through mitotic catastrophe or apoptosis [63-68].

##### **4.1. Alisertib :**

Alisertib is an investigational selective aurora kinase A inhibitor, that has demonstrated single-agent anti-tumour activity in preclinical SCLC models and synergistic activity with paclitaxel in this setting [69]. In a phase I/II trial of Alisertib in refractory solid tumours, alisertib demonstrated single agent activity with an ORR of 21% (n=48) in the relapsed SCLC subgroups of patients, considerably higher than the 4% ORR observed in patients with NSCLC. Responses were observed in both platinum sensitive (7/10) and platinum refractory disease (3/10) with an overall PFS

of 2.1 months [70]. However 43% of patients had serious drug-related adverse events.

The results of a randomised phase II study of paclitaxel +/- alisertib in relapsed SCLC (NCT02038647) [69] were recently presented. Patients with relapsed SCLC <180 days after standard first-line platinum-based chemotherapy were randomised 1:1 to alisertib 40 mg orally twice-daily on days 1-3, 8-10, 15-17 + paclitaxel 60 mg/m<sup>2</sup> IV on days 1, 8, 15 (Arm A) or matched placebo + paclitaxel 80 mg/m<sup>2</sup> (Arm B) in 28-day cycles. Patients were stratified by type of relapse following frontline platinum (sensitive vs resistant/refractory) and presence/absence of brain metastases at baseline. In 178 patients randomised the primary endpoint of PFS was reached with a PFS of 101 days (3.32 months) for alisertib and paclitaxel versus 66 days (2.17 months) [HR=0.71, p=0.038] for placebo and paclitaxel and ORRs of 22%, and 18%, respectively. However, there was no significant difference in OS (6.1 vs 5.4 months, p=0.2) in the overall population. Interestingly a significantly different PFS was observed among the subgroup of 109 patients with resistant/refractory disease where a PFS of 2.86 months for alisertib and paclitaxel versus 1.64 months for alisertib and placebo (HR=0.66, p 0.032) was demonstrated. Furthermore, in an exploratory subgroup analysis according to expression of c-myc by IHC in archival tumour biopsies a median PFS of 4.64 months for alisertib and paclitaxel versus 2.27 months for placebo and paclitaxel (HR = 0.29, p = 0.0006) was observed. These results should be interpreted with caution due to a sample size of only 33 patients (17 and 16 per arm). However, in the c-myc negative group (13 patients, 6 and 7 per arm), the converse was observed with an inferior PFS for alisertib and paclitaxel of 3.32 months compared with a PFS of 5.16 months for placebo and paclitaxel (HR 11.8, p < 0.0006). Amplification and overexpression of the Myc family, a main driver

oncogene dysregulated in many cancers and involved in the regulation of Aurora kinases transcription, occurs in 18–31% of SCLCs and may be more common in chemo-refractory disease [71]. Preclinical studies have demonstrated that aurora A kinase inhibitors are more effective in SCLC cell lines with myc family amplification [71] and/or high expression of myc [72]. A prospective study is now warranted to further evaluate the predictive significance of c-myc expression in the efficacy of alisertib and paclitaxel.

#### **4.2.Prexasertib:**

Prexasertib is a selective ATP competitive inhibitor of CHK1 and CHK2. In preclinical studies, prexasertib has activity as a single agent and works synergistically with cytotoxic DNA damaging agents, inducing cell death in SCLC models [73]. A phase I trial of prexasertib in patients with advanced refractory squamous NSCLC, head and neck cancers and anal cancers reported a partial response (PR) of 4.4% (2/45) and SD in 33% (15/45) [74]. This agent is now being explored in extensive stage chemosensitive and chemoresistant SCLC (NCT0235980).

#### **4.3.AZD1775:**

AZD1775 is an oral competitive inhibitor of Wee1. As a single agent AZD1775 is well tolerated with a favourable toxicity profile and potential to combine with cytotoxics or other DDR inhibitors [75]. A phase 1 trial of AZD1775 in combination with cisplatin, carboplatin or gemcitabine in 202 patients with refractory solid tumours demonstrated some clinical activity with 53% (95/176) of patients obtaining SD and 10% showing a PR. Of note, the response rates observed were higher in patients with mutated *TP53* than those possessing *TP53* wild type (21% vs 12%) [76]. This agent is now being explored in a phase II clinical trial in patients with relapsed SCLC

(NCT02593019) and in patients with relapsed SCLC harbouring a *MYC* amplification or *CDKN2A* mutation, combined with *TP53* mutation in a phase II trial (NCT02688907). There is also promising preclinical data for the combination of AZD1775 and the PARP inhibitor, olaparib [77], and a phase I trial is in progress for patients with relapsed SCLC (NCT02511795).

## 5. RAD51 inhibition

RAD51 plays an essential role in homologous recombination and DNA repair [78]. In response to DNA damage the RAD51 protein relocates in the nucleus and it is thought to represent sites of DNA repair reactions [79]. RAD51 has the ability to promote joint molecule formation and DNA strand exchange between homologous DNA molecules [80-82]. In SCLC DSB repair after exposure to etoposide is RAD51 mediated [83].

### 5.1. Amuvatinib:

Amuvatinib is a multi-targeted tyrosine kinase inhibitor, designed to inhibit c-KIT and PDGFR $\alpha$ . In preclinical studies it was found to sensitise tumour cells to chemotherapy and radiotherapy in vitro suppressing RAD51 [84, 85]. Amuvatinib has demonstrated synergy with etoposide in SCLC cell lines and xenographs [86]

In preclinical studies Amuvatinib had synergistic effects with DNA damaging chemotherapies [78, 84]. In a phase IB study in treatment naive patients receiving either paclitaxel/carboplatin or carboplatin/etoposide in combination with amuvatinib for metastatic solid tumours, 12% demonstrated a partial response (n= 12/100), of which 4 had neuroendocrine tumours and 2 SCLC [87]. This prompted a phase 2 study in resistant relapsed SCLC with patients receiving amuvatinib in combination



with carboplatin and etoposide (ESCAPE; TrEatment of Small Cell lung cancer with Amuvatinib in combination with Platinum Etoposide). A clinical benefit rate of 22% was reported which failed to meet the predefined study endpoint [88].

## **6. ATR kinase inhibition**

The DDR pathway is regulated by a series of kinases including ataxia telangiectasia mutated (ATM) and ATM- and Rad3-related (ATR). ATM is activated by double strand breaks and ATR recruited to single stranded DNA coated with replication protein A, arising from DSBs or stalled DNA replication forks. ATR in turn activates Chk1 resulting in cell cycle arrest, promoting repair and preventing premature mitosis [89].

Disruption of the ATM/p53 pathway is observed in up to 70% of tumours and likely confers a growth advantage [90-92]. Disruption of the ATM pathway drives a reliance on the ATR pathway for DDR. Therefore inhibiting ATR in ATM deficient tumours may result in synthetic lethality [93].

### **6.1.VX-970:**

VX-970 is a potent and highly selective inhibitor of ATR. In a preclinical study VX-970 sensitized 80% of a panel of 35 lung cancer cell lines to cisplatin, with half of these demonstrating a greater than 10 fold increase in sensitivity. When the ATR inhibitor was compared to a Chk1 inhibitor the drugs displayed different sensitization profiles with VX-970 the most effective in combination with platinum and the Chk1 inhibitors most sensitizing to gemcitabine [94]. In the same study VX-970 increased sensitivity to cisplatin in six out of seven NSCLC PDX models [94]. In addition, ATR inhibitors have been shown to increase sensitivity to topoisomerase I inhibitors in

colorectal cancer cell lines *in vitro* and *in vivo* [95], rationalising the combination of ATR inhibitors and topotecan in early phase clinical trials in SCLC.

## 7. Lurbinectidin

Lurbinectidin is a novel anticancer drug that inhibits activated transcription, induces DNA double-strand breaks generating apoptosis, and modulates tumour microenvironment. The antitumor activity and safety of this agent in patients with SCLC has been assessed in three clinical trials: two phase I in combination with doxorubicin or paclitaxel and a phase II single- agent basket trial [96]. Activity is observed for single agent lurbinectidin (response rate 36%) and in combination (response rates from 37-71%). Haematological toxicity was significant with a grade 3/ 4 neutropenia rate of 38% for single agent lurbinectidin. A phase III trial in the second line setting of lurbinectidin in combination with doxorubicin compared with standard second line therapy (topotecan or cyclophosphamide, doxorubicin and vincristine) is ongoing (ATLANTIS Study - NCT0256699).

*DNA Damage and Therapeutics Figure 3.*

## 8. Perspectives

SCLC is a complex and heterogeneous tumour and the vast majority of patients will recur with a more resistant tumour. Several targeted agents have revolutionized the treatment of other cancers but despite decades of clinical trials none have been approved for clinical use. DDR inhibitors have demonstrated activity in patients with SCLC (*see summary table 3*), although to date none have emerged with sufficient efficacy for routine clinical use. There is an unmet need to identify biomarkers that can stratify patients into advantageous groups. In fact an important limitation with the majority of trials has been the use of unselected patients within a heterogeneous cancer, in other words, targeted agents for untargeted tumours.

Currently PARP inhibitors are approved for use in BRCA mutated ovarian cancer. BRCA mutations are rare in SCLC but scoring systems have been proposed to predict for a 'BRCA like' genomic environment [97, 98]. A novel 'DNA repair score' consisting of 17 DNA repair proteins, applied to SCLC cell lines and xenografts established that baseline activation of the PI3K/mTOR pathway is associated with resistance to the PARP inhibitor BMN673 [42]. Another biomarker, SLFN11 expression, is associated with PARP inhibitor sensitivity in SCLC cell lines and PDX models [44]. In addition, high levels of SLFN11 expression (H-score  $\geq 1$ ) were associated with a trend toward improved OS and favourable tumour responses in patients with recurrent SCLC that received TMZ and Veliparib as second line regiment, but not temozolomide plus placebo in a randomised phase II clinical trial [99] highlighting evident biomarkers that could guide clinical decision making.

These biomarkers are dynamic and longitudinal sampling will be required to tailor a personalised medicine approach. As a case in point, using co-clinical models of CTC derived explant or tumour biopsy derived explant tumours the expression of SLFN11 and MGMT, biomarkers for activity of olaparib and TMZ, respectively, did not consistently correlate with the tumour responses observed to these drugs in the donor patients [47]. Correlation of identified scoring systems in clinical studies of PARP inhibition in SCLC will be important to identify patients most likely to benefit from treatment.

In conclusion, exploration of biomarkers *in vivo*, from diagnostic tumour biopsies and liquid biopsies will be crucial in identifying patients who will derive clinical benefit from DDR inhibitors. While targeting DDR mechanisms is theoretically plausible the results from clinical trials to date have yet to convince. Further investigation into the synergistic effects of DDR inhibitors administered in combination with traditional DNA

damaging therapies will expand our understanding of how these agents are best positioned in the clinical setting and biomarker studies may provide insight into mechanisms of acquired and inherent resistance.

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## Targeting DNA damage in SCLC

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## Abstract

SCLC accounts for 15% of lung cancer worldwide. Characterised by early dissemination and rapid development of chemo-resistant disease, less than 5% of patients survive 5 years. Despite 3 decades of clinical trials there has been no change to the standard platinum and etoposide regimen for first line treatment developed in the 1970's.

The exceptionally high number of genomic aberrations observed in SCLC combined with the characteristic rapid cellular proliferation results in accumulation of DNA damage and genomic instability. To flourish in this precarious genomic context, SCLC cells are reliant on functional DNA damage repair pathways and cell cycle checkpoints.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair mechanisms in order to increase treatment efficacy.

This review will summarise the rationale to target DNA damage response in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

## 1. Introduction

The incidence of lung cancer continues to rise, with small cell lung cancer (SCLC) currently accounting for ~15% of cases. The highest incidence is in Central and Eastern Europe [1] reflecting the direct link between SCLC and cigarette smoking [2]. Biologically, SCLC is characterised by a rapid cancer cell doubling time and early metastatic dissemination; two thirds of patients present with metastatic (extensive) disease (ED) [3]. Drug treatment has changed little in the past 30 years and very few patients survive beyond 5 years [4]. A platinum drug and etoposide (PE), with or without the addition of thoracic and prophylactic cranial radiation, is the universal frontline standard of care [4]. The aggressive nature of the disease leads to extremely rapid deterioration and median survival of only 3-4 months without chemotherapy [5] yet long term survival and cure can occasionally be achieved in patients with limited stage disease (LD) [6]. In patients with ED treatment is palliative with typical response rates of approximately 70%, median progression free survival (PFS) and overall survival (OS) of approximately 6 and 9 months, respectively and 1 year survival rate of approximately 30% [7]. Unfortunately SCLC recurs in the vast majority of patients. The only drug approved by the United States Food and Drug Administration for treatment of relapsed SCLC in the second line setting is topotecan [5] for which response rates are low between 7-24%, progression free survival approximately 3-4 months and overall survival approximately 6-8 months [8]. Agents such as irinotecan, temozolomide (TMZ), amrubicin and anthracycline based regimens have also shown similar activity to topotecan in the second line setting [9, 10].

SCLC is hallmarked by rapid development of acquired chemoresistance despite initial chemo and radiosensitivity (Figure 1), with recurrence after initial therapy almost inevitable, usually within one year of treatment. Around 30% of patients have primary chemoresistant or refractory tumours and the probability of response to second-line chemotherapy can be predicted according to response to first-line treatment and the time to progression after completing it [11-14]. Patients with SCLC that relapse during first line platinum combination therapy or who have a treatment free interval of 60 to 90 days or less after the end of first-line therapy (resistant/refractory disease) have a worse outcome compared to those relapsing more than 90 days after completion of first-line therapy (sensitive disease) [11, 13, 15]. Due to the increasing tumour resistance to second line treatment and often rapid clinical deterioration during or following second line treatment, very few patients receive a third line of therapy. For these reasons earlier study enrolment into trials of maintenance or first line combination studies have become more common.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy [16]. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair (DDR) mechanisms in order to enhance sensitivity and/or overcome resistance to conventional DNA damaging treatments [2]. The DDR network is highly complex and dynamic with at least 450 proteins integral to DNA repair [17]. Different DDR proteins and pathways have the ability to compensate in the absence of integrity of the optimal pathway [16]. Five major DNA repair pathways are known: base excision repair (BER) to repair single-strand breaks (SSBs); homologous recombination repair (HRR) and non-homologous end-joining (NHEJ) to repair double-strand breaks (DSBs);



mismatch repair (MMR) to repair replication errors, and nucleotide excision repair (NER) to repair bulky adducts caused by platinum salts and UV radiation, for example [16]. An armamentarium of novel DDR inhibitors, designed to inhibit distinct proteins critical for the integrity of these pathways are in various stages of preclinical and clinical development (see [16] for comprehensive review). Here we focus on the rationale to target DDR in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

## **2. Rationale to evaluate DDR inhibitors in SCLC**

In the setting of tobacco-related carcinogenesis the SCLC genome is highly damaged as evidenced by an exceptionally high mutation burden, with approximately 8.88 mutations per megabyte [3, 18]. The tumour suppressor genes *TP53* and *RB1* are the most commonly mutated, with *TP53* virtually universally mutated in SCLC. The oncogenic transcription factors *MYC* and *SOX2* are amplified in 27% of cases, and histone modifiers such as *CREBBP1* and *EP300* are mutated in 15% and 13% of cases, respectively [3, 19-21] (*Table 1. genomic alterations in SCLC*). The majority of mutations have little significance for the SCLC pathogenesis and are described as passenger mutations. The challenge is to find driver mutations in a heterogeneous disease between patients and then being able to use them as actionable targets for treatments. Performing whole genome sequencing to identify therapeutically targetable oncogenic driver mutations, George *et al.* detected *BRAF*, *KIT*, and *PIK3CA* mutations in 4 out of 110 tumours analysed [3, 19-21]. Although discrete, druggable subsets akin to those observed for non-small cell lung cancer (NSCLC) have not been identified, these results indicate that some patients might

benefit from genotyping and subsequent targeted therapy [3, 19-21]. The net consequence of the genomic aberrations in SCLC is rapid cellular proliferation in the context of accumulating DNA damage due to replication stress [22] and genomic instability. Replicative stress is the accumulation of errors during endogenous DNA replication. DNA repair pathways can maintain genomic integrity in times of replicative stress but defects in regulators, checkpoints or DNA repair pathways can result in genomic instability [23]. For instance, aberrant activation of the oncogene *MYC* in an *RB1* and *TP53* mutant background results in rapid proliferation and ultimately replication stress in SCLC [2]. To flourish in this precarious genomic context, SCLC cells are reliant on functional DDR pathways and cell cycle checkpoints. However, defects in the DDR mechanisms can be present and be compatible with tumour survival. These aberrations create potential 'Achilles heels' and opportunities to selectively increase the therapeutic effect of DNA-damaging agents on cancer cells by inhibition of the remaining intact DDR. Aberrations in DDR proteins or pathways have also been implicated in resistance to conventional DNA damaging agents [24].

Although little is known about the molecular mechanisms in SCLC that confer resistance to chemotherapy, three main mechanisms of platinum resistance have been described. The first two concern drug handling; reduced intracellular drug accumulation and increased inactivation of the drug, the third concerns increased capability for repair of DNA damage [25] (*Figure 2*). Platinum compounds damage DNA by causing DNA replication barriers from the intercalation of platinum adducts into DNA [26]. Upon uptake into cells, cisplatin is hydrolysed in the cytoplasm and the chloride atoms are displaced by water molecules [26]. Consequently, cisplatin acts as an electrophile that can react with nitrogen on nucleic acids and sulfhydryl

groups on proteins [26]. In the majority of cases, cisplatin causes 1,2-intrastrand cross-links of purine bases and thereby hinders cell division, causing DNA damage and leading ultimately to apoptosis [26, 27]. DNA damage seems to contribute most to cisplatin toxicity, which is underlined by the fact that cells with deficient DNA repair are hypersensitive to cisplatin [28]. The bulky adducts generated by cisplatin are repaired by nucleotide excision repair (NER) pathway [29] and cell death depends on the balance of DNA damage and repair [30].

In clinical studies of patients with SCLC a low expression level of excision repair cross complementation group 1 (ERCC1), a endonuclease part of the NER, correlates with clinical outcome. Low ERCC1 expression in tumours is associated with a higher response rate and longer survival of SCLC patients with limited disease (LD) [31, 32]. With respect to mechanisms of resistance to other cytotoxics, etoposide and topotecan inhibit the topoisomerase enzymes II and I respectively, culminating in DNA DSBs. Studies by Dingemans *et al.* and Karachaliou *et al.* demonstrate a correlation between the survival of SCLC patients and the expression of DNA Topoisomerase I and II [32, 33]. High expression of *TOPI*, *TOPIIA*, and *TOPIIB* is associated with a shorter PFS in LD patients, whereas high expression of *TOP2B* is associated with low response rates [32, 33]. Although circumstantial, these findings implicate a role for DDR mechanisms in chemoresistance.

A further rationale to target DDR mechanisms comes from knowledge that cancer cells often harbour defects and/or dysregulation of DDR proteins and pathways [34, 35]. While there is a paucity of data specific to SCLC, Byers *et al.* [36] conducted an elegant study that identified the DNA repair protein, poly (ADP-ribose) polymerase 1 (PARP 1) as a therapeutic target. A total of 34 SCLC cell lines were profiled for the expression of 193 total and phosphoproteins. PARP1 was found to be highly

expressed at both the mRNA and protein levels. Preclinical SCLC models were sensitive to PARP inhibition alone and the efficacy of chemotherapy was also enhanced by the addition of a PARP inhibitor [36]. Interestingly, SCLC cell lines revealed comparable or higher chemosensitivity than two breast cancer cell lines with *BRCA1* or *PTEN* mutations, and PARP inhibitor sensitivity correlated with PARP levels [36]. Clinical studies testing several PARP inhibitors are currently ongoing and are discussed below.

Simplistically, DDR inhibitors may have efficacy in patients with SCLC in two ways:

- a) A DDR inhibitor may be synergistic when combined with a conventional cytotoxic(s) through prevention of usual repair / treatment resistance.
- b) Or, a DDR inhibitor may have monotherapy activity in a genomic context that causes vulnerability in one or more DDR pathways. This is the concept of so-called 'synthetic lethality' for which the paradigm is the well evidenced efficacy of PARP inhibition in cells with defective homologous recombination repair of DNA DSBs due to *BRCA1* or *BRCA2* deficiency [37].

*Current clinical trials of DDR inhibitors in SCLC (Table 2)*

### **3. PARP Inhibitors**

The family of PARP enzymes are highly abundant nuclear proteins that mediate BER and HRR, and alternative end joining (a-EJ). PARP1 is crucial for the repair of SSBs and is activated by stalled replication forks. PARP1 mediates the attachment of ADP-ribose units to multiple proteins to restart replication forks after DNA damage repair [2]. First, PARP1 inhibitors mediate their cytotoxic effect by trapping the enzyme to the SSB by preventing the utilization of  $\text{NAD}^+$  [38]. Second, PARP1 inhibitors inhibit

PARylation and therefore binding of PARP to DNA [38]. The resulting PARP-DNA complexes lead to collapsing and stalling of replication forks and ultimately to the conversion of SSBs to DSBs leading to apoptosis [38]. The development of PARP inhibitors (PARPi) has been largely driven by the concept of synthetic lethality, in which a combination of two deficiencies (in DDR) results in cell death but cells with only one deficiency present remain viable. PARP inhibition is 1000 times more potent in *BRCA*-deficient cells in comparison to *BRCA* wild-type cells [37, 39]. Olaparib is the most extensively investigated PARPi and is approved by the US FDA for use in pretreated advanced germline *BRCA* mutated ovarian cancer [40]. As already indicated, SCLC exhibits high levels of PARP1 expression and there are preclinical data to support PARP1 inhibition for clinical evaluation as a monotherapy and in combination with DNA damaging agents [36, 41, 42]. In tumour models PARP inhibitors synergise with agents that increase the prevalence of SSBs such as temozolomide [43, 44]. In addition, in preclinical SCLC xenografts Byers *et al.* demonstrated single agent activity of olaparib, which was further increased when combined with cisplatin and etoposide or irinotecan [45]. The precise mechanism of action of PARP inhibition in SCLC is not well understood. However, non-HRR dependent mechanisms of PARP inhibitor sensitivity have recently been recognised and to date candidate biomarkers for PARPi sensitivity in SCLC identified have included a 17 DNA repair protein score [42] and SLFN11 expression [44]. Several PARP inhibitors have now entered clinical testing in patients with SCLC.

### 3.1. **Olaparib:**

In the first line setting single agent olaparib was tested as maintenance treatment in a randomised, placebo-controlled phase II, 3 arm study conducted in the United Kingdom [46]. Patients were allocated to one of two doses of olaparib (300mg twice

daily (bd) or 200mg three times daily (tds)) or placebo. Eligible patients had pathologically confirmed LD/ED-SCLC with response to first line chemotherapy or chemo-radiotherapy. Patients were stratified by metastasis-status and prior radiotherapy. In 220 patients randomised to placebo, olaparib bd or olaparib tds the median PFS was 2.6 (90% CI 1.8, 3.7), 3.6 (90% CI 3.1, 6.0) and 3.6 (90%CI 3.1, 4.7) months and the median OS was 8.9 (90% CI 7.0, 11.9), 9.9 (90% CI 7.6, 12.9) and 9.0 (90% CI 6.6, 11.8) months respectively. There was no significant difference in PFS or OS between olaparib and placebo for either the bd or the tds arm. There were more treatment discontinuations for olaparib (26 in olaparib BD, 25 olaparib TDS, 17 placebo group) and the most common toxicities were fatigue, nausea, anaemia, vomiting and anorexia.

In the setting of SCLC after platinum based chemotherapy (platinum sensitive and resistant disease), an objective response rate (ORR) of 46% was observed in a phase 1/2 study of olaparib in combination with temozolomide. An expansion to 20 patients at the recommended phase 2 dose (RP2D) is now underway [47]. In an attempt to identify predictive biomarkers, this is an innovatively designed study with inclusion of baseline and serial tumour biopsies and blood samples to establish patient derived and circulating tumour derived xenograft/explant models [48-50]. Various other trials of olaparib are ongoing (see Table 2) including strategies to combine olaparib with other DDR inhibitors rather than conventional cytotoxics (discussed later) and as 2nd or 3rd line monotherapy in a biomarker selected population with relapsed SCLC harbouring somatic BRCA 1/2 mutations, ATM deficiency or MRE11A mutations (NCT03009682). The latter study will be particularly

interesting with respect to the frequencies of these genomic aberrations in a trial eligible population of patients.

### **3.2.Veliparib:**

Veliparib is a potent PARP 1/2 inhibitor that was evaluated in combination with cisplatin and etoposide in a small phase I trial in the first line setting if ED-SCLC. This demonstrated the ability to safely deliver the combination of veliparib for 7 days of the 21 day cycle and resulted in an ORR of 71% (5/7 patients, 1 complete response (CR)). Although comparable to historical responses from chemotherapy alone the result proved that a PARP inhibitor could be tolerated in combination with chemotherapy [51]. The subsequent ECOG-ACRIN 2511 study (NCT01642251) of veliparib added to cisplatin and etoposide versus chemotherapy alone in the same 1st line setting was recently reported in abstract form [52]. A total of 128 patients with ED SCLC were randomised to receive a maximum of 4 cycles of cisplatin and etoposide with veliparib 100 mg twice daily on days 1 to 7 or matching placebo. The ORR had a mild and not statistically significant increase from 65.6% to 71.9% with the addition of veliparib ( $p=0.57$ ). The median PFS was 6.1 months for patients receiving veliparib which was statistically significantly better than for patients receiving placebo (PFS 5.5 months, HR 0.63,  $p = 0.01$ ). The median OS was 10.3 months for patients on veliparib and 8.9 months for patients on placebo which was not statistically significant (HR=0.83,  $p=0.17$ ). The veliparib and chemotherapy combination was less well tolerated with increased haematological toxicity, including neutropenia (9/9), leucopenia (9/9) and anaemia (8/9). Although statistically significant the 0.6 month difference in median PFS had questionable meaningful clinical benefit and highlights the unmet need for predictive biomarkers to select and enrich for patients most likely to benefit. The results from a randomised study of

veliparib or placebo in combination with temozolomide as a second or third line therapy in patients with relapsed platinum sensitive or refractory SCLC have also been reported [53]. The ORR was significantly better for the combination (39%) compared with that for temozolomide and placebo (14%,  $p$  value = 0.016). Disappointingly the 4 month PFS, median PFS and OS did not differ between the arms. Also, haematological toxicity was greater for the combination (Grades 3 and 4 thrombocytopenia 50% in the combination arm vs 9% in TMZ arm, G3/4 neutropenia 31% vs 7% respectively). In this study tissue samples from approximately half of the patients enrolled were available for immunohistochemical (IHC) analysis of PARP1 and SLFN11 expression. There was no correlation between either biomarker with response although a trend to high SLFN11 expression and better overall survival was observed. SLFN11 is actively recruited to sites of DNA damage, inhibiting HR [54] and activating a cellular replication-stress response [55, 56]. SLFN11 suppression has been associated with chemoresistance in SCLC models [57] and identified as a biomarker of PARP inhibitor response in SCLC PDX [44]. Circulating tumour cell enumeration was undertaken at baseline and after 1 cycle of chemotherapy. A count of <5CTCs at baseline and after one cycle was observed to be prognostic for better outcome, independent of treatment received.

### **3.3.Talazoparib:**

Talazoparib is a novel and potent PARP inhibitor with a dual effect on PARP catalytic activity and PARP trapping [58]. In a phase 1 study of 100 patients with advanced solid tumours with DNA repair pathway defects, responses were observed in patients with *BRCA* mutated breast cancer, ovarian cancer and patients with SCLC. In a subsequent expansion cohort a clinical benefit rate (partial response (PR) + stable disease (SD) >6 weeks) of 26% (6/23) was demonstrated for talazoparib



monotherapy among patients with platinum sensitive ED SCLC. Talazoparib was well tolerated with 4% grade III-IV toxicities, most commonly haematological suppression [59].

*(Table 3)*

#### **4. Mitotic inhibitors (aurora kinase and checkpoint inhibitors)**

Aurora kinases play an important role in cell proliferation, controlling chromatin segregation, dispensing genetic material to the new cell during mitosis. Aurora kinase A promote mitosis through activation of CHK1 and aurora kinase B is functionally important in cytokinesis [60].

CHK1 prevents entry into mitosis by activating the S and G2/M checkpoint and is involved in the co-ordination of HRR [61, 62].

The tyrosine kinase Wee1 negatively regulates entry into mitosis, arresting the cell at G2/M to enable DNA repair. Inhibition of Wee1 prevents G2/M arrest with the consequence that unchecked cells enter mitosis resulting in cell death through mitotic catastrophe or apoptosis [63-68].

##### **4.1. Alisertib :**

Alisertib is an investigational selective aurora kinase A inhibitor, that has demonstrated single-agent anti-tumour activity in preclinical SCLC models and synergistic activity with paclitaxel in this setting [69]. In a phase I/II trial of Alisertib in refractory solid tumours, alisertib demonstrated single agent activity with an ORR of 21% (n=48) in the relapsed SCLC subgroups of patients, considerably higher than the 4% ORR observed in patients with NSCLC. Responses were observed in both platinum sensitive (7/10) and platinum refractory disease (3/10) with an overall PFS

of 2.1 months [70]. However 43% of patients had serious drug-related adverse events.

The results of a randomised phase II study of paclitaxel +/- alisertib in relapsed SCLC (NCT02038647) [69] were recently presented. Patients with relapsed SCLC <180 days after standard first-line platinum-based chemotherapy were randomised 1:1 to alisertib 40 mg orally twice-daily on days 1-3, 8-10, 15-17 + paclitaxel 60 mg/m<sup>2</sup> IV on days 1, 8, 15 (Arm A) or matched placebo + paclitaxel 80 mg/m<sup>2</sup> (Arm B) in 28-day cycles. Patients were stratified by type of relapse following frontline platinum (sensitive vs resistant/refractory) and presence/absence of brain metastases at baseline. In 178 patients randomised the primary endpoint of PFS was reached with a PFS of 101 days (3.32 months) for alisertib and paclitaxel versus 66 days (2.17 months) [HR=0.71, p=0.038] for placebo and paclitaxel and ORRs of 22%, and 18%, respectively. However, there was no significant difference in OS (6.1 vs 5.4 months, p=0.2) in the overall population. Interestingly a significantly different PFS was observed among the subgroup of 109 patients with resistant/refractory disease where a PFS of 2.86 months for alisertib and paclitaxel versus 1.64 months for alisertib and placebo (HR=0.66, p 0.032) was demonstrated. Furthermore, in an exploratory subgroup analysis according to expression of c-myc by IHC in archival tumour biopsies a median PFS of 4.64 months for alisertib and paclitaxel versus 2.27 months for placebo and paclitaxel (HR = 0.29, p = 0.0006) was observed. These results should be interpreted with caution due to a sample size of only 33 patients (17 and 16 per arm). However, in the c-myc negative group (13 patients, 6 and 7 per arm), the converse was observed with an inferior PFS for alisertib and paclitaxel of 3.32 months compared with a PFS of 5.16 months for placebo and paclitaxel (HR 11.8, p < 0.0006). Amplification and overexpression of the Myc family, a main driver

oncogene dysregulated in many cancers and involved in the regulation of Aurora kinases transcription, occurs in 18–31% of SCLCs and may be more common in chemo-refractory disease [71]. Preclinical studies have demonstrated that aurora A kinase inhibitors are more effective in SCLC cell lines with myc family amplification [71] and/or high expression of myc [72]. A prospective study is now warranted to further evaluate the predictive significance of c-myc expression in the efficacy of alisertib and paclitaxel.

#### **4.2.Prexasertib:**

Prexasertib is a selective ATP competitive inhibitor of CHK1 and CHK2. In preclinical studies, prexasertib has activity as a single agent and works synergistically with cytotoxic DNA damaging agents, inducing cell death in SCLC models [73]. A phase I trial of prexasertib in patients with advanced refractory squamous NSCLC, head and neck cancers and anal cancers reported a partial response (PR) of 4.4% (2/45) and SD in 33% (15/45) [74]. This agent is now being explored in extensive stage chemosensitive and chemoresistant SCLC (NCT0235980).

#### **4.3.AZD1775:**

AZD1775 is an oral competitive inhibitor of Wee1. As a single agent AZD1775 is well tolerated with a favourable toxicity profile and potential to combine with cytotoxics or other DDR inhibitors [75]. A phase 1 trial of AZD1775 in combination with cisplatin, carboplatin or gemcitabine in 202 patients with refractory solid tumours demonstrated some clinical activity with 53% (95/176) of patients obtaining SD and 10% showing a PR. Of note, the response rates observed were higher in patients with mutated *TP53* than those possessing *TP53* wild type (21% vs 12%) [76]. This agent is now being explored in a phase II clinical trial in patients with relapsed SCLC

(NCT02593019) and in patients with relapsed SCLC harbouring a *MYC* amplification or *CDKN2A* mutation, combined with *TP53* mutation in a phase II trial (NCT02688907). There is also promising preclinical data for the combination of AZD1775 and the PARP inhibitor, olaparib [77], and a phase I trial is in progress for patients with relapsed SCLC (NCT02511795).

## 5. RAD51 inhibition

RAD51 plays an essential role in homologous recombination and DNA repair [78]. In response to DNA damage the RAD51 protein relocates in the nucleus and it is thought to represent sites of DNA repair reactions [79]. RAD51 has the ability to promote joint molecule formation and DNA strand exchange between homologous DNA molecules [80-82]. In SCLC DSB repair after exposure to etoposide is RAD51 mediated [83].

### 5.1. Amuvatinib:

Amuvatinib is a multi-targeted tyrosine kinase inhibitor, designed to inhibit c-KIT and PDGFR $\alpha$ . In preclinical studies it was found to sensitise tumour cells to chemotherapy and radiotherapy in vitro suppressing RAD51 [84, 85]. Amuvatinib has demonstrated synergy with etoposide in SCLC cell lines and xenographs [86]

In preclinical studies Amuvatinib had synergistic effects with DNA damaging chemotherapies [78, 84]. In a phase IB study in treatment naive patients receiving either paclitaxel/carboplatin or carboplatin/etoposide in combination with amuvatinib for metastatic solid tumours, 12% demonstrated a partial response (n= 12/100), of which 4 had neuroendocrine tumours and 2 SCLC [87]. This prompted a phase 2 study in resistant relapsed SCLC with patients receiving amuvatinib in combination

with carboplatin and etoposide (ESCAPE; TrEatment of Small Cell lung cancer with Amuvatinib in combination with Platinum Etoposide). A clinical benefit rate of 22% was reported which failed to meet the predefined study endpoint [88].

## **6. ATR kinase inhibition**

The DDR pathway is regulated by a series of kinases including ataxia telangiectasia mutated (ATM) and ATM- and Rad3-related (ATR). ATM is activated by double strand breaks and ATR recruited to single stranded DNA coated with replication protein A, arising from DSBs or stalled DNA replication forks. ATR in turn activates Chk1 resulting in cell cycle arrest, promoting repair and preventing premature mitosis [89].

Disruption of the ATM/p53 pathway is observed in up to 70% of tumours and likely confers a growth advantage [90-92]. Disruption of the ATM pathway drives a reliance on the ATR pathway for DDR. Therefore inhibiting ATR in ATM deficient tumours may result in synthetic lethality [93].

### **6.1.VX-970:**

VX-970 is a potent and highly selective inhibitor of ATR. In a preclinical study VX-970 sensitized 80% of a panel of 35 lung cancer cell lines to cisplatin, with half of these demonstrating a greater than 10 fold increase in sensitivity. When the ATR inhibitor was compared to a Chk1 inhibitor the drugs displayed different sensitization profiles with VX-970 the most effective in combination with platinum and the Chk1 inhibitors most sensitizing to gemcitabine [94]. In the same study VX-970 increased sensitivity to cisplatin in six out of seven NSCLC PDX models [94]. In addition, ATR inhibitors have been shown to increase sensitivity to topoisomerase I inhibitors in

colorectal cancer cell lines *in vitro* and *in vivo* [95], rationalising the combination of ATR inhibitors and topotecan in early phase clinical trials in SCLC.

## 7. Lurbinectidin

Lurbinectidin is a novel anticancer drug that inhibits activated transcription, induces DNA double-strand breaks generating apoptosis, and modulates tumour microenvironment. The antitumor activity and safety of this agent in patients with SCLC has been assessed in three clinical trials: two phase I in combination with doxorubicin or paclitaxel and a phase II single-agent basket trial [96]. Activity is observed for single agent lurbinectidin (response rate 36%) and in combination (response rates from 37-71%). Haematological toxicity was significant with a grade 3/4 neutropenia rate of 38% for single agent lurbinectidin. A phase III trial in the second line setting of lurbinectidin in combination with doxorubicin compared with standard second line therapy (topotecan or cyclophosphamide, doxorubicin and vincristine) is ongoing (ATLANTIS Study - NCT0256699).

*DNA Damage and Therapeutics Figure 3.*

## 8. Perspectives

SCLC is a complex and heterogeneous tumour and the vast majority of patients will recur with a more resistant tumour. Several targeted agents have revolutionized the treatment of other cancers but despite decades of clinical trials none have been approved for clinical use. DDR inhibitors have demonstrated activity in patients with SCLC (see summary table 3), although to date none have emerged with sufficient efficacy for routine clinical use. There is an unmet need to identify biomarkers that can stratify patients into advantageous groups. In fact an important limitation with the majority of trials has been the use of unselected patients within a heterogeneous cancer, in other words, targeted agents for untargeted tumours.

Currently PARP inhibitors are approved for use in BRCA mutated ovarian cancer. BRCA mutations are rare in SCLC but scoring systems have been proposed to predict for a 'BRCA like' genomic environment [97, 98]. A novel 'DNA repair score' consisting of 17 DNA repair proteins, applied to SCLC cell lines and xenografts established that baseline activation of the PI3K/mTOR pathway is associated with resistance to the PARP inhibitor BMN673 [42]. Another biomarker, SLFN11 expression, is associated with PARP inhibitor sensitivity in SCLC cell lines and PDX models [44]. In addition, high levels of SLFN11 expression (H-score  $\geq 1$ ) were associated with a trend toward improved OS and favourable tumour responses in patients with recurrent SCLC that received TMZ and Veliparib as second line regiment, but not temozolomide plus placebo in a randomised phase II clinical trial [99] highlighting evident biomarkers that could guide clinical decision making.

These biomarkers are dynamic and longitudinal sampling will be required to tailor a personalised medicine approach. As a case in point, using co-clinical models of CTC derived explant or tumour biopsy derived explant tumours the expression of SLFN11 and MGMT, biomarkers for activity of olaparib and TMZ, respectively, did not consistently correlate with the tumour responses observed to these drugs in the donor patients [47]. Correlation of identified scoring systems in clinical studies of PARP inhibition in SCLC will be important to identify patients most likely to benefit from treatment.

In conclusion, exploration of biomarkers *in vivo*, from diagnostic tumour biopsies and liquid biopsies will be crucial in identifying patients who will derive clinical benefit from DDR inhibitors. While targeting DDR mechanisms is theoretically plausible the results from clinical trials to date have yet to convince. Further investigation into the synergistic effects of DDR inhibitors administered in combination with traditional DNA

damaging therapies will expand our understanding of how these agents are best positioned in the clinical setting and biomarker studies may provide insight into mechanisms of acquired and inherent resistance.

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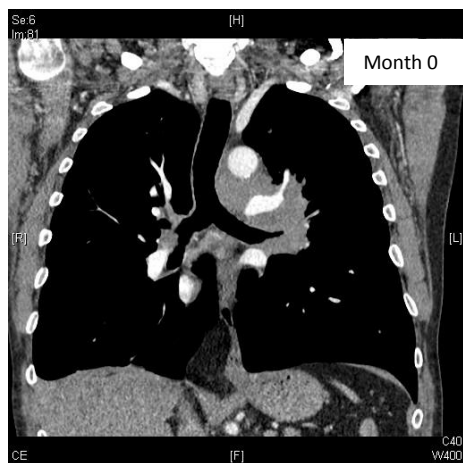
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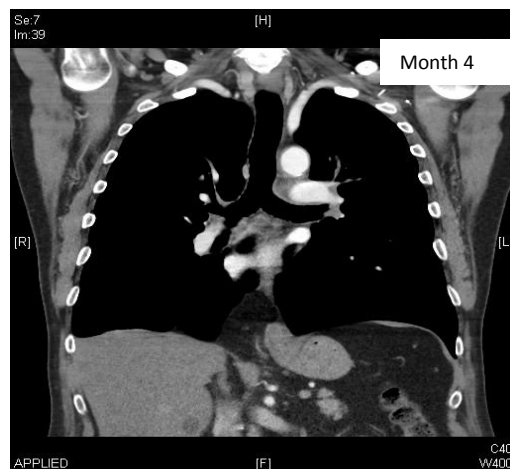
**Conflicts of Interest**

Fiona Blackhall has received consulting fees or honoraria from AstraZeneca, Pfizer, Boehringer-Ingelheim, Medivation, Novartis, MSD and BMS. Fiona Blackhall has received research funding from Abbvie, AstraZeneca, Amgen and IMSWorld.

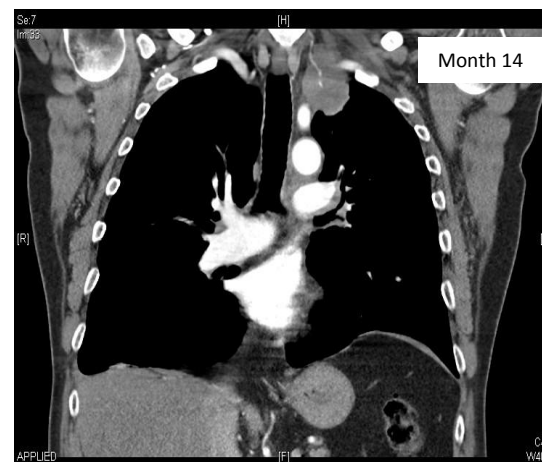
Figure



Baseline- Left hilar  
mediastinal disease



4 cycles of P/E chemotherapy.  
Partial response



Progressive disease- high  
mediastinal disease left



Post 4 cycles P/E  
chemotherapy rechallenge.  
Partial response

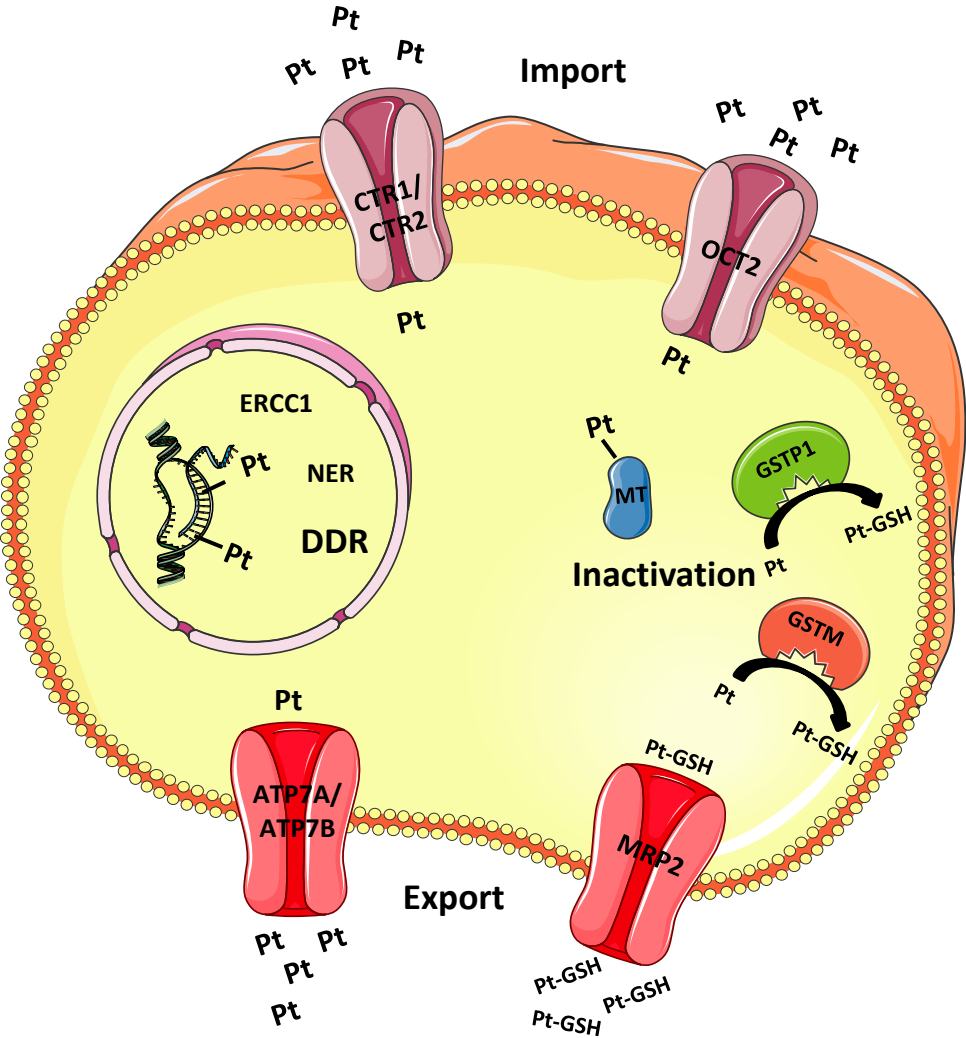


Progressive disease-  
high mediastinal/  
supraclavicular region



Post 4 cycles Topotecan.  
Partial response

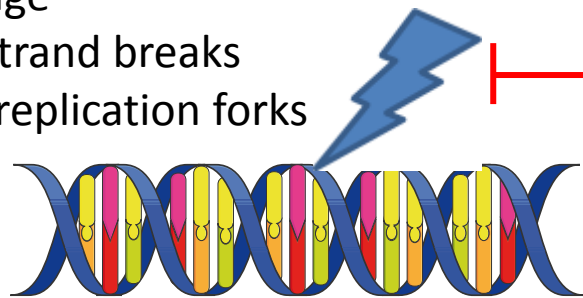
Figure



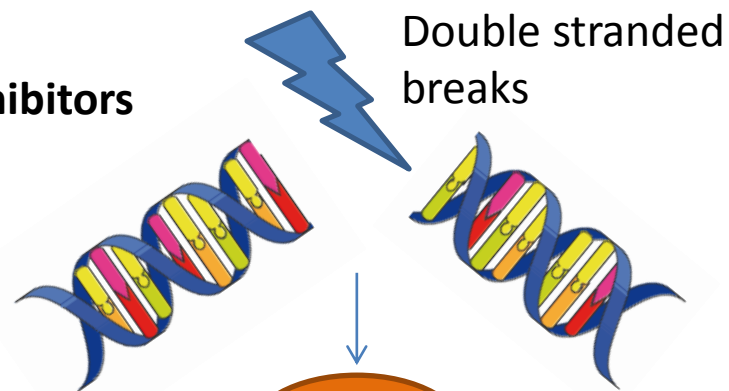
Figure

## DNA Damage-

- Single strand breaks
- Stalled replication forks



**PARP inhibitors**



**Double stranded breaks**

**VX 970**

**ATR**

**Wee1**

**AZD1775**

**Amuvatinib**

**DNA Repair**

- RAD51
- FANCE
- DNA-PK

**Chk1**

**Prexasertib**

**Aurora Kinase  
Inhibitors**

**Apoptosis**  
• p53

**Spindle assembly  
checkpoint**

**Replication  
fork control**

**Intra- S  
checkpoint**

**G2/M  
checkpoint**

**G1/S  
checkpoint**

**ATM**

**DNA Repair**  
• BRCA 1

**Chk2**

**Apoptosis**  
p53

Figure 1: CT images of disease during treatment for SCLC

Figure 2: Cellular fate of Cisplatin

Figure 3. DNA damage and therapeutics

Gene	Alteration	Pathway involved in	Consequence	Reference
TP53 (98%)	Inactivation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3, 18, 20]
RB1 (91%)	Inactivation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3, 18, 20]
RBL1 (6%)	Inactivation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3]
RBL2 (6%)	Inactivation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3]
TP73 (13%)	Activation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3]
CDKN2A (5%)	Inactivation	Cell Cycle Regulation	G1/S transition, proliferation, cell survival	[3]
KIT (6%)	Activation	Receptor kinase/PI3K signalling	Proliferation, cell survival, translation	[3].
FGFR1 (6%)	Activation	Receptor kinase/PI3K signalling	Proliferation, cell survival, translation	[3]
PTEN (9%)	Inactivation	Receptor kinase/PI3K signalling	Proliferation, cell survival, translation	[3]
EP300 (13%)	Inactivation	Transcriptional Regulation	Chromatin modifications	[3, 18, 20]
CREBBP (15%)	Inactivation	Transcriptional Regulation	Chromatin modifications	[3, 18, 20]
MYCL1 (9%)	Activation	Transcriptional Regulation	Cell cycle progression, cell growth	[3]
MYCN (4%)	Activation	Transcriptional Regulation	Cell cycle progression, cell growth	[3]
MYC (6%)	Activation	Transcriptional Regulation	Cell cycle progression, cell growth	[3]
NOTCH family genes (25%)	Inactivation	Notch signalling/neuroendocrine differentiation	Neuroendocrine markers	[3]
SOX2 (27%)	Amplification	Maintenance of pluripotency of stem cells	SCLC proliferation	[18]

Table 1: Genomic alterations in SCLC, percentages based on George et al.



Table

TARGET	COMPOUND	Phase	Patients	Estimated Enrollment	Primary Outcome	Status	CLINICAL TRIAL IDENTIFIER(S)
Wee1	AZD1775	II	Relapsed SCLC	45	ORR	Recruiting	NCT02593019
Wee 1	AZD1775	II	Relapsed Small Cell Lung Cancer Patients With MYC Family Amplification or CDKN2A Mutation Combined With TP53 Mutation	28	ORR	Not yet recruiting	NCT02688907
PARP	Veliparib in Combination With Carboplatin and Etoposide	II	Treatment-naïve Extensive Stage Disease Small Cell Lung Cancer	215	MTD RP2D	Recruiting	NCT02289690
PARP	Cisplatin and Etoposide With or Without Veliparib	II	Extensive Stage Small Cell Lung Cancer or Metastatic Large Cell Neuroendocrine Non-small Cell Lung Cancer	168	MTD PFS	Not actively recruiting	NCT01642251
PARP	Veliparib and Irinotecan Hydrochloride	I	Cancer That Is Metastatic or Cannot Be Removed by Surgery	48	MTD, OBD RP2D	Recruiting	NCT00576654
PARP	Liposomal Irinotecan and Veliparib	I	Solid Tumors	48	MTD Adverse events	Recruiting	NCT02631733
PARP	Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib	I/II	Relapsed/Refractory Small Cell Lung Cancer	75	MTD RP2D	Recruiting	NCT02769962
PARP	Olaparib Monotherapy	II	Relapsed Small Cell Lung Cancer Patients With BRCA 1/2 Mutations, ATM Deficiency or MRE11A Mutations	28	ORR	Recruiting	NCT03009682
PARP	Olaparib, Cediranib Maleate, and Standard Chemotherapy	II	Treatment naïve SCLC	PFS	132	suspended	NCT02899728
PARP	Cediranib in Combination With Olaparib	II	Advanced Solid Tumors	ORR	126	Recruiting	NCT02498613
PARP	Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib	I/II	Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers	ORR RP2D	338	Recruiting	NCT02484404

PARP	MEDI4736 in Combination With Olaparib	I/II	Advanced Solid Tumors	OCR Adverse events	147	Recruiting	NCT02734004
ATR Kinase	Safety, Tolerability, and Pharmacokinetics of VX-970 in Combination With Cytotoxic Chemotherapy	I	Advanced Solid Tumors	ORR safety	205	Recruiting	NCT02157792
ATR Kinase	Topotecan With VX-970, an ATR Kinase Inhibitor	I/II	Small Cell Cancers	MTD CRR	70	Recruiting	NCT02487095
Aurora A Kinase	Alisertib (MLN8237) in Combination With Paclitaxel Versus Placebo in Combination With Paclitaxel as	Ib/II	Second Line SCLC	PFS	178	Active, not recruiting	NCT02038647
Aurora A Kinase	Alisertib (MLN8237) in Combination With Weekly Paclitaxel	I/II	Advanced Solid Tumors		9	Completed	NCT02367352
CHK inhibitor	Prexasertib	II	Extensive Stage Disease Small Cell Lung Cancer	ORR	116	Active, not recruiting patients	NCT02735980

Table 2: Current clinical trials of DDR inhibitors in SCLC

**Table**

DDR pathway	Study Drug	Unique Identifier	Study Design	Patient Selection	No of Patients	Outcome	Ref
PARP Inhibitor	Olaparib maintenance after first line treatment	ISRCTN73164486	Phase II Randomised, double blind placebo controlled	SCLC, responded to first line combination chemotherapy	220	Olaparib did not improve PFS or OS Median PFS was 2.6 (90% CI 1.8, 3.7), 3.6 (90% CI 3.1, 6.0) and 3.6 (90%CI 3.1, 4.7) months in the placebo, olaparib bd and tds arms, respectively	[98]
PARP Inhibitor	Olaparib and Temozolomide	NCT02446704	Phase I/II	Relapsed advanced SCLC	13	ORR 46% Median PFS 5.6 months Phase II expansion now recruiting	[46]
PARP inhibitor	Veliparib and cisplatin/etoposide	NCT01642251 *	Phase I	Treatment naïve extensive SCLC	7	ORR 71% (5/7)	[50]
PARP inhibitor	Veliparib with cisplatin/etoposide vs Placebo with cisplatin /etoposide alone	NCT01642251 *	Phase I/II	Extensive SCLC	128	Median PFS 6.1 veliparib group vs 5.5 standard chemotherapy (HR 0.63 p0.01) Median OS 10.3 months veliparib vs 8.9 (HR 0.83 p0.07)	[51]
PARP inhibitor	Veliparib or placebo and Temozolomide	NCT01638546	Phase II Randomised	Relapsed SCLC	104	ORR 39% veliparib and placebo vs 14% placebo and temozolomide. PFS, OS no significant difference	[52]
PARP inhibitor	Talazoparib	NCT01286987	Phase I	Pretreated SCLC, Ewings Sarcoma and germline BRCA mutation carriers (gBRCAm)	Stage 2-Total 54 pts 15 SCLC 2ES 27 gBRCAm	Response in 2/11 (18%) SCLC patients Clinical Benefit Rate 55%	[99]
Aurora Kinase Inhibitor	Alisertib	NCT01045421	Phase II	Refractory solid tumours	Total 249 patients 60-SCLC 53- Breast Cancer 26-NSCLC	ORR 21% in SCLC patients (3 platinum sensitive+ 7 platinum resistant/48 SCLC patients) PFS 2.5months	[69]

					55-head and neck cancer 55-gastro-oesophageal cancer		
Aurora Kinase Inhibitor	Alisertib +paclitaxel vs Alisertib + placebo	NCT02038647	Phase II	Relapsed SCLC	178	PFS 101 days alisertib and paclitaxel vs 66 days paclitaxel and placebo. HR 0.71 p=0.038 No significant difference in OS	[68]
RAD51 inhibitor	Amuvatinib plus standard chemotherapy	NCT00881166	Phase IB	Treatment naïve or moderated pretreated [86]metastatic solid tumours	100	PR 12% (12/100) of which 4 had neuroendocrine tumours and 2 SCLC	[86]
RAD51 Inhibitor	Amuvatinib and carboplatin/etoposide	NCT01357395	Phase II	Relapsed or refractory SCLC	23	CBR (SD+PR) 12% (5/23)	[87]
Checkpoint Inhibitor	Prexasertib	NCT01115790	Phase I	Advanced refractory squamous, NSCLC, head and neck and anal cancer	45	PR 4.4% (2/45) SD 33% (15/45)	[73]
Wee1 Inhibitor	AZD1775 with cisplatin/carboplatin or gemcitabine	NCT00648648	Phase I	Refractory solid tumours	202	53% SD (95/176) 10% PR (17/176)	[75]

Table 3: Studies of DDR pathways in SCLC