PARP inhibitors for small cell lung cancer and their potential for integration into current treatment approaches

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Abstract: Small cell lung cancer (SCLC) is a very aggressive, highly lethal, neuroendocrine tumor that constitutes 15% of all lung cancer cases. It is characterized by its rapid disease progression and high relapse rate leading to poor survival for diagnosed patients. Recently, poly (ADP-ribose) polymerase inhibitors (PARPi) have emerged as a novel therapeutic strategy for SCLC. Preclinical studies have demonstrated that PARPi possesses cytotoxic activity as a single-agent and in combination with other anti-cancer agents. Predictive biomarkers of response to PARPi, such as SLFN11, have also been described in SCLC. This review aims to summarize the recent preclinical investigations and the relevant clinical trials that evaluate PARPi in SCLC. Here, we highlight the potential role of PARPi in a biomarker-selected manner and in combination with chemotherapy, targeted agents, radiotherapy and immunotherapy.

Keywords: Small cell lung cancer (SCLC); poly (ADP-ribose) polymerase inhibitors (PARPi); chemotherapy; radiation sensitizer; immunotherapy

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Introduction

Lung cancer has remained the most common cancer worldwide since 1985, with approximately 1.8 million new cases diagnosed each year (1,2). Among the major lung cancer subtypes, small cell lung cancer (SCLC) represents the sixth leading cause of cancer-related mortality, accounting for 13–15% of all lung cases (3,4). Clinically, SCLC is considered an aggressive and lethal high-grade neuroendocrine malignancy that is pathologically, molecularly, and biologically very distinct from other forms of lung cancer. Almost all SCLC cases have homozygous loss of RB1, which encodes the key regulator of the G1-S cell cycle checkpoint, and TP53, a gene critical for multiple DNA damage response (DDR) pathways (5-11). This can, in part, explain the initial responsiveness of SCLC to various DNA damaging agents, such as those that induce covalent DNA adducts and crosslinks [cisplatin, carboplatin, temozolomide (TMZ)], or those that produce single-strand/double-strand DNA breaks (ionizing radiation, etoposide, topotecan, irinotecan).

The standard of care for first-line treatment of SCLC consists of a platinum-based doublet chemotherapy regimen for all patients, concurrent with radiotherapy (RT) for those with limited-stage disease. Despite a high (70–80%) initial response rate to these first-line regimens, the 5-year overall survival (OS) rates for patients diagnosed with SCLC is a dismal 6.5% (12). Until 2019, with the exception...
of the FDA approval of atezolizumab with chemotherapy for extensive-stage SCLC (ES-SCLC) patients, the general treatment paradigm has remained unchanged for the previous several decades (13,14). Therefore, novel therapeutic interventions are needed and are an active area of research (15-17).

One such novel therapeutic are inhibitors of poly-(ADP)-ribose polymerase (PARP), which have demonstrated efficacy against SCLC in preclinical and clinical data over the past several years. Poly (ADP-ribose) polymerase inhibitors (PARPi) have the potential to enhance cytotoxic response to chemotherapy, radiotherapy, and immunotherapy in SCLC. This review will highlight the advances made in these areas.

Current application of PARPi in oncology

PARP is a family of proteins that orchestrate various cellular processes and have important roles in DNA repair and genome integrity. PARP1 activates base excision repair (BER) in response to DNA single-strand breaks (SSBs) where PARP1 binds to SSBs and facilitates the recruitment of DNA repair proteins. When PARP1 function is impaired, the BER process is halted and double-strand breaks (DSBs) develop due to a destabilized replication fork (18). As a result, malignancies deficient in the DSB repair pathway of homologous recombination (HR) are vulnerable to PARP inhibition. PARPi were first demonstrated to have efficacy in ovarian cancers with BRCA1/2 mutations—which are deficient in HR (19). Subsequently, PARPi clinical efficacy has extended to other histologies harboring BRCA1/2 mutations (19-27) with most PARPi carrying FDA approval for treating BRCA1/2-mutated ovarian and breast cancers (Table 1) (30-37).

The various PARPi generally have similar activity in their degree of polymerase inhibition, however, the PARPi differ in their ability to poison and trap PARP to the DNA SSB lesions which consequently devolve into cytotoxic DSBs upon DNA replication (38). Talazoparib has been demonstrated to be the most potent PARP trapper followed by niraparib, then olaparib and rucaparib, with veliparib being the least potent trapper (28,29). These differences between their potency in PARP trapping may inform their observed efficacy and side effect profiles.

Recently, studies have examined the utility of PARPi beyond BRCA1/2-mutant tumors (39). Several groups have demonstrated that large chromosomal structural alterations, characteristic of these BRCA1/2-mutant cancers, can be quantitated by three correlated HR deficiency (HRD) metrics: loss of heterozygosity (LOH), large-scale state transition (LST), and telomeric allelic imbalance (N_{AI}) (40-43). These HRD scores correlate with sensitivity to platinum agents of sporadic triple-negative breast and ovarian cancers (40-42,44,45). This suggests that PARPi may have therapeutic benefits in any malignancy harboring HRD independent of the canonical BRCA1/2 mutations. As BRCA mutations are rare (≤2%) in SCLC, this concept of non-BRCA dependent PARPi sensitivity lay the foundation for subsequent investigations (10,11).

PARP as a therapeutic target in SCLC

Pre-clinical evidence and studies

Rationale for PARPi in SCLC

In 2012, Byers et al. conducted a landmark study where reverse phase protein array (RPPA) for proteomic analysis of 34 SCLC and 74 non-SCLC (NSCLC) cell lines identified potential targets unique to SCLC. The analysis revealed that SCLC cell lines had high PARP1 protein expression relative to NSCLC. In addition, SCLC patient tumors demonstrated high PARP1 protein expression when compared to other neuroendocrine tumors and NSCLC. In vitro cell line drug response studies with olaparib and rucaparib confirmed that most SCLC cell lines tested were highly sensitive to treatment with PARPi in contrast to NSCLC cell lines (46). However, PARPi drug sensitivity was not universal for all SCLC cell lines tested. Therefore, interest towards identifying molecular mechanisms of sensitivity as potential predictive biomarkers increased.

Potential predictive biomarkers of PARPi response

Schlafen family member 11 (SLFN11) was recently identified as a putative predictive biomarker for SCLC sensitivity to PARPi. Multiple independent groups demonstrated that high SLFN11 gene or protein expression levels positively correlate with increased PARPi treatment sensitivity (47-51). Polley et al. examined 63 SCLC cell-lines in response to treatment with multiple PARPi (talazoparib, olaparib, niraparib, rucaparib, AZD-2461) in their screen of 103 FDA approved oncology drugs and 423 investigational agents (47). Results indicated that increased gene expression of SLFN11 correlated with decreased IC_{50} (i.e., inhibitory concentration producing 50% growth inhibition) values to all tested PARPi (R=−0.42). Of note, expression levels of neither PARP1 nor PARP2 had any predictive value (47).
| Drug          | Date of FDA Approval | Population                                      | Indication                                                                 | Dosing     | References   | Specificity | Ki      | Relative trapping capacity (28,29) |
|--------------|----------------------|-------------------------------------------------|---------------------------------------------------------------------------|------------|--------------|-------------|---------|-----------------------------------|
| Olaparib     | 2017                 | gBRCAm advanced ovarian cancer                  | Received three or more prior lines of chemotherapy                        | 300 mg BID | (30)         | PARP1, PARP2 | 5 nM, 1 nM | +++                              |
|              | 2018                 | Recurrent epithelial ovarian, fallopian tube, primary peritoneal cancer | Tumors must have CR/PR to platinum-based chemotherapy                      | 300 mg BID | (31)         |             |         |                                   |
|              | 2018                 | gBRCAm HER2-negative metastatic breast cancer   | Previous treatment with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting | 300 mg BID | (32)         |             |         |                                   |
|              | 2019                 | gBRCAm metastatic pancreatic adenocarcinoma     | No disease progression after 16 weeks of a first-line platinum-based chemotherapy regimen | 300 mg BID | (30)         |             |         |                                   |
| Rucaparib    | 2018                 | Recurrent epithelial ovarian, fallopian tube, primary peritoneal cancer | Tumors must have CR/PR to platinum-based chemotherapy                      | 600 mg BID | (33)         | PARP1       | 4 nM    | +++                              |
| Niraparib    | 2017                 | Recurrent epithelial ovarian, fallopian tube, primary peritoneal cancer | Tumors must have CR/PR to platinum-based chemotherapy                      | 300 mg QD  | (34)         | PARP1, PARP2 | 3.2 nM, 4 nM | ++++                             |
|              | 2019                 | Advanced ovarian, fallopian tube, primary peritoneal cancer with HRD-positive status | Previous treatment with three or more chemotherapy regimens               | 300 mg QD  | (35)         |             |         |                                   |
| Talazoparib  | 2018                 | gBRCAm HER2-negative breast cancer, locally advanced or metastatic | Patient selection for therapy is based on FDA-approved companion diagnostic for talazoparib | 1 mg QD    | (36)         | PARP1, PARP2 | 1.2 nM, 0.9 nM | ++++++                           |

Data as of February 2020. PARP, poly (ADP-ribose) polymerase; gBRCAm, germline BRCA-mutated; CR, complete response; PR, partial response; BID, twice daily; QD, once daily; Ki, catalytic inhibitory constant; HRD, homologous recombination deficiency; HER2, human epidermal growth factor receptor 2.
Similarly, a significant correlation between \textit{SLFN11} expression levels and response to talazoparib was identified in a study by Murai \textit{et al.} (48). Importantly, the relationship between \textit{SLFN11} expression and PARPi sensitivity was determined to be causal, where CRISPR-mediated genetic knockout of \textit{SLFN11} in 4 cell lines with high \textit{SLFN11} (prostate DU145, leukemia CCRF-CEM and MOLT4, and Ewing's sarcoma EW8) resulted in resistance to both talazoparib and olaparib relative to their parental cell lines. Further confirmation was achieved when exogenous expression of \textit{SLFN11} was induced in leukemia K562 cells (that have low \textit{SLFN11} endogenous transcript) and resulted in hypersensitivity to both talazoparib and olaparib. Murai \textit{et al.} concluded that \textit{SLFN11} is a dominant determinant of PARPi sensitivity in these cancer cells (48).

Specific to SCLC, Lok \textit{et al.} observed that \textit{SLFN11} gene and protein expression levels correlated to PARPi response in SCLC cell lines and patient-derived xenograft (PDX) mouse models (49). The study showed that high expression of \textit{SLFN11} positively correlated with increased sensitivity to various PARPi (i.e., olaparib, rucaparib, veliparib, and talazoparib) in cell line datasets. Functionally, genetic knockdown and knockout of \textit{SLFN11} in SCLC cell lines conferred resistance to PARPi. Immunohistochemical (IHC) staining of \textit{SLFN11} confirmed these findings in multiple PDX models treated with talazoparib (49). These studies suggested that \textit{SLFN11} could be used as a predictive biomarker of response to PARPi monotherapy in SCLC.

Stewart \textit{et al.} reported that there may be two potential biomarkers (\textit{SLFN11} and ATM) with predictive capability of PARPi response in SCLC. In this study, 170 proteins quantified by RPPA were investigated as potential predictive biomarkers in response to single-agent treatment with talazoparib. Results revealed that low ATM and high \textit{SLFN11} protein expression were significantly associated with treatment response in SCLC PDX models. While high CHK1, IGF1R beta, and IRS1 protein levels correlated with resistance. These findings were validated at the mRNA level which showed the strongest association between talazoparib response and high \textit{SLFN11}, low ATM, and low \textit{CHEK1} expression in SCLC PDX models (50).

Multiple laboratories have investigated the mechanisms by which \textit{SLFN11} may confer PARPi sensitization (52-54). Mu \textit{et al.} reported the interaction of \textit{SLFN11} with replication protein A (RPA) led to the suppression of HR. \textit{SLFN11} destabilized RPA1-ssDNA complexes necessary for efficient downstream DNA repair by HR (52). Murai \textit{et al.} observed that \textit{SLFN11} was recruited to DNA damage sites where it binds with RPA and subsequently to the minichromosome maintenance protein complex (MCM) DNA helicase that is essential for DNA replication. Although \textit{SLFN11} did not directly engage in replication initiation, \textit{SLFN11} unwound heterochromatin, blocked the progression of the replication fork, and ultimately hindered the DNA repair process (53). Li \textit{et al.} reported indirect inhibition of ATM and ATR protein synthesis by \textit{SLFN11}. The absence of these DNA repair proteins promoted sensitization to the effects of DNA damaging agents (54). Continued investigation into the contribution of these mechanisms to PARPi sensitivity would be of considerable basic and translational interest as these therapeutics are being actively investigated in multiple clinical trials of several histologies, including SCLC.

**Clinical evidence and studies**

**Single-agent PARPi trials**

In a phase I trial (NCT01286987), 113 patients with recurrent breast, ovarian, prostate, and pancreatic cancers containing deficiencies in DNA repair pathways were recruited, in addition to 23 relapsed SCLC patients. This study was designed to assess the safety and efficacy of talazoparib monotherapy. The dose escalation cohort of this study evaluated 39 patients, none of which were SCLC, and determined the maximum tolerated dose (MTD) to be 1.0 mg of talazoparib daily. The subsequent cohort of this study assessed 71 patients, including all 23 SCLC patients, who were administered talazoparib 1.0 mg daily. Talazoparib demonstrated the highest bioavailability and anti-tumor activity in patients presenting with \textit{BRCA} mutations [objective response rate (ORR) >40%] (55). Of the 23 SCLC patients, 2 patients had a partial response (ORR =9%) that lasted between 3–4 months. Both patients previously had an objective response to prior platinum therapy and were platinum-free for up to 6 months. The median progression-free survival (PFS) of these patients was 11.1 weeks [95\% confidence interval (CI): 4.3–13.0 weeks]. An additional 4 SCLC patients had stable disease (SD) that lasted at least 16 weeks [clinical benefit rate (CBR), 26% >16 weeks] (55). These data suggest that incorporating a predictive biomarker to select SCLC patients that may benefit from PARPi monotherapy would be prudent.

As such, there is an ongoing biomarker-selected PARPi monotherapy phase II clinical trial (NCT03009682), investigating the efficacy of olaparib in relapsed SCLC patients whose tumors harbor mutations in HR-related
genes including BRCA1/2, ATM, BLM, MRE11, RAD50, NBN, RAD51, RAD51 paralogs, RECQL family members, and other deleterious HR pathway alterations. Results from this biomarker informed clinical trial are eagerly awaited (summarized in Table 2).

Given that the benefit of single-agent PARPi for SCLC therapy may have limited efficacy outside of biomarker-selected patients, combining PARPi with other therapeutics is a rational next step. In subsequent sections, we will review the landscape of PARPi combination studies with chemotherapy, targeted therapeutics, radiotherapy and immunotherapy.

**PARPi and drug combinations in SCLC**

Chemotherapy remains the standard of care for treating SCLC patients. ES-SCLC patients treated with chemotherapy have a low median survival of about 10 months (63,64) with immunotherapy increasing that to about 12 months (65,66). There is a critical need to improve treatment efficacy and outcomes for SCLC patients that PARPi may be able to contribute toward. Several preclinical studies demonstrated that PARPi chemosensitizes SCLC. These data informed the subsequent development of related clinical trials.

**Preclinical evidence and studies**

Byers et al. first reported that the addition of olaparib to the standard platinum-based chemotherapy regimen, cisplatin and etoposide (CE), potentiated the anti-tumor effects in SCLC (46). Owonikoko et al. similarly reported synergism between veliparib combined with a platinum-based agent (cisplatin/carboplatin) and etoposide in SCLC cell lines as well as xenograft mouse models (67). Teicher et al. demonstrated enhanced sensitivity to carboplatin/etoposide treatment with talazoparib in some SCLC cell lines (68). Several preclinical reports indicated that PARPi can also sensitize SCLC to other chemotherapeutic agents. For example, Murai et al. observed that talazoparib sensitizes cancer cells to the DNA-alkylating agent TMZ, and that sensitization was dependent on SLFN11 expression (48). Lok et al. also found evidence of synergy to the combination of talazoparib and TMZ (49).

Beyond PARPi combinations with chemotherapy, multiple groups have examined combining novel targeted therapies with PARPi (69-71). Lallo et al. showed that the combination of PARP inhibitor olaparib and WEE1 inhibitor adavosertib (AZD1775) can significantly improve the efficacy of the single-agent activity of olaparib in SCLC circulating tumor cell patient-derived xenografts (CDX) (69). A study in abstract form by Gay et al. also demonstrated synergism between an ATR inhibitor (AZD6738) and olaparib that increased the cytotoxic effects in SCLC cell lines (70). While Sen et al. indicated that a CHK1 inhibitor (LY2606368) synergizes with olaparib to decrease cell viability and cause tumor regression in a triple-knockout RB⁻/⁻/p53⁻/⁻/p130(RPP) genetically engineered mouse model (GEMM) (71). These studies collectively demonstrated the potential of a combinatorial approach as an effective therapeutic strategy for the incorporation of PARPi into the management of SCLC.

**Clinical evidence and studies**

**PARPi combination trials with cisplatin and etoposide**

The combination of chemotherapy and PARPi has been studied in clinical trials. Two independent studies evaluated the feasibility of veliparib in combination with CE as a therapeutic strategy in SCLC (59,60). Owonikoko et al. completed a phase I/II clinical trial (NCT01642251) to evaluate the safety and efficacy of veliparib combined with CE in SCLC patients. A total of 128 ES-SCLC patients were recruited and treated with four cycles of CE along with veliparib or placebo. The toxicities were balanced between the two treatment groups with the exception of higher grade 3+ lymphopenia (8% vs. 0%; P=0.06) and neutropenia (49% vs. 32%; P=0.08) in the veliparib group compared to placebo. The primary endpoint of the study was to examine if the veliparib combination would reduce the PFS hazard ratio by 37.5% as analysed by a one-sided log rank test with an α of 0.10. Results demonstrated a higher median PFS (6.1 vs. 5.5 months; one-sided P value =0.06) and median OS (10.3 vs. 8.9 months; P=0.17) in the veliparib group, which indicated that the addition of veliparib may improve current CE treatment (59). In another phase I dose-escalation study (NCT 02289690), Atrafi et al. reported that 16 of the 25 ES-SCLC patients (64%) had confirmed responses to the combination of veliparib and carboplatin/etoposide with this proportion increasing to 83% (5 of 6) of SCLC patients treated at the recommended phase II dose of veliparib. To date, the phase II portion of this study is ongoing (60).

**PARPi combination trials with TMZ**

Farago et al. reported a phase I/II clinical trial (NCT02446704), where the phase II of this study
Table 2 Clinical trials of PARP inhibitors in SCLC

| PARPi   | Phase | Treatment | Patient selection criteria                                                                 | Number of SCLC patients enrolled | Study start year | Trial status          | NCT number       | Associated references |
|---------|-------|-----------|------------------------------------------------------------------------------------------|----------------------------------|------------------|-----------------------|-------------------|----------------------|
| **Monotherapy** |       |           |                                                                                         |                                  |                  |                       |                  |                      |
| Olaparib | II    | N/A       | Relapsed SCLC patients harboring HR-pathway gene mutations                                | 28                               | 2016             | Recruiting           | NCT03009682       | N/A                  |
| Niraparib | III   | N/A       | Patients with ES-SCLC                                                                     | 591                              | 2018             | Recruiting           | NCT03516084       | N/A                  |
| Talazoparib | I     | N/A       | Patients with advanced tumors with HR mutations                                          | 23                               | 2011             | Completed            | NCT01286987       | (55)                 |
| **PARPi + drug combination** |       |           |                                                                                         |                                  |                  |                       |                  |                      |
| Olaparib | I/II  | TMZ       | Patients with previously treated SCLC                                                     | 50                               | 2015             | Recruiting           | NCT02446704       | (56)                 |
|          | I     | Adavosertib | Patients with relapsed SCLC                                                              | 15                               | 2015             | Completed            | NCT02511795       | (57)                 |
|          | I     | CLRX101    | Patients with relapsed SCLC                                                              | 123                              | 2016             | Recruiting           | NCT02769962       | N/A                  |
|          | II    | Cediranib   | Patients with stage III SCLC                                                             | 126                              | 2016             | Recruiting           | NCT02498613       | N/A                  |
|          | II    | Cediranib maleate | SCLC patients with stable disease after initial therapy                                 | 132                              | 2017             | Suspended            | NCT02899728       | N/A                  |
|          | II    | Ceralasertib | Patients with platinum refractory ES-SCLC                                                | 72                               | 2016             | Active, not recruiting | NCT02937818       | N/A                  |
|          | II    | Ceralasertib | Patients with relapsed SCLC                                                              | 45                               | 2018             | Recruiting           | NCT03428607       | N/A                  |
| Veliparib | II    | TMZ       | Patients who have returned or have not responded to TMZ                                  | 104                              | 2012             | Completed            | NCT01638546       | (58)                 |
|          | I/II  | Cisplatin and Etoposide | Patients with ES- SCLC                                                                  | 128                              | 2012             | Completed            | NCT01642251       | (59)                 |
|          | I/II  | Carboplatin and Etoposide | Patients with ES- SCLC                                                                  | 25                               | 2014             | Completed            | NCT02289690       | (60)                 |
|          | I/II  | Topotecan  | Patients sensitive or refractory to chemotherapy                                         | 30                               | 2016             | Recruiting           | NCT03227016       | N/A                  |
| Niraparib | Ib/Ii | TMZ       | Patients with ES-SCLC with a response to chemotherapy                                    | 64                               | 2019             | Recruiting           | NCT03830918       | N/A                  |
| Pamiparib | I/II  | TMZ       | Patients with SCLC                                                                       | N/A                              | 2017             | Recruiting           | NCT03150810       | N/A                  |
| Rucaparib | I/II  | PLX038    | Patients with SCLC                                                                       | 62                               | 2020             | Not yet recruiting   | NCT04209595       | N/A                  |
| Talazoparib | II    | TMZ       | Patients with previously treated ES-SCLC                                                  | 28                               | 2018             | Recruiting           | NCT03672773       | N/A                  |
|          | II    | ZN-c3     | Patients with SCLC                                                                       | N/A                              | 2019             | Recruiting           | NCT04158366       | N/A                  |

Table 2 (continued)
| PARPi   | Phase | Treatment | Patient selection criteria                                                                 | Number of SCLC patients enrolled | Study start year | Trial status     | NCT number       | Associated references |
|---------|-------|-----------|-------------------------------------------------------------------------------------------|----------------------------------|------------------|------------------|-------------------|-----------------------|
| **PARPi + RT**                                                                                               |                                   |                                |                   |
| Olaparib | I     | RT        | Patients with ES-SCLC                                                                    | 24                               | 2018             | Recruiting      | NCT03532880       | N/A                   |
| Olaparib | I     | RT + durvalumab | Patients with ES-SCLC                                                                      | 54                               | 2019             | Recruiting      | NCT03923270       | N/A                   |
| Talazoparib | I   | RT         | Patients with ES-SCLC                                                                    | 24                               | 2020             | Not yet recruiting | NCT04170946     | N/A                   |
| **PARPi + ICB**                                                                                               |                                   |                                |                   |
| Olaparib | II    | PD-L1 ab MEDI4736 | Patients with prior platinum-based chemotherapy and 60% have chemo-resistance          | 20                               | 2015             | Recruiting      | NCT02484404       | (61)                  |
| Olaparib | I/II  | PD-L1 ab MEDI4736 | Patients with relapsed SCLC                                                              | N/R                             | 2016             | Recruiting      | NCT02734004       | (62)                  |
| Pamiparib | I    | PD-1 ab tislelizumab | Patients with ES-SCLC                                                                    | N/R                             | 2016             | Recruiting      | NCT02660034       | N/A                   |
| Rucaparib | II   | PD-1 ab nivolumab | Patients with platinum-sensitive SCLC                                                   | 36                               | 2019             | Recruiting      | NCT03958045       | N/A                   |

Adavosertib (AZD1775), WEE1 inhibitor; ZN-c3, WEE1 inhibitor; Ceralasertib (AZD6738), ATR inhibitor; CLRX, nanoparticle of camptothecin; Cediranib (Pubchem CID: 9933475) and Cediranib maleate (Pubchem CID:11226834), VEGF receptor tyrosine kinase inhibitor; PLX038, a peglated prodrug of SN38 (an antineoplastic drug); Pamiparib (BGB290), PARP inhibitor; Tislelizumab (BGB-A317), PD1 antibody. Data as of February 2020. SCLC, small cell lung cancer; ES-SCLC, extensive stage small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; HR, homologous recombination; TMZ, temozolomide; RT, radiotherapy; ICB, immune checkpoint blockade; ab, antibody; PD-L1, programmed-death ligand 1; PD-1, programmed cell death-1; N/A, not applicable; N/R, not reported.
consisted of 50 patients that were administered 200 mg of olaparib orally twice daily combined with 75 mg/m² of TMZ daily on days 1–7 per 21 days. Results from this study showed an ORR of 41.7%, PFS of 4.2 months, and OS of 8.5 months (56).

Another phase II, randomized, double-blinded clinical study conducted by Pietanza et al. (NCT01638546) also showed the promise of PARPi in SCLC therapy. In their study, 104 patients with recurrent SCLC were recruited and treated with either TMZ 150–200 mg/m² on days 1–5 per 28 days in combination with veliparib 40 mg twice daily or placebo for days 1–7 per 28 days. Although the results showed no significant differences in 4-month PFS and OS between the two groups, significant differences were observed in the ORR where patients receiving TMZ/veliparib had a higher ORR than TMZ alone (39% vs. 14%; P=0.016). Interestingly, in an exploratory analysis, significantly prolonged PFS and OS was observed in the TMZ/veliparib treated patients with high protein expression of SLFN11 (58).

PARPi combination trials with other drugs

In addition to combination studies of PARPi with first-line chemotherapeutic agents, clinical trials evaluating the efficacy of other drug combinations with PARPi for SCLC are currently ongoing. In a phase I clinical study (NCT02511795) of 15 relapsed SCLC patients, the relative safety of olaparib in combination with adavosertib is being evaluated (57). Other clinical trials that are ongoing include a phase II study (NCT02498613) of olaparib and cediranib (VEGF inhibitor) in multiple cancer histologies, including SCLC, and a phase II trial (NCT03227016) of veliparib and topotecan in SCLC patients sensitive or refractory to chemotherapy (summarized in Table 2).

PARPi and RT in SCLC

RT is an effective treatment strategy for various cancers and has been proven to improve local tumor control and survival rates for limited-stage SCLC patients when combined with chemotherapy (72,73), while reports of the effectiveness of thoracic RT for ES-SCLC have been mixed (74–76). Results from a phase III randomized clinical study by Slotman et al. in 495 ES-SCLC patients reported that consolidative radiation therapy (cRT; 30 Gy/10 fractions over 2 weeks) to the thorax when added to prophylactic cranial irradiation (PCI) significantly improved the secondary endpoints of PFS at 6 months (24% vs. 7%, P=0.001) and OS at 2 years (13% vs. 3%, P=0.004) but not its primary endpoint of OS at 1 year (33% vs. 28%, P=0.066) (75). In another clinical study (RTOG0937), 86 ES-SCLC patients were randomized to PCI alone or to cRT (45 Gy/15 fractions over 3 weeks) to intrathoracic disease and up to 4 extracranial metastases in addition to PCI. This more aggressive RT strategy did not improve OS at 1 year (60.1% in PCI alone vs. 50.8% in PCI + cRT) (76). With these mixed results for the role of RT in ES-SCLC, novel strategies to understand and improve the application of RT for SCLC patients are warranted.

Pre-clinical evidence and studies

PARP1 plays a crucial role in several DDR pathways, and inhibiting the function of PARP1 perturbs the cell's ability to respond to RT-induced DNA damage. Indeed, Owonikoko et al. showed that SCLC cell lines were significantly sensitized to RT when combined with veliparib (67). PARP trapping also contributed to radiosensitization as documented by Laird et al. who observed that increased radiosensitization of SCLC cell lines and PDXs was most prominent with the more potent PARP trapper, talazoparib, as compared to veliparib, a lower potency PARP trapper (77). In addition to understanding the mechanisms by which radiosensitivity is achieved, pharmacodynamic imaging biomarkers may also help advance the application of PARPi in these settings (78,79).

Clinical evidence and studies

PARPi combination trials with radiotherapy

The preclinical data led to the development of a phase I clinical trial (NCT03532880) to assess the safety of olaparib with cRT in SCLC patients. In this trial, ES-SCLC patients that have undergone 4–6 cycles of a platinum-based agent and etoposide are being recruited. Patients will receive varying doses (ranging from 0 to 300 mg) of olaparib orally, twice daily, and cRT (30 Gy/10 fractions) similar to the Slotman et al. study (75). In addition, a similarly designed phase I study (NCT04170946) will examine this approach with talazoparib combined with the same cRT dose in ES-SCLC patients (summarized in Table 2). Of note, there are studies of olaparib in combination with RT in other histologies that are out of the scope of this review, but are listed here (NCT01562210, NCT02227082,
NCT02229656).

**PARPi and immune oncology in SCLC**

Increasing evidence demonstrates the cGAS-STING pathway as a relevant mechanistic link between DNA damage and innate immune activation (80,81). The activation of the cGAS-STING pathway leads to the recruitment and phosphorylation of TANK binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF-3), which ultimately activates the production of type I interferons (IFNs) (82). The secretion of IFNs, along with several other chemokines, promotes the recruitment of cytotoxic CD8+ T lymphocytes to tumor sites to effectively kill cancer cells (83).

Harding *et al.* demonstrated that DNA damage mediates innate immune activation in a cell cycle and cGAS-STING dependent manner. The inhibition of cell cycle progression or the impairment of the cGAS-STING pathway resulted in the loss of innate immune activity (80). Similarly, results from Mackenzie *et al.* highlighted the role that genomic instability plays in driving the formation of micronuclei following DNA damage where the cGAS molecule enters and triggers the subsequent downstream STING phosphorylation during the telophase of the cell cycle (81).

**Preclinical evidence and studies**

These findings prompted the investigation of novel approaches to harness DNA damage-induced innate immune activation for cancer therapy. Olaparib was subsequently reported by Sen *et al.* to activate the cGAS-STING pathway in SCLC, which enhanced the phosphorylation of TBK1 and IRF3 and ultimately stimulated the secretion of chemokines CCL5 and CXCL10. Olaparib also significantly increased the protein and surface expression levels of programmed-death ligand 1 (PD-L1) in SCLC models. The combination of olaparib and an anti-PD-L1 antibody was further evaluated in RPP immune-competent GEMMs. An evident increase in CD8+ cytotoxic T cell infiltration was accompanied by a decrease in tumor volume in these models (84).

**Clinical evidence and studies**

**PARPi combination trials with immunotherapy**

Despite these promising preclinical findings, a recent clinical trial (NCT02484404) by Thomas *et al.* found that the combination of olaparib and a PD-L1 inhibitor (durvalumab) had modest efficacy. In this trial, 20 relapsed ES-SCLC patients were treated with 300 mg of olaparib twice a day and 1,500 mg of durvalumab every four weeks. Only 2 (10.5%) of the evaluable 19 patients had a complete or partial response to this treatment; the median PFS was 1.8 months. Grade 3 or 4 adverse effects were reported in 45% patients, with most being hematologic (61). In another phase II study (NCT02734004) that included 38 relapsed SCLC patients, Krebs *et al.* reported in abstract form that the combination of olaparib and durvalumab was well tolerated and 2 patients had confirmed partial or complete responses, however the primary endpoint of disease control rate (complete response, partial response and stable disease) at 12 weeks of 29% was in the futility region for this Bayesian designed study (62). An additional phase I trial (NCT02660034) that also includes relapsed SCLC is currently ongoing to assess the safety of PARP inhibitor pamiparib (BGB290) combined with anti-PD1 antibody tislelizumab (BGB-A317) (summarized in Table 2). Additional research is needed to optimize these novel immunotherapy-based combinations.

**Conclusions**

The prognosis for patients diagnosed with SCLC remains poor due to the aggressive nature and the frequent acquired resistance of this disease. The lack of effective and durable therapies contributes to its grim prognosis. Continual advances in our understanding of SCLC biology has shed light on targetable vulnerabilities, including PARP. Preclinical and growing clinical evidence suggest that PARPi can enhance treatment response in SCLC by acting as sensitizers of chemotherapy, targeted therapies, radiotherapy, and immunotherapy. Additionally, identifying biomarkers of SCLC treatment response to PARPi may optimize patient selection strategies. PARPi could be part of a future wave of novel therapeutics with the potential to impact SCLC patient outcomes.

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