

# Current Evidence and Future Perspectives about the Role of PARP Inhibitors in the Treatment of Thoracic Cancers

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**Abstract:** In recent years, poly (ADP-ribose) polymerase (PARP) inhibition has become a promising therapeutic option for several tumors, especially for those harboring a BRCA 1–2 mutation or a deficit in the homologous recombination repair (HRR) pathway. Nevertheless, to date, PARP inhibitors are still not largely used for thoracic malignancies neither as a single agent nor in combination with other treatments. Recently, a deeper understanding of HRR mechanisms, alongside the development of new targeted and immunotherapy agents, particularly against HRR-deficient tumors, traced the path to new treatment strategies for many tumor types including lung cancer and malignant pleural mesothelioma. The aim of this review is to sum up the current knowledge about cancer-DNA damage response pathways inhibition and to update the status of recent clinical trials investigating the use of PARP inhibitors, either as monotherapy or in combination with other agents for the treatment of thoracic malignancies. We will also briefly discuss available evidence on Poly(ADP-Ribose) Glycohydrolase (PARG) inhibitors, a novel promising therapeutic option in oncology.

**Keywords:** lung cancer, PARP inhibitors, PARG inhibitors, homologous recombination repair, malignant pleural mesothelioma, targeted treatment

## Introduction

Thoracic malignancies have emerged as models for development of novel targeted therapies due to a deeper understanding of key molecular alterations driving tumor development and progression, in particular considering oncogene-addicted non-small-cell lung cancer (NSCLC):<sup>1</sup> it is estimated that around 70% of advanced NSCLC patients have druggable mutations in numerous genes, including epithelial growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), Kirsten rat sarcoma virus (*KRAS*), V-raf murine sarcoma oncogene homolog B1 (BRAF), *MET*, human epidermal growth factor receptor (HER2), and others. On the other hand, the identification of novel targetable alterations is still an unanswered need considering small-cell lung cancer (SCLC) and malignant pleural mesothelioma (MPM).

In recent years interest in developing drugs targeting mutations in different mechanisms involved in DNA repair is growing: poly (ADP-ribose) polymerases (PARP) and genes related to DNA homologous recombination repair (HRR) are crucially involved in the process of protecting cells from DNA damaging agents such as chemotherapy or ionizing radiation.

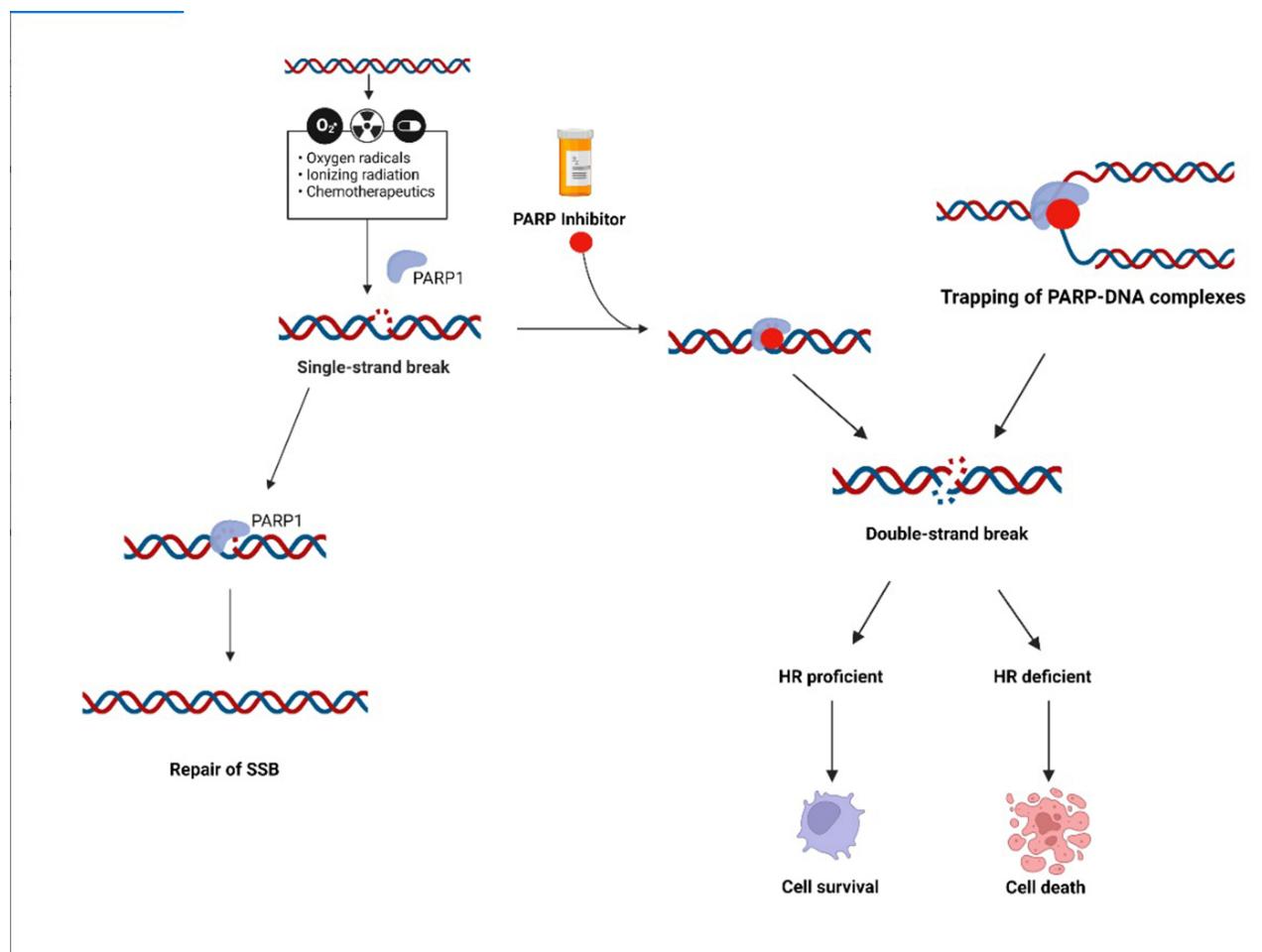
In particular, the DNA repair mechanisms involved in maintaining genomic integrity can be divided into base-excision repair (BER), nucleotide-excision repair (NER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end-joining (NHEJ) recombination repair. Poly (ADP-ribose) polymerase-1 and -2 (PARP-1 and PARP-2) are nuclear enzymes that synthesize ADP-ribose polymers using Nicotinamide Adenine Dinucleotide (NAD)<sup>+</sup> as a substrate; PARP-1 and -2 are essential components of BER, responsible for the protection of DNA damage induced by

radiation and monofunctional alkylating agents.<sup>2</sup> In addition, some damage to DNA can be repaired directly; for example, methylation of guanine bases is directly reversed by the protein O6-methylguanine DNA methyltransferase (MGMT).

Poly(ADP-ribose) glycohydrolase (PARG) antagonizes the action of PARP enzymes, hydrolyzing the ribose-ribose bonds present in poly(ADP-ribose). Similarly to PARPs, PARG is involved in DNA replication and repair and PARG depleted/inhibited cells seem to be much more sensitive to DNA damaging agents exposure, thus providing an increased storage of perturbed replication intermediates which can lead to synthetic lethality. Moreover, PARG shares a main role in parthanatos, a caspase-independent cell death modality.<sup>3</sup> Although agents able to specifically target PARP enzyme, universally known as PARP inhibitors (PARPi), have been initially developed for the treatment of BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2) mutated tumors, they are now being explored in a wide variety of cancers presenting somatic deficiencies within the HRR pathways (Figure 1).<sup>4</sup>

Therefore, BRCA mutation and HRR status are exploited as biomarkers of PARPi response and the evaluation for the HRR-signature is currently of great interest in scientific research given its promising therapeutic implications.

The synthetic lethal interaction between PARP inhibitors and BRCA1/2 mutations has been documented since the first human clinical trial of PARP inhibitor olaparib in 2009. In the next few years olaparib was approved for ovarian, breast, and pancreatic cancer in 2014, rucaparib for ovarian cancer was approved in 2016, and niraparib for ovarian cancer was approved in 2017. In 2018, talazoparib was approved for breast cancer treatment.<sup>5</sup>



**Figure 1** PARP inhibitor, mechanism of action. Chemotherapy, ionizing radiation can promote single-strand breaks (SSB) in the DNA. PARP, through the pathway of base excision repair (BER), is involved in SSB repair. In the presence of a PARP inhibitor the SSB cannot be repaired by BER pathway and can be turned into a double-strand break (DSB). The homologous recombination (HR) pathway is involved in DSB repair. A HR-deficient cell cannot repair DSB, the DSB accumulation is toxic and causes apoptosis and cell death. Created with BioRender.com.

Although the introduction of PARPi as monotherapy or in combination with chemotherapy has proven to be ineffective in thoracic tumors, a thorough exploration of these new drugs in the biological and immunological landscape underlying HRR-deficient cancers is auspicious considering the advent of new targeted therapy and immunotherapeutic agents.

In this regard, although nowadays immunotherapy represents a solid therapeutic option in most thoracic malignancies, there are still a lot of patients getting no benefit from it due to a “cold” tumor microenvironment of unknown reasons. Novel combinations with unexploited therapeutic agents such as PARPi may help to significantly increase their number.

In this review, we briefly provide an overview of current clinical trials investigating several therapeutic strategies of different PARPi in combination with chemotherapy, radiotherapy, immunotherapy, and other targeted agents, in patients with small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), and malignant pleural mesothelioma (MPM).

In contrast to PARPi, the therapeutic potential of PARG inhibitors (PARGi) has been largely ignored. Nevertheless, interest in these molecules is rising as they may represent a novel valuable option in cancer treatment, both as single agents and in combination with cytotoxic drugs or radiotherapy.

## Non-Small Cell Lung Cancer (NSCLC)

### PARPi with or without Chemotherapy

#### Biological Background and Preclinical Data

Although early clinical trials suggested that only tumors with germline and somatic mutations in BRCA 1/2 genes would benefit from PARP inhibition, new evidence has recently shown that these targeted agents can also be effective in other somatic deficiencies of the HRR pathway that altogether define the “BRCAness” phenotype.<sup>4</sup>

In particular, both BRCA mutations and BRCAness alterations have been detected in patients with NSCLC<sup>6,7</sup> and studies on NSCLC models have already shown that mutations of genes involved in DNA repair, for example ERCC1 (excision repair cross-complementation group 1) deficiencies, led to PARPi sensitivity.<sup>8,9</sup>

However, a higher prevalence of loss of heterozygosity (LOH) of the mutant allele was identified in lung cancer patients with germline BRCA mutations.<sup>7</sup> The process of LOH, in which a wild-type allele is lost and only an inactivated allele is left in the cancer genome, is frequently involved in the function loss of tumor suppressor genes and a large number of potential tumor suppressors were identified by analyzing sites of prevalent LOH in human cancers.<sup>10</sup> Therefore, molecular features other than BRCA mutation also need to be considered.

The SAFIR02-Lung is an open-label, randomized, Phase II trial investigating the efficacy of targeted therapies and immune checkpoint inhibitors (ICIs) compared with standard-of-care in patients with advanced epithelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type NSCLC without progression after first-line chemotherapy, based on high-throughput genome analysis.<sup>11</sup>

Considering the 379 patients with a druggable alteration identified, BRCA mutations were found in 20 patients (5.3%), though only 2.1% harbored a pathogenic BRCA1/2 mutation, with 75% of somatic mutations and 75% targeting BRCA 2 gene. Interestingly, while many genomic alterations in NSCLC are more common in females as they are usually related with non-smoking habits,<sup>12</sup> all patients with pathogenic BRCA mutations were men and mainly heavy smokers. The overall response rate to chemotherapy was 13%. In 12 patients (3.2%), BRCA mutations of uncertain relevance were found, leading to an 8.3% overall response rate to treatment. Biallelic inactivation with a high HRD score were seen in one-third of tumors carrying pathogenic BRCA mutations or variations of uncertain relevance and overall survival of this cohort was 12.8 months.

In conclusion, pathogenic BRCA1/2 mutations occur in 2.1% of patients with advanced NSCLC and the predictive role of BRCA mutation for making treatment decisions in NSCLC seems limited based on clinical response (low platinum sensitivity) and molecular features (discrepancy between biallelic inactivation and high HRD score).

These results, although from a small cohort, surely contribute to determining BRCA mutation prevalence in a real-world population of NSCLC patients and are also coherent with literature: Heeke et al,<sup>13</sup> who considered a DNA sequencing database of around 52,000 patients that underwent NGS or Sanger sequencing panel testing between July 2013 and September 2017, found a BRCA mutation in around 1–2% of patients analyzed.

Focusing on other HRR genes, changes in coding sequence of ATM (ataxia-telangiectasia mutated) were discovered in 12% of lung adenocarcinomas during large-scale genomics research.<sup>14</sup>

ATR (Ataxia-telangiectasia and Rad3 related) kinase inhibitors sensitize lung cancer cell lines to cisplatin in vitro and in cell line and patient-derived xenografts in vivo<sup>15–18</sup>: cisplatin and ATR kinase inhibitors have been demonstrated to cooperate in vitro to kill ATM-deficient lung cancer cells and in vivo to resolve ATM-deficient xenografts.<sup>15,16,18</sup> A multicenter Phase 1/1b clinical trial with AZD6738 (NCT02264678) is currently ongoing to test this hypothesis.<sup>19</sup>

Jette et al<sup>20</sup> tested the effects of PARP inhibitor olaparib and ATR inhibitor VE-821 in ATM-knockout A549 cells lung adenocarcinoma cells: considering drug sensitivity data from the Genomics of Drug Sensitivity in Cancer (GDSC) project in lung cancer cell lines, IC<sub>50</sub> (half-maximal inhibitory concentration) values for both olaparib and talazoparib were positively linked with ATM mRNA levels and gene amplification status. Conversely, ATM loss was linked to a considerable drop in the IC<sub>50</sub> for olaparib. In cells with ATM deletion, olaparib caused phosphorylation of DNA damage markers and reversible G2 arrest, whereas olaparib with VE-821 caused cell death, evidencing the potential efficacy of PARP inhibitors in ATM mutated tumors.

PTEN (Phosphatase and tensin homolog) loss caused by a variety of inherited germline mutations, somatic mutations, epigenetic and transcriptional silencing, post-translational modifications, and protein–protein interactions occurs in 4–8% of NSCLC and seems to predict a response to PARPi in lung cancer cell lines.<sup>21</sup>

Sargazi et al<sup>22,23</sup> found that the combination of valproic acid, an histone deacetylase inhibitor capable of down-regulating the DNA repair genes pathway, and AZD2461, a novel PARP1, PARP2, and PARP3 inhibitor, effectively induces apoptosis in prostate cancer cell cultures (PC-3) harboring mutations in PTEN. Although the same anti-proliferative effect has already been evidenced in breast cancer cells (MCF-7), there is still no evidence of similar activity in NSCLC models.<sup>24</sup>

Considering the combination of PARPi with other therapeutic agents, chemotherapy with platinum compounds or other alkylating drugs and ionizing radiation are considered quite promising as they act on tumor cells by damaging DNA; on the other hand, the existence of DNA repairing abnormalities is a possible mechanism involved in the tumor sensitivity to therapies<sup>25,26</sup> and activation of DNA repair pathways induced by these treatment modalities contributes to tumor resistance,<sup>27</sup> thus offering a strong biological rationale for combining DNA-damaging agents with PARPi.

In preclinical studies, veliparib has demonstrated increased cytotoxicity when administered with platinum compounds, topoisomerase inhibitors, and alkylating agents in general.<sup>28,29</sup> The combination of veliparib plus temozolomide (TMZ) was investigated in multiple xenograft models: tumor burden, expression of poly (ADP-ribose) polymer, and O6-methylguanine methyltransferase were used to assess the combination effectiveness in xenografts from divergent histologic tumor types, including B-cell lymphoma, SCLC, NSCLC, ovarian, breast, pancreatic, and prostate models implanted in subcutaneous, orthotopic, and metastatic sites. Veliparib (25 mg/kg/day, orally, twice daily for 5–6 days) seems to enhance TMZ efficacy (50 mg/kg/day, orally, once daily for 5 days), although different levels of effectiveness were reported (from 55 to 100% of tumor growth inhibition), including several regressions. Most interestingly, the addition of PARPi to TMZ seems to overcome both TMZ primary and secondary resistance in cancer cells.

### Clinical Evidence and Predictive Factors of Response and Efficacy

Starting from this preclinical rationale, several clinical trials are ongoing in investigating PARPi either as a single agent or in combination with other therapies in the treatment of thoracic malignancies.

A randomized phase II trial investigated the addition of iniparib to a standard treatment with gemcitabine and cisplatin. One hundred and nineteen Stage IV NSCLC patients were randomly assigned to receive gemcitabine (1,250 mg/m<sup>2</sup>, days 1–8) and cisplatin (75 mg/m<sup>2</sup>, day 1) with or without iniparib (5.6 mg/kg, days 1, 4, 8, and 11) every 3 weeks for six cycles. Even if the experimental arm improved activity (overall response rate (ORR)=25.6%; 95% Confidence Interval (CI)=13.0–42.1% vs 20%; 95% CI=11.9–30.4%), no statistically significant and clinically relevant benefit was found in terms of PFS (median PFS=4.3; 95% CI=2.8–5.6 vs 5.7; 95% CI=4.6–6.6 months, Hazard Ratio (HR)=0.89; 95% CI=0.56–1.40 and median OS=8.5; 95% CI=5.5 to not reached vs 12; 95% CI=8.9–17.1 months, HR=0.78; 95% CI=0.48–1.27). Toxicity was similar between the two cohorts, with no higher incidence of neutropenia/febrile neutropenia or serious systemic infections in the experimental arm.

The failure of adding iniparib to a chemotherapy backbone in this context may be related with its peculiar mechanism of action that differs from other PARPi. In fact, this is since iniparib acts by eliciting cell response by non-selective cysteine adduct alteration of multiple proteins.<sup>30</sup> Moreover, this proof-of-concept trial was not powerful enough to properly assess efficacy of iniparib + chemotherapy combination, even if it is highly likely a single-arm study design would have produced similar results.

The combination of the PARPi veliparib (days 1–7 q21 schedule) with carboplatin and paclitaxel (AUC6 and 200 mg/m<sup>2</sup>, respectively, day 3 q21 schedule) in naïve stage IV NSCLC patients has been investigated in a phase II trial enrolling 158 patients. No differences in PFS, OS, and ORR between the veliparib and placebo group have been founded, even if an interesting exploratory analysis<sup>31</sup> highlighted a trend toward a PFS benefit in patients with squamous histology (above 48% of the ITT population). In addition, the study also stratified patients by smoking history and revealed that recent smokers who were given veliparib had significantly better PFS and OS than former smokers (HR=2.09; *p*=0.02 and HR=1.62; *p*=0.23) and never-smokers (HR=1.02; *p*=0.97 and HR=1.30; *p*=0.63).

These results led to the design of a Phase III trial investigating the efficacy and safety of veliparib in combination with conventional chemotherapy for untreated advanced squamous NSCLC.<sup>32</sup> Patients were randomized to receive carboplatin and paclitaxel with either veliparib 120 mg twice daily or placebo twice daily for up to six cycles. Primary outcome was OS in the veliparib arm among current smokers, biomarker analysis was performed on archival tumor samples using a 52-gene expression histology classifier (LP52) whose positive predictive value had been proved in two different trials evaluating veliparib in NSCLC patients. Unfortunately, no significant OS benefit with veliparib in current smokers was found (median OS=11.9 vs 11.1 months, HR=0.90; 95% CI=0.74–1.10; *p*=0.26) even if a trend toward better OS was found in the veliparib cohort in the overall population (median OS=12.2 vs 11.2 months, HR=0.85; 95% CI=0.75–0.97). Focusing on patients with biomarker-evaluable tumor samples, an OS benefit due to veliparib was confirmed in the LP52-positive population (median 14.0 vs 9.6 months; HR=0.66; 95% CI=0.49–0.89). To sum up, veliparib in combination with first-line chemotherapy provided no therapeutic advantage in current smokers with advanced squamous NSCLC, but the LP52 classifier might help to identify a subset of patients who could benefit from PARP inhibition.

Another phase II study (NCT02154490) evaluating the clinical efficacy of the PARP inhibitor talazoparib in advanced stage and platinum sensitive squamous NSCLC harboring HRR deficiency failed to demonstrate efficacy in the primary analysis population, so it was closed early for futility.

Finally, first results from the aforementioned SAFIRO2-Lung trial have recently been published: among 116 patients receiving NGS-driven target therapies (including PARPi olaparib), no difference in PFS was found in any molecular subgroup. Median PFS was 2.7 months (95% CI=1.6–2.9) vs 2.7 months (95% CI=1.6–4.1) both in the experimental and in the SOC arm (HR=0.97; 95% CI=0.7–1.36; *p*=0.87). Though no subgroup analysis exclusively considering olaparib is currently available, the results of the target therapy arm are definitely quite disappointing.<sup>11</sup>

Ongoing clinical trials evaluating the role of PARPi with or without chemotherapy in NSCLC patients are listed in [Table 1](#). Published clinical trials evaluating the role of PARPi with or without chemotherapy in NSCLC patients are listed in [Table 2](#).

## PARPi + Radiotherapy

### Biological Background and Preclinical Data

In the field of radiation therapy, ionizing radiation combined with radiotherapy-enhancing chemicals has the potential to improve the efficacy of radiotherapy as a therapeutic method while reducing harmful side-effects and potential damage to healthy surrounding tissues.

In particular, PARPi combination with radiotherapy is an interesting matter because of radiation's DNA disrupting effect and the paramount role of the PARP enzyme in DNA repair. It follows that PARPi may act as potential radiosensitizers, especially for BRCA mutated tumors exploiting PARP enzyme as their main tool to fix DNA alterations: there is evidence in literature that the absence of PARP-1 and -2 enzymes, that are both triggered by DNA damage and assist DNA repair, enhances tumor sensitivity to ionizing radiation by extending strand breaks and triggering a cell-death signaling cascade. This effect could be amplified in tumors with HRR abnormalities and through a synthetic lethality mechanism. However, the impact

**Table I** Main Ongoing Clinical Trials Evaluating the Role of PARPi +/- Chemotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Ph	Biomarker Selection	Country	Estimated Sample Size	Primary Outcome Measure/s
NCT04171700 LODESTAR	Rucaparib	–	Solid tumors	≥2nd line	II	HRD positive	US	220	Best ORR by investigator
NCT03845296 Lung-MAP	Rucaparib	–	Squamous NSCLC	Stage IV	II	LOH high and/or deleterious BRCA1/2	US	64	ORR
NCT00576654	Veliparib	CPT-11	Solid tumors	Stage IV	I	–	US	36	OBD, MTD, RP2D
NCT03377556 Lung-MAP	Talazoparib	–	Squamous NSCLC	2nd line	II	HRD positive	Canada, US	51	ORR
NCT04672460	Talazoparib	–	Solid tumors	Metastatic or advanced	I	–	Australia, US	75	AUC24
NCT04644068	AZD5305	Paclitaxel Carboplatin	Solid tumors	Metastatic or advanced	I/II	–	Global	715	DLT/AEs
NCT02498613	Cediranib Olaparib	–	Solid tumors	Metastatic or advanced	II	–	Canada, US	126	ORR

**Abbreviations:** Ph, phase; ORR, Observed Response Rate; HRD, Homologous recombination deficiency; LOH, Loss of Heterozygosity; CPT-11, Irinotecan; OBD, optimal biologic dose; MTD, maximally tolerated dose; RP2D, recommended phase II dose; AUC24, 24H-Area Under Curve; DLT, Dose-Limiting Toxicity; AEs, Adverse Events; US, United States; UK, United Kingdom; NSCLC, non-small-cell lung cancer.

of PARPi is not limited to modifying DNA damage repair as PARPi show numerous properties that are essential for their radio-sensitizing action such as chromatin remodeling inhibition, G2/M arrest, and a vasodilatory action.<sup>33</sup>

A third of individuals with NSCLC are diagnosed at a locally advanced stage, a setting where chemo-radiotherapy (CRT) eventually followed by immunotherapy rather than surgery is the current standard of care. Despite technological progress in radiation therapy, tumor intrinsic radio-resistance still affects patients' outcome and offers an interesting application for PARPi in this setting.

Albert et al<sup>34</sup> found that veliparib and concomitant radiation reduced endothelial tubule development in vitro and reduced vessels formation in vivo, suggesting that this method may also target tumor angiogenesis. Veliparib hindered DNA repair in H460 lung cancer cells, as evidenced by increased production of the DNA strand break marker histone -H2AX (H2A histone family member X), seems to favor tumor cells death due to both apoptosis and autophagy. Veliparib also delayed tumor growth in murine models at well-tolerated doses: cancer cells proliferation was delayed by 1 day for veliparib alone, 7 days for radiation alone, and 13.5 days for combination treatment for a 5-fold increase in tumor volume. After the combined treatment, immunohistochemical staining of tumor sections suggested an increase in terminal deoxyribonucleotide transferase-mediated nick-end labeling apoptotic staining and a decrease in Ki-67 proliferative staining.

Another trial analyzed the effect of PARPi olaparib on H1299 lung cancer cell line with depletion or mutation of p53 gene using the  $\gamma$ H2AX focus formation assay to examine the influence of olaparib on induction and repair of double-stranded DNA breaks after exposure to radiation. Even at 0.01  $\mu$ M, and after a brief exposure interval (2 h) olaparib demonstrated a promising radio-sensitizing effect and, although p53-knockout H1299 cells were more radio-resistant than p53 wild-type, a benefit from olaparib administration was demonstrated in both subgroups. As tumor cells may be exposed to low amounts of olaparib and/or have varying levels of p53 mutation, these properties could be useful to guide therapeutic radiotherapy pre-planification.

**Table 2** Main Published Clinical Trials Evaluating the Role of PARPi +/- Chemotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Ph	Biomarker Selection	Country/ies	Sample Size	Primary Outcome Measure/s	Result
NCT01086254	Iniparib	Gemcitabine Cisplatin	NSCLC	Stage IV	II	–	France, Germany, Italy, Spain, UK	119	ORR	Neg
NCT01560104	Veliparib	Carboplatin Paclitaxel	NSCLC	Previously untreated metastatic or advanced	II	–	Not provided	160	PFS	Negative (in squamous histology the trend of apparent advantage in PFS supported the design of an ad hoc phase III)
NCT02106546	Veliparib	Carboplatin Paclitaxel	SqNSCLC	Previously untreated metastatic or advanced	III	–	Europe, Brazil, Canada, Egypt, Mexico, Netherlands, New Zealand, Puerto Rico, Russian Federation, South Africa, Turkey, US	970	OS in current smokers	Neg
NCT02154490	Talazoparib	Docetaxel	SqNSCLC	Stage IV	II	HRD positive	Canada, US	1864	PFS; ORR; OS	Closed (the study failed to show efficacy in the primary analysis population so it closed earlier)

**Abbreviations:** Ph, phase; ORR, Observed Response Rate; PFS, Progression-Free Survival; OS, Overall Survival; HRD, Homologous recombination deficiency; US, United States; UK, United Kingdom; NSCLC, non-small-cell lung cancer.

### Clinical Evidence and Predictive Factors of Response and Efficacy

A Phase I–II study (SWOG S1206) evaluated the addition of veliparib to CRT for patients affected by unresectable NSCLC<sup>35</sup>: in the Phase I dose-finding part of the trial, patients received weekly carboplatin (AUC 2) and paclitaxel (45 mg/m<sup>2</sup>) during concurrent thoracic radiotherapy (2 Gy fractions/day, total dose 60 Gy) and veliparib administered at three different dose levels (40, 80, and 120 mg, respectively) throughout radiotherapy duration. No dose-limiting toxicity (DLT) was seen at veliparib dose of 120 mg twice daily, which was selected for the next phase II part of the study. Thirty-one patients were subsequently randomized to receive veliparib or placebo during thoracic radiotherapy with concurrent weekly carboplatin and paclitaxel, followed by two cycles of consolidation treatment with carboplatin and paclitaxel plus either veliparib or placebo. No difference in PFS was detected between the two arms but an interesting benefit in 1-year OS (89% vs 54%) was found in the veliparib arm, though ORR slightly favored placebo (56% vs 69%).

In addition, another recent study with a similar design,<sup>36</sup> the M14-360/AFT-07 phase I trial, confirmed the good tolerability with promising antitumor activity with a mPFS of 19.6 months for the combination of veliparib + CRT with carboplatin and paclitaxel followed by veliparib plus chemotherapy in 48 stage III NSCLC patients.

A phase I study evaluated the safety of olaparib in association with loco-regional radiotherapy, with and without concurrent cisplatin for locally advanced NSCLC.<sup>37</sup> The dose of olaparib was increased in two groups respectively treated with radiation (66 Gy/24 fractions in 2.75 Gy/fraction) with and without daily cisplatin (6 mg/m<sup>2</sup>) using the time-to-event continuous reassessment technique with a 1-year DLT period. The maximum tolerable dose (MTD) was determined as the highest dose level having a DLT probability of less than 15%. The study enrolled 28 patients with loco-regional or oligometastatic disease, of whom 11 were treated with olaparib 25 mg twice daily and 17 with olaparib 25 mg once daily. Due to hematologic and late esophageal DLT, the lowest dose level with cisplatin was over the MTD, while 25 mg once daily was the MTD for olaparib without cisplatin. Severe pulmonary adverse events were detected in five patients across all dose levels with a latency of 1–2.8 years, probably due to radiation exposure to the lungs as observed in preliminary studies. Olaparib lowered PARP levels (determined in peripheral blood cells) by more than 95% and stopped radiation-induced PARylation at the MTD. After an average of 4.1 years, 2-year loco-regional control was 84% and median overall survival was 28 months. However, considering high rates of esophageal and hematologic toxicity, a combination of moderately hypofractionated radiation with low-dose daily cisplatin and olaparib was not acceptable and, even without cisplatin, severe pulmonary damage occurred, thus suggesting that more conformal radiation schedules saving the lungs and esophagus should be investigated.

Ongoing clinical trials evaluating the role of PARPi with or without radiotherapy in NSCLC patients are listed in Table 3. Published clinical trials evaluating the role of PARPi with or without radiotherapy in NSCLC patients are listed in Table 4.

**Table 3** Main Ongoing Clinical Trials Evaluating the Role of PARPi + Radiotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Phase	Biomarker Selection	Country/ies	Sample Size	Primary Outcome Measure/s
NCT01386385	Veliparib	RT + Carbo + PTX vs Placebo + RT + Carbo + PTX	NSCLC	Locally advanced	I/II	–	US	53	MTD determined according to incidence of DLT; PFS
NCT04550104 Concorde	Olaparib	Radiotherapy	NSCLC	Locally advanced	I	–	UK	200	DLT within 13.5 months of starting radiotherapy, RP2D of each DDRi-RT combination

**Abbreviations:** Ph, phase; PFS, progression-free survival; Carbo, carboplatin; PTX, paclitaxel; US, United States; UK, United Kingdom; RP2D, recommended phase II dose; DLT, Dose Limiting Toxicities; MTD, maximum tolerated dose; DCR12, disease control rate at 12 weeks; DDR, DNA Damage Repair; NSCLC, non-small-cell lung cancer.



**Table 4** Main Published Clinical Trials Evaluating the Role of PARPi + Radiotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Ph	Biomarker Selection	Country/ies	Sample Size	Primary Outcome Measure/s	Result
NCT01562210	Olaparib	Cis RT	NSCLC	Locally advanced	I	–	US	220	Incidence; DLT	Neg
NCT01386385	Veliparib	Carbo PTX RT	NSCLC	Unresectable stage III	I/II	–	US	53	MDT; DLT; PFS	Good tolerability; Neg
NCT02412371	Veliparib	Carbo PTX RT	NSCLC	Locally advanced	I	–	Czechia, Greece, Spain	48	DLT	Good tolerability

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; DLT, Dose Limiting Toxicities; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer.

## PARPi + Immunotherapy

### Biological Rationale and Preclinical Data

In the last years the introduction of ICIs in the treatment algorithm of almost every tumor specimen has deeply changed clinical practice. NSCLC was among the first tumor type to receive the benefits from this therapeutic revolution.<sup>38–44</sup>

There is robust evidence about the deep correlation between inhibition of DNA repair pathways and ICIs activity.<sup>45,46</sup> DDR alterations lead to an increase in the tumor mutational burden (TMB) and intrinsic immunogenicity due to tumor-specific neoantigen formation,<sup>46</sup> while the stimulator of IFN genes (STING) pathway that activates innate antitumor immunity acts as an additional DNA damage recognition mechanism via neo-antigen independent pathways (Figure 2).<sup>47</sup>

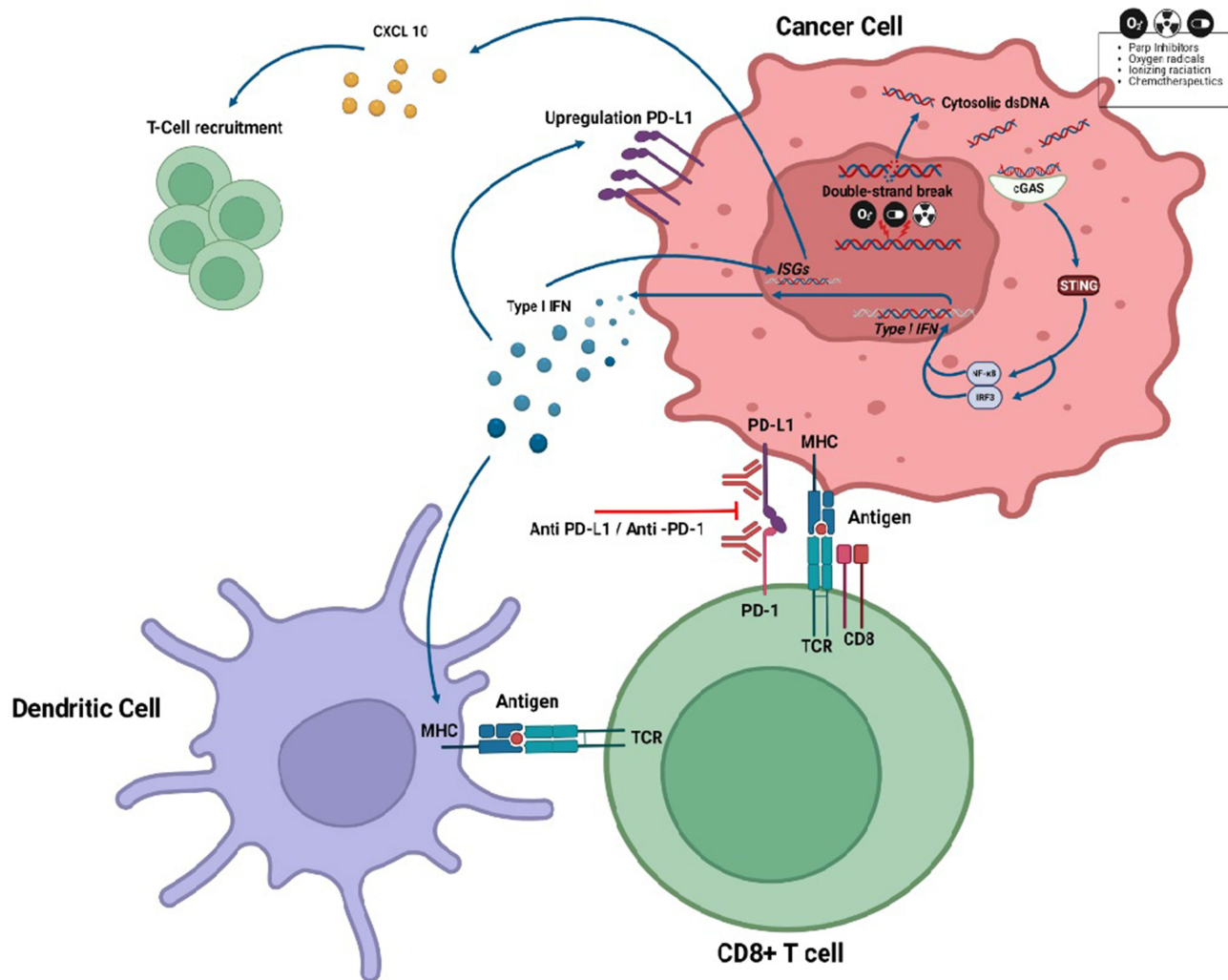
The role of PARPi, such as niraparib, combined with anti-programmed cell death-1 (PD-1), has been evaluated in BRCA-proficient and BRCA-deficient preclinical models of sarcoma, lung squamous cell carcinoma, colon adenocarcinoma, breast cancer, and urothelial carcinoma. Following evidence supporting niraparib's role in increasing CD4+ and CD8+ immune cell infiltration and type I and type II interferon pathways activity,<sup>48</sup> many clinical trials evaluating the combination of PARPi and ICIs have been designed, in particular including NSCLC patients where immunotherapy is a main option in the clinicians' therapeutic arsenal.

### Clinical Evidence and Predictive Factors of Response and Efficacy

The tumor mutational landscape seems to play an important role in predicting clinical response to ICIs. In NSCLC patients treated with anti-PD1 pembrolizumab, TMB has been associated with clinical efficacy in terms of PFS, ORR, OS, and durable clinical benefit,<sup>49,50</sup> as from a biological standpoint higher TMB levels enhance CD8-positive T-cell intratumoral infiltration and inflammatory T-cell-mediated response.<sup>51</sup> Finally, DDR mutations in NSCLC patients treated with ICIs have been associated with longer PFS (5.4 vs 2.2 months) and OS (18.8 vs 9.9 months) in a study by Ricciuti et al.<sup>52</sup>

Based on this rationale, several trials were designed to evaluate the association of PARPi and ICIs in NSCLC (Table 5). Among these, JASPER study is a multicenter, open-label, 2-stage Phase 2 trial evaluating the association of the PARPi niraparib in combination with the PD-1 inhibitor pembrolizumab as first-line treatment in patients affected by metastatic and/or locally advanced NSCLC. Patients were enrolled in two cohorts, according to PD-L1 expression evaluated by tumor proportion score (TPS):  $\geq 50\%$  (cohort 1) and 1–49% (cohort 2): ORR (primary endpoint) was 56.3% with two complete responses and 20.0% in cohort 1 and 2 while focusing on secondary endpoints, in the two groups median duration of response (DoR) was 19.7 and 9.4 months and PFS was 8.4 and 4.2 months, respectively. OS was not reached for patients with TPS  $\geq 50$  vs 7.7 months for the 1–49% group.<sup>53</sup>

The safety profile detected on JASPER study was concordant with known safety profiles of single agents niraparib and pembrolizumab.<sup>53</sup> With the strong bias of an indirect comparison with limited numbers, it is remarkable that, considering pembrolizumab monotherapy provided and ORR of 44.8% on patients with TPS  $\geq 50\%$  in the KEYNOTE-024 trial that led to its registration in the stage IV NSCLC setting,<sup>39</sup> the addition of PARPi seems to improve the ORR to 56.3% in the same patients' subgroup. The study was not powerful enough to compare efficacy between cohorts 1 and 2.



**Figure 2** Interlink between DNA damage and immune checkpoint inhibitors (ICIs) via cGAS-STING activation. In homologous recombination (HR) proficient and HR deficient tumor cells the action of chemotherapeutics, ionizing radiation and PARPi generates cytosolic double-stranded DNA (dsDNA) fragments. These fragments of cytosolic dsDNA bind to cyclic GMP-AMP synthase (cGAS) and activate the stimulator of interferon genes (STING) that, through NF- $\kappa$ B and IRF-3, induce type I IFN and other transcriptional targets. The binding between the type I IFN to the IFN receptor stimulates the transcription of IFN-stimulated genes (ISGs) and production of cytokines like CXCL10 that promote the T-Cell recruitment. The IFN I also determines a PD-L1 upregulation on the cancer cell surface and promotes the tumor neoantigen presentation on the major histocompatibility complex (MHC) of dendritic cell to the T-cell receptor (TCR). Created with BioRender.com.

The clinical role of PARPi in NSCLC was also studied in a phase 1 open-label dose-escalation trial (NCT02944396).<sup>54</sup> Twenty-five patients were treated with veliparib and nivolumab, a PD-1 inhibitor, plus chemotherapy with carboplatin and paclitaxel or carboplatin and pemetrexed, a four-drug combination that had never been studied before, and were subsequently divided into five dosing cohorts: the first one was treated with veliparib 120 mg twice daily in combination with nivolumab 360 mg (Q3W), carboplatin AUC 6 mg/mL·min and paclitaxel 200 mg/m<sup>2</sup> (C/PAC regimen), whereas the other four groups received veliparib, 80/120/200/240 mg, respectively, twice daily in combination with nivolumab 360 mg (Q3W), carboplatin AUC 6 mg/mL·min, and pemetrexed 500 mg/m<sup>2</sup> (C/PEM regimen).

Chemotherapy and veliparib were administered for six cycles as nivolumab and pemetrexed were then continued as maintenance therapy until disease progression or unacceptable toxicity occurred. The safety profile was concordant with known data available for the combination of nivolumab plus double chemotherapy<sup>55</sup> as the addition of veliparib did not increase the rate of hematologic toxicities and the drug combination was well tolerated.<sup>54</sup> ORR (primary endpoint) in the overall cohort was 40%, quite similar to the 38% showed in a CheckMate227 trial that considered NSCLC patients treated with nivolumab plus chemotherapy.<sup>56</sup>

**Table 5** Main Ongoing Clinical Trials Evaluating the Role of PARPi + Immunotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Phase	Biomarker Selection	Country	Estimated Sample Size	Primary Outcome Measure/s
UNITO-001	Niraparib	Dostarlimab	NSCLC; MPM	≥2nd line	II	HRR-mutated and PDL1 ≥ 1%	Global	70	PFS
NCT03976323 KEYLYNK-006	Olaparib	Pembrolizumab Compared to: Pembrolizumab	Non-squamous NSCLC	Maintenance	III		Global	792	PFS, OS
NCT03775486 ORION	Olaparib	Durvalumab Compared to: Durvalumab	NSCLC	Maintenance	II		Global	327	PFS
NCT04380636 KEYLINK-012	Olaparib	Pembrolizumab Compared to: Pembrolizumab + placebo	NSCLC	Maintenance	III		Global	870	PFS, OS
NCT03976362 KEYLINK-008	Olaparib	Pembrolizumab Compared to: Pembrolizumab + placebo	Squamous NSCLC	Maintenance	III		Global	735	PFS, OS
NCT03334617 HUDSON trial	Olaparib	Durvalumab	NSCLC	≥2nd line	II	HRR-mutated	Western	200	ORR
NCT03559049	Rucaparib	Pembrolizumab	NSCLC	Maintenance	I/II		US	55	PFS
NCT04173507 Lung-MAP	Talazoparib	Avelumab	Non-squamous NSCLC	≥2nd line	II	STK11 positive	US	44	ORR, DCR12
NCT02484404	Olaparib	Durvalumab +/- cediranib	Solid tumors	≥2nd line	I/II		US	112	RP2D, safety of doublet therapies of Durvalumab/olaparib and Durvalumab/cediranib
NCT03330405 Javelin Parp Medley	Talazoparib	Avelumab	Solid tumors	N line	II		Global	296	DLT, OR

(Continued)

Table 5 (Continued).

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Phase	Biomarker Selection	Country	Estimated Sample Size	Primary Outcome Measure/s
NCT03565991 Javelin BRCA/ATM	Talazoparib	Avelumab	Solid tumors	N line	II	BRCA/ATM defect	Global	200	OR
NCT03772561 MEDIPAC	Olaparib	Durvalumab + AZD5363	Solid tumors	N line	I		Singapore	40	ORR, best objective response
NCT03842228	Olaparib	Durvalumab + Copanlisib Hydrochloride	Solid tumors	N line	I	DDR-mutated	US	102	Safety, RP2D
NCT04169841 GUIDE2REPAIR	Olaparib	Durvalumab + Tremelimumab	Solid tumors	≥2nd line	II	HRR-mutated	France	270	PFS
NCT03637491	Talazoparib	Avelumab + Binimetinib	Solid tumors	2nd and 3rd line	I/II	RAS-mutated	Belgium, Singapore, US	127	DLT, OR
NCT03061188	Veliparib	Nivolumab	Solid tumors	≥2nd line	I		US	50	MTD
NCT04276376	Rucaparib	Atezolizumab	Solid tumors	≥2nd line	II	DDR-deficient or platinum sensitive	France	1000	ORR

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; UK, United Kingdom; RP2D, recommended phase II dose; ORR, objective response rate; DLT, dose limiting toxicities; MTD, maximum tolerated dose; OS, overall survival; DCR12, disease control rate at 12 weeks; DDR, DNA damage repair HRR, homologous recombination repair; NSCLC, non-small-cell lung cancer; MPM, malignant pleural mesothelioma.

Given the good safety profile shown in several trials with the combination of PARPi and immunotherapy, future studies with large sample size could better investigate the efficacy of PARPi in addition to immunotherapy in NSCLC.

Published clinical trials evaluating the role of PARPi with or without immunotherapy in NSCLC patients are listed in Table 6.

## PARPi + Targeted Agents

### Biological Rationale and Preclinical Data

Scientific research on PARPi acquired/innate resistance is based on studies with combinations of different DNA Damage Response Inhibitors (DDRi). In pre-clinical models with ATM deficiency, the combination of ATR inhibitor and PARPi improved the efficacy of PARPi.<sup>20</sup>

A member of the antiapoptotic BCL-2 proteins, MCL-1, is an important prosurvival agent due to its DNA repair function.<sup>57</sup> Mattoo et al<sup>58</sup> recently demonstrated both in vitro and in xenografts that mTOR inhibitors everolimus or AZD2014 deplete MCL-1 expression and lead to DNA repair suppression, thus increasing sensitivity to PARPi olaparib. In addition, inhibition of another important protein of the same axis as m-TOR, PI3K, caused DNA homologous recombination repair impairment and sensitization to PARP inhibitor olaparib in triple negative breast cancer cells in vivo<sup>59</sup> and also in ex vivo cultured PIK3CA wild type ovarian cancer tissues independently of BRCA genes status.<sup>60</sup>

The role of vascular endothelial growth factor (VEGF) inhibition-driven hypoxia in providing DNA damage and genetic instability has already been highlighted.<sup>61</sup> In particular, an interesting preclinical experience from Bizzarro et al<sup>62</sup> demonstrated a wide anti-tumor activity due to the combination of olaparib and the VEGFR inhibitor cediranib on patient-derived ovarian cancer xenografts, regardless of the HRR status.

The role of PARPi therapy has also been studied in lung cell lines with EGFR mutation: the EGFR-mutant cells showed sensitivity to PARPi in vitro and in vivo due to an EGFR kinase-independent regulation of DNA repair.<sup>63</sup>

### Clinical Evidence and Predictive Factors of Response and Efficacy

OLAPCO trial is a phase 2 basket trial recruiting patients in a range of tumor types with the potential to identify novel tumor indications for combination therapy with olaparib based on molecular markers from genetic profiling performed on their tumors prior to study entry. Patients with tumors harboring PTEN, PIK3CA, AKT, or ARID1A mutations or other molecular alterations leading to dysregulation of the PI3K/AKT pathway will be treated with target inhibitor AZD5363 plus olaparib. Another arm of the same trial, whose first results have already been published,<sup>64</sup> has demonstrated an 8.3%

**Table 6** Main Published Clinical Trials Evaluating the Role of PARPi +/- Immunotherapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Phase	Biomarker Selection	Country	Estimated Sample Size	Primary Outcome Measure/s
NCT03307785 IOLite	Niraparib	Dostarlimab, Bevacizumab	Solid Tumors	≥2nd line	I		US	66	Number of participant with DLT
NCT04475939 ZEAL-IL	Niraparib	Pembrolizumab Compared to: Pembrolizumab + placebo	NSCLC	Maintenance	III		Global	650	PFS, OS
NCT02944396	Veliparib	Nivolumab; Pemetrexed; Carboplatin; Paclitaxel	NSCLC	1st line	I		US	184	RP2D, PFS
NCT03308942 JASPER	Niraparib	Pembrolizumab or Dostarlimab	NSCLC	1st line	II		US	136	ORR

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; UK, United Kingdom; RP2D, recommended phase II dose; ORR, objective response rate; DCR, disease control rate; DLT, dose limiting toxicities; NSCLC, non-small-cell lung cancer.

overall response rate and 62.5% clinical benefit rate among a 25 patients cohort with different solid tumors, though none with NSCLC, treated with ATR selective inhibitor ceralasertib. The same drug in combination with carboplatin, durvalumab, or olaparib is also under evaluation in an ongoing phase I dose escalation study in patients affected by advanced solid tumors.<sup>65</sup>

Focusing on the PIK3CA-AKT-mTOR pathway, a phase Ib NCT04586335 clinical trial is currently evaluating safety, tolerability, and preliminary efficacy of novel PIK3CA inhibitor CYH33 in combination with olaparib in patients with DDR gene mutations and/or PIK3CA mutations. The study aims at recruiting at least 350 patients and comprehends a dose escalation part followed by a dose expansion phase.

Two different trials, NCT02588105 and NCT04267939, respectively, are evaluating PARP inhibitors olaparib and niraparib in combination with ATR inhibitor AZD0156 and ATM inhibitor BAY1895344 (Elimusertib). Both studies are still ongoing and no results have been published yet. On the other hand, first data from the NCT02723864VX trial by Mitra et al<sup>66</sup> showed a promising activity producing two partial responses (6%) and 22 stable disease (65%, median four cycles, range=2–11) in 37 heavily pretreated patients with solid tumors though high toxicity (in particular anemia, 41% G3) prevented adequate veliparib delivery and the drug combination has not been studied further.

Following strong preclinical rationale and satisfactory results obtained in ovarian cancer, the phase II NCT02498613 trial is studying the mutual administration of PARPi olaparib with anti-VEGF target agent cediranib in patients with solid tumors. With the limitations of no report available focusing on NSCLC cohort, preliminary data considering other tumor specimens are encouraging (14% ORR in biomarker-unselected 37 patients with heavily pre-treated, metastatic triple-negative breast cancer)<sup>67</sup> with a manageable toxicity, though 24% of patients reported hypertension often requiring prompt antihypertensives initiation.

Despite the combination of PARPi olaparib, EGFR inhibitor gefitinib in EGFR mutant NSCLC did not show a significant benefit in terms of PFS, compared to EGFR inhibitor alone in the phase 1–2 GOAL trial,<sup>68</sup> further analysis evidenced that olaparib may instead be effective in a subset of patients with higher expression of BRCA1 mRNA (PFS 12.9 vs 9.2 months,  $p=0.0449$ ).<sup>69</sup>

The tolerability and efficacy of the combination of niraparib and the 3rd generation EGFR inhibitor osimertinib, is under investigation in a phase I trial recruiting patients with EGFR-mutated advanced NSCLC (NCT03891615).

However, further studies are needed to better stratify those patients who might benefit from these therapeutic combinations.

Main ongoing clinical trials evaluating the role of PARPi with DDRi and other targeted agents in NSCLC patients are listed in [Table 7](#).

## Small Cell Lung Cancer (SCLC)

### PARPi Alone or in Association with Chemotherapy

#### Biological Rationale and Preclinical Data

Despite the introduction in clinical practice of chemo-immunotherapy combining standard platinum etoposide with atezolizumab<sup>70</sup> and, more recently, durvalumab,<sup>71</sup> SCLC prognosis still remains abysmal, with a median overall survival of 13 months according to CASPIAN trial last update. It follows that there is much interest in novel drugs or alternative therapeutic strategies in order to improve patients' outcomes.

There is preclinical evidence in the literature suggesting that SCLC is often characterized by alterations of the DNA damage repair pathways, in particular RB1 and TP53 lack of function<sup>72</sup> or SOX2 and MYC genes amplification.<sup>73</sup> Moreover, PARP enzyme and other DNA repair proteins,<sup>74</sup> significant overexpression,<sup>75</sup> and alterations among several HRR system genes identified in SCLC cell lines slightly contribute to tumorigenesis and growth,<sup>74</sup> strongly supporting the idea of investigating PARPi in this disease setting treatment, alone or in combination with chemotherapy.<sup>76</sup>

#### Clinical Evidence and Predictive Factors of Response and Efficacy

PARPi alone as maintenance treatment after front-line chemotherapy has shown no significant benefit in terms of PFS and OS in the 220 patients recruited in the STOMP trial<sup>77</sup> and randomized to receive PARPi olaparib or placebo after partial or complete response to first-line chemotherapy or chemoradiotherapy for SCLC proving no differences in PFS

**Table 7** Main Ongoing Clinical Trials Evaluating the Role of PARPi +/- Target Therapy in NSCLC Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Ph	Biomarker Selection	Country	Estimate Sample Size	Primary Outcome Measure/s
NCT02264678	Olaparib	Ceralasertib	Adv Solid Malig - H&N SCC, NSCLC, Gastric, Breast and Ovarian Cancer	2nd line	I/II	ATM Pro / Def	Global	119	Safety and tolerability
NCT02723864	Veliparib	VX-970 + Cisplatin	Solid tumors	N line	I	-	US	60	Number of participants with worst Grade 2 or higher adverse events in >5% of participants at least possibly related to study drugs
NCT02576444 OLAPCO	Olaparib	AZD5363/AZD1775/ AZD6738	Solid tumors	N line	II	-	US	64	ORR
NCT04267939	Niraparib	BAY1895344	Solid tumors (excluding prostate cancer)	≥2nd line	I	DDR deficiency	US	56	MTD, RP2D, Incidence and severity of treatment emergent adverse events (TEAEs)
NCT02588105	Olaparib	AZD0156	Solid tumors	N line	I	-	Global	225	Safety and tolerability
NCT03891615	Niraparib	Osimertinib	NSCLC	≥2nd line	I	EGFR-mutated	US	30	MTD Niraparib
NCT04586335	Olaparib	CYH33	Solid tumors	≥2nd line	Ib	DDR3 gene mutation, PIK3CA hotspot mutation	N/A	350	Dose limiting toxicity, ORR
NCT02498613	Olaparib	Cediranib	Solid tumors	≥2nd line	II	-	N/A	126	ORR

**Abbreviations:** Ph, phase; US, United States; UK, United Kingdom; MDT, maximum dose tolerated; DDR, DNA damage repair; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma; EGFR, epidermal growth factor receptor.

between olaparib and placebo cohorts for either twice-a-day schedule (HR=0.87; 90% CI=0.64–1.18; stratified logrank  $p=0.29$ ) or the three-times-a-day schedule arm (HR=0.89; 90% CI=0.67–1.20;  $p=0.43$ ). There was also no significant difference in OS between olaparib and placebo for both treatment schedules (HR=0.97; 90% CI=0.69–1.37;  $p=0.7$  and HR=1.05; 90% CI=0.76–1.46;  $p=0.73$ , respectively).

Also, another phase III trial (NCT03516084) evaluating niraparib as maintenance therapy following first-line chemotherapy was stopped early due to the slow accrual.

It follows that interest in the potential role of PARPi as main actors in a maintenance strategy has declined and the most promising role for these therapeutic agents in SCLC seems to be in combination rather than following chemotherapy in the extended disease (ED) setting.

The phase II ECOG-ACRIN 2511 trial (NCT01642251)<sup>78</sup> studied veliparib in association with standard chemotherapy with cisplatin and etoposide versus chemotherapy alone in 128 patients with treatment-naïve ED-SCLC: median PFS was 6.1 months (95% CI=5.9–6.7 months) vs 5.5 months (95% CI=5.0–6.1 months) with an HR of 0.63 and a statistically significant  $p=0.001$ . However, no significant improvement in terms of both median OS (10.3 versus 8.9 months, HR=0.83; 80% CI=0.64–1.07), and ORR (71.9% vs 65.6%, two-sided  $p=0.57$ ) were found.

A phase II trial investigated the efficacy of veliparib combined and following as a maintenance therapy with carboplatin and etoposide in first-line ED-SCLC treatment.<sup>79</sup> One hundred and eighty-one patients were randomized 1:1:1 to receive veliparib plus chemotherapy followed by veliparib maintenance, veliparib plus chemotherapy followed by placebo, or placebo plus chemotherapy followed by placebo until unacceptable toxicity or progression, with PFS as the primary endpoint. An improvement in PFS (HR=0.67; 80% CI=0.50–0.88;  $p=0.059$ ) with no OS benefit and an acceptable safety profile was shown in the veliparib arms.

Pietanza et al<sup>80–82</sup>

Several other clinical trials investigating the efficacy of PARPi combined with cytotoxic agents in ED-SCLC after first-line platinum-based chemotherapy are currently ongoing.

Clinical trials evaluating the role of PARPi with or without chemotherapy in SCLC patients are listed in Table 8.

## PARPi + Radiotherapy

### Biological Rationale and Preclinical Data

Radiotherapy plays an important role in the management of SCLC as thoracic CRT, typically with an etoposide and platinum-based regimen, is still is standard of care in limited stage (LS) SCLC.<sup>83</sup> Results from two meta-analys

**Table 8** Main Ongoing Clinical Trials Evaluating the Role of PARPi Alone or + Chemotherapy in SCLC Treatment

Trial	PARPi	Other Agent(s)	Setting	Ph	Biomarker Selection	Country	Estimated Sample Size	Trial Status	Primary Outcome Measure/s
NCT03009682 (SUKSES-B)	Olaparib	-	≥2nd line	II	HRR pathway mutation(s)	SOUTH KOREA	28	Completed	ORR
NCT03516084	Niraparib	Placebo	Maintenance after induction with platinum doublet	III	-	CHINA	591	Early stopped	PFS/OS
NCT02446704	Olaparib	TMZ	≥2nd line	I/II	-	US	66	Active, not recruiting	MTD, ORR
NCT02769962	Olaparib	EP0057, a Nanoparticle Camptothecin	≥2nd line	I/II	-	US	123	Recruiting	MTD, PFS
NCT03227016	Veliparib	Topotecan	≥2nd line	I/II	-	GERMANY	30	Recruiting	DLT/AEs
NCT03672773 (TRIO-US L-07)	Talazoparib	Low-dose TMZ	≥2nd line	II	-	US	28	Active, not recruiting	ORR

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; MDT, maximum dose tolerated; ORR, objective response rate; AEs, adverse events; DLT, dose-limiting toxicity; OS, overall survival; TMZ, Temozolomide.



es revealed that the addition of radiotherapy to chemotherapy provides a small but significant improvement of 3 years overall survival (5.4%),<sup>84</sup> in particular in younger patients under 55 years of age. Moreover, radiation treatment also improved locoregional progression by 25% (95% CI=16.5–34.1%) compared with chemotherapy alone.<sup>85</sup>

Conversely, radiotherapy is not routinely adopted for the treatment of ED-SCLC, and the mainstay of treatment is a combination strategy of chemotherapy and immunotherapy. Traditionally, radiotherapy in this setting is primarily used with palliative intent of chest symptoms<sup>86</sup> or as consolidation after response/stability to first line therapy. However, a systematic review found that consolidation radiotherapy provides a PFS benefit (HR=0.72,  $p<0.0001$ ; 95% CI=0.61–0.83,  $I^2=0\%$ ) but no improvement in OS (HR=0.88,  $p=0.36$ ; 95% CI=0.66–1.18,  $I^2=52\%$ ) compared to an exclusive chemo-immunotherapy regimen.<sup>87</sup>

With these varied results, new strategies need to be developed in order to better define the role of radiotherapy in the contest of ED-SCLC.

It is hypothesized that PARP inhibition in combination with other DNA damaging agents such as radiotherapy may result in increased sensitivity of tumor cells due to deficiency in DNA repair.<sup>88</sup>

SCLC has a very high level of PARP enzyme expression in comparison to other cancer types, thus suggesting a biologically relevant role for this protein in SCLC development and progression. In particular, it was demonstrated in SCLC lines that the sensitivity to PARPi is associated with elevated expression of PARP-1<sup>89</sup> and preclinical investigation also highlighted that PARP inhibition with veliparib enforces the cytotoxic effects of radiation in SCLC both in vitro and in vivo.<sup>90</sup>

Laird et al<sup>91</sup> also showed that PARP trapping is effective in the radiosensitization of SCLC cell lines and patient-derived xenograft (PDX) models and that talazoparib, at the same concentration determined to cause equivalent enzymatic inhibition, may be an even better radiosensitizer than veliparib.

### Clinical Evidence and Predictive Factors of Response and Efficacy

Several early phase trials are testing the combination of PARP inhibition and radiation in ED-SCLC.

An ongoing phase I trial (NCT03532880) is evaluating the safety of olaparib together with consolidative radiotherapy as well as reporting on the clinical outcomes for patients treated with this approach. This study plans to enroll 24 patients with SCLC receiving varying doses of olaparib orally twice daily for 3 weeks (administered at 50 mg to 300 mg until progression or unacceptable toxicity) and thoracic radiation once daily 5 days per week beginning 1 week after the initiation of olaparib for a total of 30 Gy in 10 fractions. The coprimary end-points are MTD of olaparib in association with radiotherapy and the safety of the combination based on the adverse events profile.

An additional analogous phase I trial (NCT04170946) will explore the same strategy with talazoparib in combination with the exactly alike consolidative radiation therapy regimen in ED-SCLC patients and another phase I/II trial (NCT04728230) of sequential treatment with olaparib, thoracic radiotherapy, and durvalumab or olaparib plus durvalumab as consolidation and maintenance therapy in ED-SCLC patients post-chemo-immunotherapy is also ongoing.

Finally, a phase I trial combining PARPi and CTLA-4 inhibitors and thoracic radiotherapy is currently underway. The trial specifically includes three arms to assess the activity and safety of durvalumab plus thoracic radiotherapy, durvalumab combined with tremelimumab plus thoracic radiotherapy, and durvalumab combined with olaparib plus thoracic radiotherapy in ED-SCLC after first-line chemotherapy (NCT03923270).

Ongoing clinical trials evaluating the role of PARPi with radiotherapy in SCLC patients are listed in [Table 9](#).

## PARPi + Immunotherapy

### Biological Rationale and Preclinical Data

The recent integration of immunotherapy in the first-line treatment of SCLC has improved patients' OS and provided a new therapeutic option in a disease with such an abysmal prognosis as SCLC.<sup>92</sup>

Due to the molecular signaling pathways between intracellular DNA and PD-L1 expression, interest in the potential synergy between PARP inhibitors and immune checkpoint inhibitors is rising.

The cGAS (cyclic GMP–AMP synthase)-STING pathway is the main cellular cytosolic double-stranded DNA (dsDNA) sensor, enabling innate immunity to respond to virus and bacteria attacks, inflammation, and eventually

**Table 9** Main Ongoing Clinical Trials Evaluating the Role of PARPi + Radiotherapy in SCLC Treatment

Study Name	PARPi	Other Agent(s)	Selected Population	Ph	Country	Study Start Year	Estimated Number of SCLC Patients Enrolled	Trial Status	Primary Outcome Measure/s
NCT03532880	Olaparib	Low-dose RT	Patients with ED-SCLC	I	US	2018	24	Recruiting	MTD Safety
NCT04170946	Talazoparib	Consolidative thoracic RT	Patients with ED-SCLC	I	US	2020	24	Recruiting	MTD Safety
NCT04728230	Olaparib	Durvalumab + Carboplatin + Etoposide +/- RT	Patients with ED-SCLC	I/II	US	2021	63	Recruiting	Incidence of dose limiting toxicity
NCT03923270	Olaparib	RT + Durvalumab Compared to: Durvalumab + Tremelimumab	Patients with ED-SCLC	I	US	2019	54	Recruiting	SAEs PFS

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; MDT, maximum dose tolerated; SAEs, unacceptable serious adverse events; ED-SCLC, extended disease small cell lung cancer; RT, radiotherapy.

cancer.<sup>93,94</sup> dsDNA interacts with cGAS, promoting a conformational change catalyzing the formation of 2',3'-cyclic GMP-AMP (Cyclic guanosine monophosphate–adenosine monophosphate) and producing the activation of the STING pathway (Figure 2),<sup>95,96</sup> thus leading to the recruitment and phosphorylation of TANK binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF-3)<sup>97</sup> and inducing interferon stimulated genes expression including PD-L1.<sup>98,99</sup>

PARPi increase DNA damage and upregulate the PD-L1 expression by cGAS-STING pathway and there are preclinical studies suggesting that PARPi synergize with PD-1/PD-L1 blockade regardless of the BRCA status.<sup>48,100</sup> Overall, these results provide a mechanistic rationale to exploit the PARPi immunomodulatory effect to reinforce immune-checkpoint blockade.

Sen et al<sup>101</sup> have shown that olaparib activates the cGAS-STING pathway in SCLC, promoting the phosphorylation of TBK1 and IRF3 and the secretion of chemokines CCL5 and CXCL10 and increased surface expression levels of PD-L1 in SCLC models.

This study also highlighted that, as PARP inhibition with olaparib alone does not impact CD8+ cytotoxic T-cell infiltration, the simultaneous inhibition of PARP and PD-L1 leads to a clear rise in CD8+ cytotoxic T-cell infiltration and reduces regulatory T-cells levels in a triple-knockout RB-/-/p53-/-/p130-/- genetically engineered mouse model.

### Clinical Evidence and Predictive Factors of Response and Efficacy

Despite these auspicious preclinical results, available evidence on PARPi plus ICIs combinations in SCLC patients has been questionable until today.

The results of a phase II trial by Thomas et al<sup>102</sup> (NCT02484404) demonstrated that only two (10.5%) out of 19 evaluable relapsed ED-SCLC patients treated with durvalumab 1,500 mg every 4 weeks with olaparib 300 mg twice a day responded with a median PFS and OS of 1.8 months (95% CI=0.9–2.4) and 4.1 months (95% CI=2.4–9.2), respectively, and the most common treatment-related adverse event was cytopenia (45% G3–4). Of note, it has been observed that pre-existing tumor CD8+ T-cell infiltration predicts tumor response, suggesting that an inflamed-phenotype at baseline may help to identify patients who are most likely to respond to an ICI-based strategy in SCLC.

Similar results were reported in the phase II MEDIOLA study<sup>103</sup> (NCT02734004) that analyzed 38 patients with relapsed SCLC receiving the same doses of olaparib and durvalumab but with a 4-week olaparib run-in period: only two patients had confirmed partial or complete responses and DCR at 12 weeks was 29%, below the futility boundary (<40%).

Another multicenter, open-label, phase 1a/b trial<sup>104</sup> (NCT02660034) enrolled 49 patients with advanced solid tumors including patients with SCLC in order to assess the safety and activity of pamiparib, a novel oral PARP 1–2 inhibitor,

combined with tislelizumab, an anti-PD-1. After a median follow-up of 8.3 months, ORR was 20% and treatment combination was well tolerated with anemia as the most common G3–4 adverse event.

An additional phase II trial (NCT03958045) including patients with pathological (biopsy) or cytologically confirmed stage IV SCLC achieving either partial or complete response after frontline chemotherapy with platinum doublet, is currently assessing survival and response rate of the combination of rucaparib and nivolumab as a maintenance therapy.

Other studies aiming to evaluate novel immunotherapy-based combinations as maintenance therapy following first-line treatment are currently underway (Table 10).

## PARPi + DDR Inhibitors

### Biological Rationale and Preclinical Data

Both in vitro and in vivo SCLC models support the rationale of combining PARPi with other drugs targeting the HRR pathways, especially the ATR/CHK1 (Checkpoint kinase 1) axis.<sup>105</sup> Preclinical models showed a higher activity of ATR

**Table 10** Main Ongoing Clinical Trials Evaluating the Role of PARPi + Immunotherapy in SCLC Treatment

Study Name	PARPi	Other Agent(s)	Selected Population	Ph	Country	Study Start Year	Estimated Number of SCLC Patients Enrolled	Primary Outcome Measure/s
NCT02484404	Olaparib	Durvalumab	Patients progressed to prior platinum-based chemotherapy	II	US	2015	384	Safety RP2D ORR
NCT02734004	Olaparib	Durvalumab	Patients with relapsed SCLC	I/II	Global	2016	264 patients enrolled	Safety DCR ORR
NCT02660034	Pamiparib	Tislelizumab	Patients with ED-SCLC	I	Western	2016	229 patients enrolled	Number of participants experiencing AEs, DLT, ORR, PFS, DOR, DCR, CBR, OS
NCT03958045	Rucaparib	Nivolumab	Patients with platinum-sensitive ED-SCLC	II	US	2019	36	PFS
NCT04624204	Olaparib	Compared to: Olaparib + Pembrolizumab Or Pembrolizumab alone	Patients with LD-SCLC	III	Global	2020	672	PFS OS
NCT03958045	Rucaparib	Nivolumab	Patients with platinum-sensitive ED-SCLC	II	US	2019	36	PFS
NCT04334941	Talazoparib	Atezolizumab	Patients with ED-SCLC	II	US	2020	94	PFS

(Continued)

**Table 10** (Continued).

Study Name	PARPi	Other Agent(s)	Selected Population	Ph	Country	Study Start Year	Estimated Number of SCLC Patients Enrolled	Primary Outcome Measure/s
NCT03830918	Niraparib	Temozolomide + Atezolizumab	Patients with ED-SCLC	I/II	US	2019	74	RP2D of Niraparib + Temozolomide PFS
NCT02937818	Olaparib	Ceralasertib Compared to Durvalumab + Tremelimumab or Adavosertib + Carboplatin	Patients with ED-SCLC	II	Western	2016	72	Number of participants with overall response

**Abbreviations:** Ph, phase; PFS, progression-free survival; US, United States; PE, primary endpoint; MDT, maximum dose tolerated; SAEs, unacceptable serious adverse events; ED, extended disease; RP2D, recommended phase II dose; ORR, objective response rate; DCR, disease control rate; UK, United Kingdom; N/R, not reported; AEs, adverse events; DLT, dose-limiting toxicity; DOR, duration of response; DCR, disease control rate; CBR, clinical benefit rate; OS, overall survival; SCLC, small-cell lung cancer.

inhibitors in tumors with TP53/ATM lack of function<sup>15</sup> and CHK1 inhibition effectively overcome PARPi resistance in vitro, supporting the rationale for testing combination treatment.<sup>106</sup>

### Clinical Evidence and Predictive Factors of Response and Efficacy

Though there are concerns regarding patients' selection, safety profile and possible mechanisms of resistance, the rationale for combining different HRR inhibitors is strong and several ongoing clinical trials will provide clinical evidence about this novel strategy.

Adavosertib, a WEE1 kinase inhibitor, in association with olaparib has been tested in a phase Ib study (NCT02511795),<sup>107</sup> showing a promising ORR of 30.8%. A phase II trial (NCT03428607, SUKSES-N2) investigating combination treatment with ceralasertib, a CHK1 inhibitor, and olaparib as second-line treatment of ED-SCLC has completed its enrollment, and primary analysis results are awaited soon.

Main ongoing clinical trials evaluating the role of PARPi with DDRi in SCLC patients are listed in [Table 11](#).

## Malignant Pleural Mesothelioma (MPM)

### PARPi Alone or in Association with Chemotherapy

#### Biological Rationale and Preclinical Data

Until a few years ago, the only therapeutic option with proven effectiveness in the treatment of MPM was platinum and pemetrexed chemotherapy,<sup>108</sup> but promising new options have recently emerged from the use of immunotherapy, in

**Table 11** Main Ongoing Clinical Trials Evaluating the Role of PARPi + DDR Inhibitors in SCLC Treatment

Trial	PARPi	Other Agent(s)	Setting	Ph	Biomarker Selection	Country	Estimated Sample Size	Trial Status	Primary Outcome Measure/s
NCT02511795	Olaparib	AZD1775 (Adavosertib)	≥2nd line	Ib	–	US, CANADA	128	Completed	DLT/AEs
NCT04158336	Talazoparib	ZN-c3 (WEE1Ki)	≥2nd line	I	–	US	110	Recruiting	MTD
NCT03428607 (SUKSES-N2)	Olaparib	AZD6738 (Ceralasertib)	≥2nd line	II	–	SOUTH KOREA	45	Completed	ORR

**Abbreviations:** ORR, overall response rate; US, United States; PH, phase; MTD, maximum dose tolerable; DLT, dose limiting toxicities; AEs, adverse effects.

particular the combination of Nivolumab and Ipilimumab (Checkmate 743).<sup>109</sup> In MPM, activating mutations are rare and genomic losses/alterations are more widespread, hence alternative treatments to current standards are still an open issue.

In addition, better understanding of cancer biology has opened the targeted therapies era also for neglected tumors such as MPM.

In particular, an important percentage (5–10%) of patients with MPM with germline mutations in the DDR genes pathway have shown a relevant sensitivity to asbestos<sup>110</sup> and BRCA1/2 or mutations of other genes involved in the HRR pathway have been observed in many MPM patients.<sup>111</sup> Moreover, more than 20% of MPM showed somatic inactivating mutations in the BRCA-1 associated gene (BAP1),<sup>112</sup> which seem to play an important role in tumor pathogenesis.<sup>113</sup> Hence, the idea that cells presenting mutated BAP1 may require PARP-1 enzyme to survive has led to the initiation of several preclinical studies exploring the potential efficacy of PARPi in this setting.<sup>114</sup>

Interestingly and partially negating the potential interaction between BAP1 gene and PARP enzyme specific inhibition, two different preclinical studies have shown that both niraparib and olaparib had potential efficacy against MPM cells, regardless of the presence of BAP1 mutations.<sup>115,116</sup> Borchert et al,<sup>117,118</sup> performing analysis with luminescence assays, also highlighted the promising combination of PARPi with cisplatin-based chemotherapy.

### Clinical Evidence and Predictive Factors of Response and Efficacy

Further exploring evidence from preclinical studies, many trials have been evaluating the efficacy and tolerability of PARPi in MPM.<sup>112,119</sup> Ghafoor et al<sup>120</sup> studied olaparib in 23 patients with advanced MPM with somatic or germline mutations of DNA repair genes in a phase 2 single-center trial. Patients were given olaparib 300 mg twice daily in 21-day cycles until disease progression or intolerable toxicity. Definitive results were quite disappointing in particular in the germline mutation cohort: in germline and somatic BAP1 mutants, median PFS was 2.3 months (95% CI=1.3–3.6 months) versus 4.1 months (95% CI=2.7–5.5 months) with a median OS of 4.6 months (95% CI=3.1–4.9 months) vs 9.6 months (95% CI=5.5 months–not estimable) ( $p=0.0040$ ). Among ongoing clinical trials, the UNITO-001, a prospective phase 2 single arm study, is evaluating the combination of niraparib and dostarlimab in metastatic mesotheliomas with both HRR deficiency and PD-L1 positivity (TPS>1%). The primary endpoint is PFS, secondary endpoints are overall survival, objective response, duration of response, and safety.<sup>121</sup>

The TALAMESO trial (NCT04462809) is an open-label phase II trial with three independent cohorts including patients with advanced malignant pleural (cohort A) or peritoneal (cohort B1 and B2) mesotheliomas without any sign of disease progression after four to six cycles of platinum-based chemotherapy (including a minimum one cycle of pemetrexed). The primary endpoint is the non-progression proportion (defined as the proportion of patients free of progression 6 months after talazoparib start); secondary endpoints are PFS, toxicity, and safety assessment.

The MiST trial is a Phase II, single arm study that is testing the efficacy of rucaparib in MPM patients with BAP1 or BRCA mutation.<sup>122</sup> The primary endpoint is DCR, secondary endpoints are ORR, toxicity, and safety assessment. Moreover, new studies with PARPi started in mesothelioma with homologous recombination deficiency associated with BRCA1 mutation.<sup>123</sup>

The main ongoing clinical trials evaluating the role of PARPi in MPM patients are listed in [Table 12](#).

## PARG Inhibitors in Thoracic Malignancies

### Biological Rationale and Preclinical Data

Poly (ADP-ribose) glycohydrolase is the primary hydrolase involved in the degradation of PAR. PARG localizes at replication forks by binding PCNA and promotes recovery from prolonged replication stress.

PARG isoforms have a cytoplasmic and perinuclear distribution and seem to migrate to the nucleus when activated due to genotoxic insult. However, how the different isoforms fully contribute to PAR metabolism and its significance is yet to be elucidated.

The consensus opinion is that PARP and PARG share an important function in downstream cellular processes enhancement. Just like PARP, PARG inhibition weakens cancer cells' resistance to DNA damaging agents due to PARG enzymes' role in DNA repair mechanisms.

**Table 12** Main Ongoing Clinical Trials Evaluating the Role of PARPi in MPM Treatment

Trial	PARPi	Other Agent(s)	Tumor Type	Setting	Ph	Biomarker Selection	Country	Estimated sample Size	Primary Outcome Measure/s
MiST	Rucaparib	–	MPM	≥2nd line	I	BRCA1/BAP1 negative	United States	200	DCR
TALAMESO	Talazoparib	–	MPM	Maintenance therapy	II		France	40	Non progression proportion
UNITO-001	Niraparib	Dostarlimab	MPM	Stage IV	II	HRR-mutated and PD-L1 ≥ 1%	Italy	70	PFS
LuPARP	Olaparib	<sup>177</sup> Lu-DOTA-TATE	MPM NET Thymoma	Metastatic or advanced	I	Somatostatin receptor positive	Australia	52	Dose limited toxicity, maximum tolerated dose recommended Phase 2 dose
NERO	Niraparib	–	MPM	≥2nd line	II		UK	84	PFS

**Abbreviations:** PFS, progression-free survival; UK, United Kingdom; DCR, disease control rate; MPM, malignant pleural mesothelioma; PH, phase; NET, neuroendocrine tumors.

In contrast to PARP inhibitors, a clear correlation between HR deficiency and PARGi-related synthetic lethality still needs to be fully demonstrated.<sup>3–124</sup>

## Clinical Evidence and Predictive Factors of Response and Efficacy

Depletion of HR involved proteins such as BRCA1, BRCA2, PALB2, ABRAXAS, and BARD1 in MCF7 breast cancer lines was shown to elicit synthetic lethal interactions with PARG inhibition.<sup>125</sup>

Pillay et al,<sup>126</sup> evaluating PARGi PDD00017273 on ovarian cancer cell lines, found that cancer cells were differentially sensitive to PARG and PARP inhibition. In particular, a “replication catastrophe” event (identified as pan-nuclear  $\gamma$ H2AX staining) due to underlying DNA replication vulnerabilities occurred upon PARGi administration; on the other hand, the same chain reaction was not seen with the PARPi olaparib. Despite the analysis being performed only on in vitro models, this study suggests that low expression of key replication factors promoting DNA fork stabilization may be a biomarker predictive of PARGi effectiveness also alternatively to PARPi. Moreover, BRCA1 mutated cells with acquired resistance to PARPi due to loss of 53BP-1 were still more sensitive to the PARGi COH34 than BRCA1 wildtype cells.<sup>127</sup> PARGi have also been reported to be synthetic lethal in XRCC1 depleted and deficient cells.<sup>128</sup> It follows that PARGi may have efficacy in XRCC1 tumors, probably because of the function of XRCC1 in stabilizing stalled forks. Furthermore, PARG depletion via siRNA was reported to be synthetic lethal with dual specificity phosphatase 22 (DUSP22) via suppression of the mTOR/PI3k/AKT in lung cancer.<sup>129</sup>

Nevertheless, PARG depletion did not show synthetic lethality with BRCA1 mutations in different cancer cell lines<sup>130</sup> and PARG overexpression was even related with tumor-promoting genes downregulation and suppression in prostate cancer PC-3 cell lines.<sup>131</sup>

Focusing on the potential association of PARGi with other drugs, evidence supporting a chemosensitizing effect of PARG inhibition has already been reported in literature, in particular considering DNA-damaging agents. Chen and Yu<sup>127</sup> described that a novel small molecule identified from the NCI database, COH34, specifically inhibiting PARG can sensitize different tumor cell lines with DNA repair defects to topoisomerase I inhibitors and DNA-alkylating agents, which are widely used in cancer chemotherapy, such as cisplatin, temozolomide, and doxorubicine. Pillay et al<sup>126</sup> demonstrated a similar effect of gemcitabine in combination with PARGi PDD00017273 in ovarian cancer cell lines.

Finally, Jain et al<sup>132</sup> evaluated PARG as a target in ductal pancreatic adenocarcinoma models using both genetic silencing of PARG and established small-molecule PARGi PDDX-01/04. Homologous repair-deficient cells compared with homologous repair-proficient cells were more sensitive to PARGi in vitro, while in vivo silencing of PARG significantly decreased tumor growth. PARGi also seemed to synergize with DNA-damaging agents, in particular oxaliplatin and 5-fluorouracil, that are commonly used in pancreatic cancer treatment.

A potential synergistic effect between PARG inhibition and radiation therapy has been reported in different *in vitro* models due to the occurrence and accumulation of mitotic defects, finally culminating in cancer cell apoptosis.<sup>133</sup>

Most interestingly, Gravells et al<sup>134</sup> provided a comparison of the potential radiosensitizing effect of PARP inhibitor olaparib and novel PARG inhibitor PDD00017273: both olaparib and PDD00017273 altered the repair of radiation-induced DNA damage, resulting in delayed resolution of RAD51 foci compared with control cells but only PARG inhibition was able to effectively induce a perturbed mitotic progression leading to cell death, thus suggesting that PARG plays different functions in the cell compared with inhibition of PARP1/2/3, likely via reversal of tankyrase enzyme activity. However, solid evidence of the potential application of PARGi radiosensitizing effect in clinical practice is still lacking.

Despite preclinical evidence in selected scenarios, PARG inhibition still represents a niche option in cancer treatment and we still lack a clinical trial demonstrating some sort of benefit. Nowadays, there is great expectation in the phase I–II NCT05787587 trial that is going to evaluate PARG Inhibitor IDE161 efficacy in patients with advanced solid tumors harboring BRCA1/2 loss of function alterations and/or other defects in the homologous recombination (HR) pathway.

## Conclusions

Despite FDA approval in HR-deficient castration resistant prostate cancer and BRCA1/2 mutated ovarian, breast, and pancreatic tumors, the efficacy of PARPi is restricted by inevitable drug resistance, whereas dose-limiting toxicities are frequently linked to its use in conjunction with chemotherapy and targeted medicines. ICIs have shown persistent responses in a variety of solid tumors, however single agent action is only seen in a small proportion of patients and drug resistance is still a problem.<sup>135</sup> Based on the success of both drug classes and considering the growing evidence in literature on the potential synergy between PARP inhibition and immunotherapy, a combination strategy may represent a turning point.<sup>135</sup> Preclinical data revealed that the activation of the cGAS-sting pathway by PARP inhibition results in an important PD-L1 expression on cancer cells creating an appropriate tumor immune microenvironment to take advantage of ICB. The combination of ICB and PARPi has been encouraged by clinical trials showing improved survival outcomes in prostate, breast, ovarian, and SCLC, regardless of mutational status or even in the case of platinum sensitivity.

Considering NSCLC, trials investigating PARPi as monotherapy did not show improved outcomes, but associations with other therapies, such as immunotherapy, might result in better outcomes.<sup>136,137</sup>

PD-L1 expression has been identified as putative predictive biomarkers of response for ICB therapy selection in NSCLC; however, these have not been consistently shown to have predictive potential in the context of PARPi and ICB combination strategies.<sup>138</sup> Similarly, in SCLC and prostate cancer, no clear correlation between PD-L1 expression and treatment response has been demonstrated.<sup>102,139</sup>

In this regard, new technologies such as Next Generation Sequencing (NGS) might be crucial in opening new paths as the identification of reliable molecular predictive factors other than MMR deficiency constitutes a critical issue that must be thoroughly addressed in future investigations. As most clinical trials designed so far lacked an adequate patient selection, new studies are underway and will help determine the potential role for PARPi in thoracic malignancies treatment.

Another open question is also the low oral bioavailability of PARPi, as these drugs effective and safe delivery during clinical cancer therapy still represents a challenge. In this regard, the development of drug delivery has advanced because of nanotechnology: this term commonly refers to structures that are up to several hundred nanometers in size.<sup>140</sup> In recent decades, a number of nanoformulations, as drug delivery systems (DDSs), have been reported for the treatment of cancers, such as liposomes, polymeric micelles, hydrogels, nanoemulsions, nanosuspensions, and nanoparticles.<sup>141</sup> Drug delivery systems could provide protection for drugs in blood circulation, increasing the amount of time of their circulation and they could gather in the leaking vasculature of the tumor and cancer cells releasing the chemotherapeutic moiety into the tumor microenvironment. At the same time nanoparticles are unable to pass through the body's organs and tissues, so nanosystems may not only enhance drug efficiency but also reduce adverse side-effects.<sup>142</sup>

In conclusion, PARPi represent a solid reality in numerous solid tumors and several trials are exploring their potential employment in diseases such as thoracic malignancies where they might represent a novel therapeutic option. However,

these drugs still face several serious downsides, including resistance mechanisms and unintended adverse effects and their efficacy as single agents still need to be fully demonstrated in the context of thoracic malignancies. In this regard, considering available evidence in the literature we already discussed in our review, interest is growing in exploring the potential synergistic effect and consequently combined administration of PARPi and PARGi with other agents such as chemotherapy, immunotherapy, or radiotherapy. Novel strategies such as tumor profiling with NGS might be helpful in determining reliable predictive factors guiding patients selection in clinical practice.

In addition, with the recent introduction of nanomedicine, off-site toxicity or drug resistance might be reduced in the next few years, thus opening new interesting scenarios for PARPi and PARGi in clinical practice.

## Abbreviations

SCLC, Small Cell Lung Cancer; NSCLC, Non-Small Cell Lung Cancer; MPM, malignant pleural mesothelioma; EGFR, epithelial growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; KRAS, Kirsten rat sarcoma virus (*KRAS*); BRAF, V-raf murine sarcoma oncogene homolog B1; HER2, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; HRR, Homologous Recombination Repair; PARPi, poly (ADP-ribose) polymerase inhibitors; PARG, poly (ADP-ribose) glycohydrolase; PARGi, poly (ADP-ribose) glycohydrolase inhibitors; NAD, Nicotinamide Adenine Dinucleotide; BER, Base-Excision Repair; NER, Nucleotide-Excision Repair; MMR, Mismatch Repair; HR, Homologous Recombination; NHEJ, Non-Homologous End-Joining; PARP-1, poly (ADP-ribose) polymerase-1; PARP-2, poly (ADP-ribose) polymerase-2; MGMT, MethylGuanineDNA Methyltransferase; BRCA1, Breast Cancer gene 1; BRCA2, Breast Cancer gene 2; ERCC1, Excision repair cross-complementation group 1; LOH, Loss Of Heterozygosity; EGFR, Epithelial Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; PFS, Progression Free Survival; ATM, Ataxia-Telangiectasia Mutated; ATR, Ataxia-Telangiectasia and Rad3 related; GDSC, Genomics of Drug Sensitivity in Cancer; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CAS9, CRISPR Associated Protein 9; IC<sub>50</sub>, Half Maximal Inhibitory Concentration; PTEM, Phosphatase and Tensin Homolog; TMZ, Temozolomide; GCI, Gemcitabine/Cisplatin/Iniparib; GC, Gemcitabine/Cisplatin; ORR, Overall Response Rate; OS, Overall Survival; HR, Hazard Ratio; CI, Confidence Interval; WES, Whole Exome Sequencing; H2AFX, H2A Histone Family Member X; CRT, Chemoradiotherapy; DLT, Dose Limiting Toxicity; MTD, Maximum Tolerable Dose; ICIs, Immune Checkpoint Inhibitors; TMB, Tumor Mutational Burden; STING, Stimulator of IFN Genes; PD-1, Programmed Death-protein 1; PD-L1, Programmed Cell Death Ligand-1; TPS, Tumor Proportion Score; DOR, Duration of Response; DDRi, DNA Damage Response Inhibitors; ED, Extended Disease; LS, limited stage; PDX, Patient-Derived Xenograft; cRT, Consolidative Radiation Therapy; c-GAS, Cyclic GMP–AMP synthase; cGAMP, Cyclic Guanosine monophosphate–Adenosine Monophosphate; dsDNA, Double Stranded DNA; TBK1, TANK Binding Kinase 1; IRF-3, Interferon Regulatory Factor 3; CHK1, Checkpoint Kinase; BAP1, BRCA1-Associated Protein-1; DCR, Disease Control Rate; TPS, Tumor Proportion Score; VEGF, Vascular Endothelial Growth Factor; SSB, Single-strand breaks; ISGs, IFN-stimulated genes; MHC, major histocompatibility complex; TCR, T cell receptor; NGS, Next Generation Sequencing.

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