Original Article

Efficacy and safety of PARP inhibitor in non-small cell lung cancer: a systematic review with meta-analysis

Alejandro Olivares-Hernández[1,2]^, Jonnathan Roldán-Ruiz[1,2], José Pablo Miramontes-González[3,4], Irene Toribio-García[5], Juan Luis García-Hernández[2], Luis Posado-Domínguez[1,2], Lorena Bellido-Hernández[1,2,6], Juan Jesús Cruz-Hernández[1,2,6], Emilio Fonseca-Sánchez[1,2,6], Edel del Barco-Morillo[1,2,6]

[1]Department of Medical Oncology, University Hospital of Salamanca, Salamanca, Spain; [2]Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain; [3]Department of Internal Medicine, University Hospital Rio Hortega, Valladolid, Spain; [4]Faculty of Medicine, University of Valladolid, Valladolid, Spain; [5]Department of Cardiology, University Hospital of Leon, León, Spain; [6]Faculty of Salamanca, University of Salamanca, Salamanca, Spain

Contributions: (I) Conception and design: A Olivares-Hernández, J Roldán-Ruiz, E del Barco-Morillo; (II) Administrative support: JJ Cruz-Hernández, E Fonseca-Sánchez; (III) Provision of study materials or patients: A Olivares-Hernández, JP Miramontes-González, JL García-Hernández, L Bellido-Hernández, E del Barco-Morillo; (IV) Collection and assembly of data: A Olivares-Hernández, I Toribio-García, L Posado-Domínguez; (V) Data analysis and interpretation: A Olivares-Hernández, J Roldán-Ruiz, I Toribio-García, E del Barco-Morillo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alejandro Olivares-Hernández, MD, PhD. Lung Cancer Unit, Department of Medical Oncology, University Hospital of Salamanca, Paseo de San Vicente, 182, 37007 Salamanca, Spain; Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain. Email: aolivares@saludcastillayleon.es; Irene Toribio-García, MD. Department of Cardiology, University Hospital of Leon, Calle Altos de Nava, s/n, 24008 León, Spain. Email: itoribio@saludcastillayleon.es; Jonnathan Roldán-Ruiz, MD. Department of Medical Oncology, University Hospital of Salamanca, Paseo de San Vicente, 182, 37007 Salamanca, Spain; Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain. Email: jroldanr@saludcastillayleon.es.

Background: Non-small cell lung cancer (NSCLC) has undergone a major change in the last decade in terms of survival and prognosis due to the introduction of new drugs in the last 10 years. One of the drugs with the most promising preliminary results in NSCLC are PARP inhibitors (iPARPs), whose clinical trials have very heterogeneous results. The use of iPARPs in NSCLC may lead to increased survival in several selected patients, and their use may become a standard in the coming years. However, there is currently controversy about the efficacy and safety of these drugs in NSCLC. Therefore, future studies are needed to evaluate their role in these tumours. The aim of this review is to evaluate the efficacy and safety of iPARPs in the treatment of NSCLC.

Methods: We performed a systematic review with meta-analysis using the different clinical trials (PubMed, COCHRANE, Science Direct, EMBASE and the clinical trial registry) that evaluated the efficacy and safety of iPARP in NSCLC by PRISMA criteria. The primary endpoint was to evaluate the efficacy of iPARPs in the treatment of NSCLC through overall and progression-free survival (OS and PFS). Two authors independently reviewed the articles and abstracts (A.O.H. and J.R.R.), with subsequent confirmation by a third independent reviewer (E.B.M.). The heterogeneity of the included studies in the meta-analysis was assessed by using the I^2 statistic.

Results: A total of 14 articles were included for analysis (2,651 patients). A total of 1,503 patients were randomised in iPARP arms and 1,148 patients were included in control arms. Three clinical trials were conducted in localised or locally advanced NSCLC and 11 in advanced or metastatic stages. The global OS of the meta-analysis showed a hazard ratio (HR) of 0.85 [95% confidence interval (CI): 0.74–0.97] with a heterogeneity (I^2) of 0% (P=0.84). PFS showed a HR of 0.93 (95% CI: 0.74–1.17) with an I^2=51% (P=0.07).

^ ORCID: 0000-0003-1992-6105.

The overall adverse event rate (grade 1–5) was similar in both iPARP and placebo arms.

Conclusions: iPARPs are a future promising in the treatment of NSCLC in terms of efficacy and safety. Proper patient selection [homologous recombination deficiency (HRD) positive] is key for future clinical trials. The studies conducted to date open a new approach for a novel treatment modality in NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); PARP inhibitor (iPARP); systematic review; homologous recombination deficiency (HRD); biomarker

Submitted Jun 25, 2023. Accepted for publication Dec 08, 2023. Published online Dec 18, 2023.
doi: 10.21037/cco-23-58
View this article at: https://dx.doi.org/10.21037/cco-23-58

Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers (1,2). Approximately two-thirds of all NSCLC patients have advanced disease at diagnosis (stage IIIB to IV) and are treated with systemic therapies using chemotherapeutic agents, immunotherapy or drugs directed against molecular targets (3,4). Despite the great advances in terms of response, survival and toxicity that are being achieved in these patients, new target therapies are being investigated in NSCLC given the great advances in the molecular characterisation of lung cancers (5,6).

Poly (ADP-ribose) polymerase (PARP) enzymes are a family of nuclear enzymes involved in the recognition and repair of single DNA breaks (7-9). The main activity of PARP is poly-ADP ribosylation of key chromatin components and other proteins involved in DNA repair (10). PARP1 can open chromatin and facilitate the entry of DNA repair factors (11). Therefore, PARP inhibitors (iPARPs) have emerged as a new avenue of research for the treatment of NSCLC, with very promising results at the preclinical level (12).

The activity of iPARPs was originally established in tumours with *BRCA1* and *BRCA2* gene mutations showing homologous recombination deficiency (HRD) (13,14). Subsequently, its activity was also characterised in HRD tumours with mutations in other homologous recombination (HR)-associated genes such as *RAD51C* (15), *RAD51D* (16), *PALB2* (17) or *BARD1* (18). Given these findings in tumours such as ovarian or prostate tumours, it has also been suggested that they may have potential benefit in tumours where HRD is not fully studied and known, such as NSCLC (19,20).

The Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have approved several iPARPs for the treatment of different tumours such as ovarian, breast, prostate or pancreatic tumours (*Figure 1*) (21). To date, few studies have evaluated the efficacy of iPARPs in NSCLC; however, the data are promising in some cases, and thus, a pooled assessment is essential to understand these new treatments, which could have important implications (22,23). The presence of tobacco in carcinogenesis has meant that some molecular pathways have not been fully studied in NSCLC. One of the most promising pathways is HRD. The percentage of lung cancer with HRD is currently unknown, and its influence may derive both from treatment with iPARPs and immune checkpoint inhibitors for example.

Studies to date with iPARPs have not provided answers as to how these treatments may benefit patients with

Highlight box

Key findings

- PARP inhibitors (iPARPs) are a very promising treatment in non-small cell lung cancer (NSCLC); however, future clinical trials require proper patient selection marked by the presence of NSCLC with homologous recombination deficiency (HRD).

What is known and what is new?

- Treatment with iPARPs is an effective and standardised alternative for ovarian, pancreatic and prostate tumours. Currently, in NSCLC it is a promising treatment but with no known role yet in these tumours.
- In properly selected patients with NSCLC HRD, iPARP represent a very promising treatment option.

What is the implication, and what should change now?

- It is essential that future clinical trials correctly select NSCLC patients in whom iPARPs are to be used. The use of biomarkers predictive of response to iPARPs will allow for future standardisation of this treatment in NSCLC.

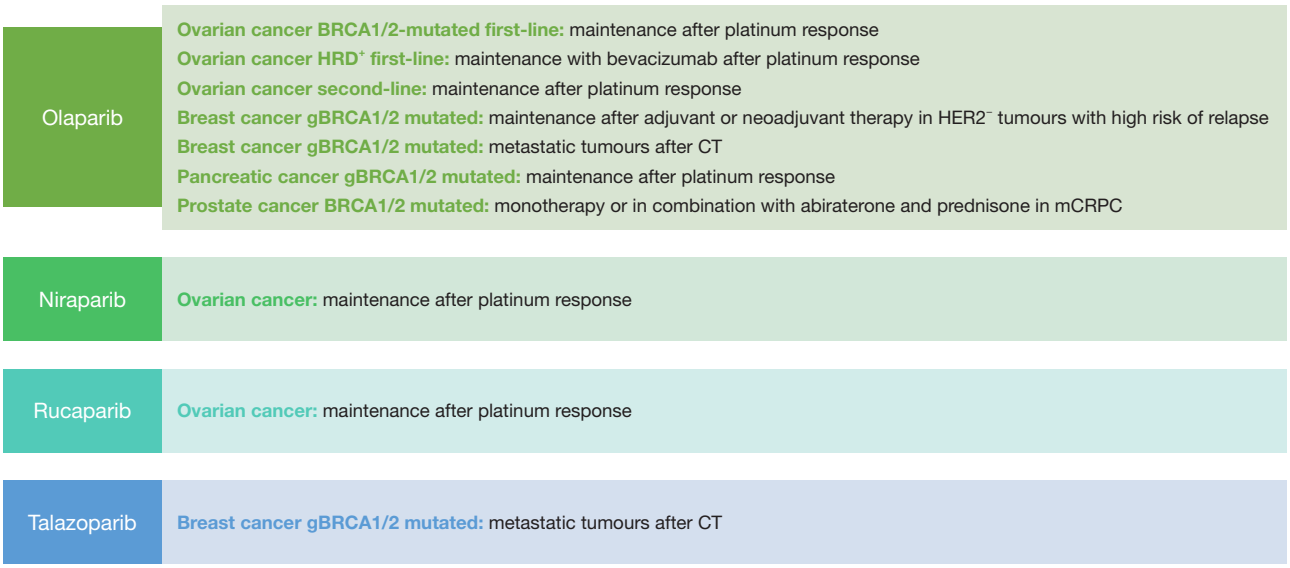

Figure 1 Main iPARPs approved by the EMA for the treatment of solid tumours with their therapeutic indications. iPARPs, poly ADP ribose polymerase inhibitors; EMA, European Medicine Agency; HRD, homologous recombination deficiency; gBRCA1/2, germline mutation in BRCA1/2; HER2, receptor tyrosine-protein kinase erbB-2; CT, computed chemotherapy; mCRPC, metastatic castration-resistant prostate cancer.

NSCLC in clinical practice. For this reason, the aim of this systematic review is to evaluate the efficacy and safety of iPARPs in the treatment of NSCLC using the different clinical trials currently conducted and published in this field. We present this article in accordance with the PRISMA reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-58/rc).

Methods

Search protocol and strategy

Following the quality criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we searched PubMed, COCHRANE, Science Direct, EMBASE and the clinical trial registry (http://www.clinicaltrials.gov/) for clinical trials and systematic reviews aimed at evaluating the efficacy in terms of response and survival of iPARP in NSCLC. Publications in English, French and Spanish from 2014 to 2023 were evaluated and included. The flow chart of the study is shown in *Figure 2*.

Search terms and combinations included (non-small-cell lung cancer OR lung cancer) AND (iPARP OR PARP inhibitor) AND (niraparib OR iniparib OR olaparib OR talazoparib OR veliparib OR rucaparib). In addition, the following filters were applied: "clinical trial", "meta-analysis", "review" and "systematic review". No restrictions were applied in terms of study type, publication type, publication date or language.

Selection of studies (inclusion and exclusion criteria)

Studies eligible for systematic review were phase I, II or III clinical trials that evaluated the efficacy and safety of iPARPs (in monotherapy or combination) in NSCLC. The criteria were as follows:

Inclusion criteria:

- Clinical trials or systematic reviews uniquely evaluating the association between iPARPs and the treatment of NSCLC;
- iPARP treatments are associated with combinations with chemotherapy, radiotherapy, immunotherapy or drugs against molecular targets;
- Included studies should indicate response in terms of RECIST1.1 (Response Evaluation Criteria in Solid Tumours) criteria, survival in terms of overall survival (OS) and progression-free survival (PFS) and toxicity in terms of CTCAEv4.0 (Common Terminology Criteria for Adverse Events).

Exclusion criteria:

- Clinical trials published as preliminary abstracts or

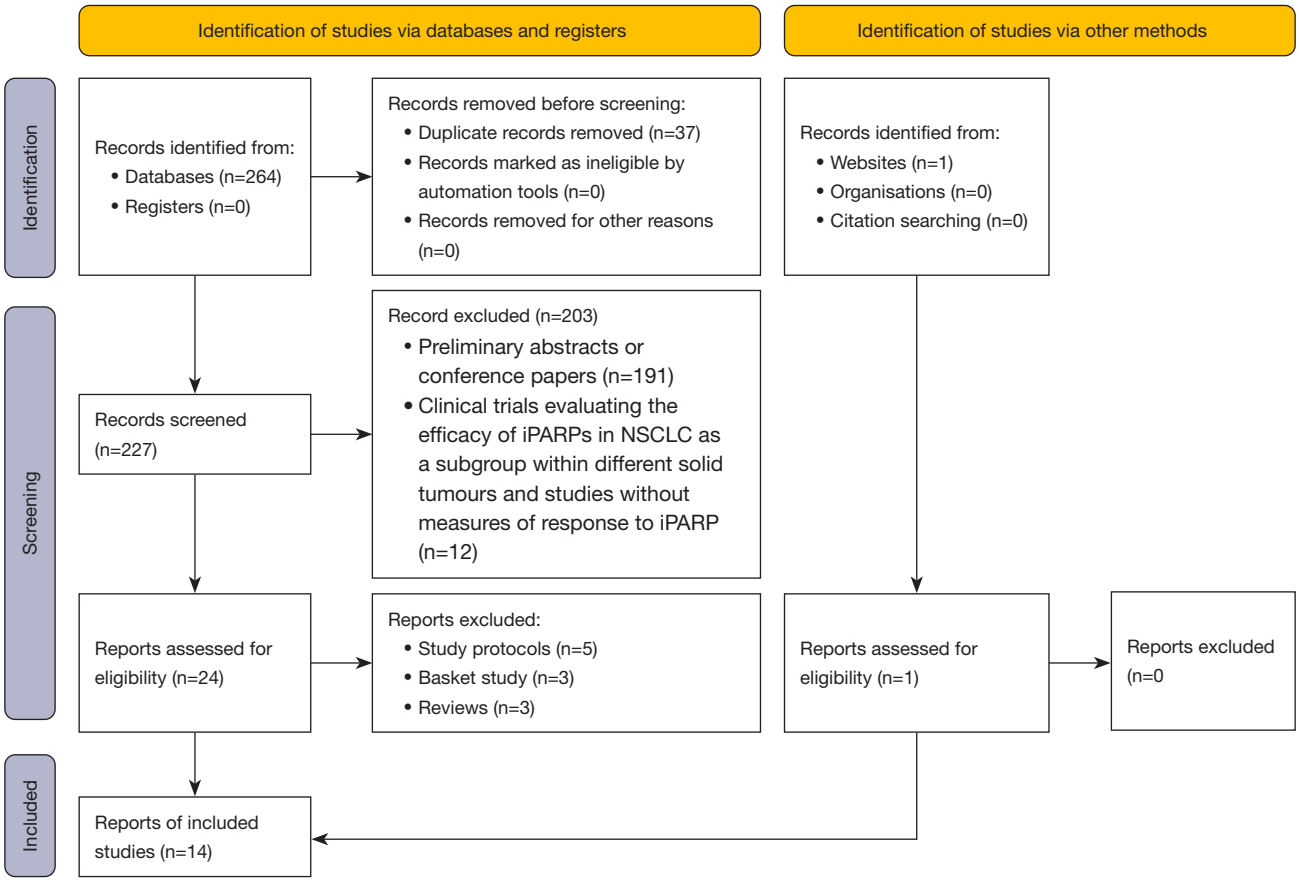

Figure 2 PRISMA flow chart of the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

conference papers without definitive results;

- ❖ Clinical trials or reviews reporting duplicate results, study protocols or editorials;
- ❖ Clinical trials evaluating the efficacy of iPARPs in NSCLC as a subgroup within different solid tumours, without analysis in stand-alone NSCLC;
- ❖ Studies with non-assessable measures of response to iPARP treatment.

Quality assessment and publication bias

Two authors independently reviewed the articles and abstracts (A.O.H. and J.R.R.). Those publications that passed the inclusion criteria were analysed in depth and selected for the present review with confirmation by a third independent reviewer (E.B.M.). Publication bias was assessed using Egger's test and a funnel plot (P value of 0.05 showed asymmetry of the plot).

Data extraction and statistical analysis

Data extracted by the two investigators independently were: title, first author, year of publication, number of patients included, type of population selected, tumour stage, histological subtype, phase of clinical trial, clinical trial arms (concomitant treatments to iPARP), primary objective, secondary objectives, OS, PFS, response and toxicity.

Survival, response and toxicity data have been pooled in a database that was subsequently transformed into a summary data table. The variables in the database were analysed with variables expressed in qualitative and quantitative terms, trying to express the data as homogeneously as possible. The statistical software SPSS, version 28 (IBM®) was used to analyse the data.

In the meta-analysis, study heterogeneity was calculated using the I^2 test. A value <25% indicated low heterogeneity, a value of 25–50% medium heterogeneity and a value >50%

high heterogeneity. Statistical significance was set at P<0.05, with all values reported bilaterally. The influence of each of the studies was compared with a sensitivity analysis.

Results

General characteristics of the sample

The literature search identified a total of 14 articles that were included for analysis. Overall, a total of 2,651 patients were included. Of these patients, 1,503 patients were randomised to receive iPARP alone or in combination with other systemic treatment and 1,148 patients were included in the control arms who were given standard treatment. The most commonly used chemotherapy schedule, adding both experimental and control arms, was carboplatin/paclitaxel (total 1,860 patients).

Seven studies (50%) evaluated iPARP in first line, all used veliparib in combination with carboplatin/paclitaxel, two of them included unresectable stage III patients and evaluated the use of radiotherapy plus veliparib plus chemotherapy schedules. There were also studies including patients in more advanced lines of treatment and one study to evaluate a subsequent maintenance strategy with iPARP *vs.* placebo.

Eight (57.1%) studies were phase II clinical trials, four (28.6%) were phase I clinical trials and only two (14.3%) studies were phase III clinical trials. The main characteristics of the studies are listed in *Table 1*. One phase III study stratified and assessed LP52 (clinical and genomic predictor of iPARP response). In the combination group of veliparib plus chemotherapy (carboplatin/paclitaxel) or chemotherapy alone was 13% LP52$^+$. In LP52$^-$, 25% were in the veliparib plus chemotherapy (carboplatin/paclitaxel) group and 18% in chemotherapy alone. No clinically significant differences were observed between treatment groups based on epidemiology or tumour pathology.

Efficacy analysis of iPARP in localised or locally advanced stages

Three clinical trials have evaluated the role of iPARPs in localised or locally advanced stages. All three studies have analysed this role in combination with radiotherapy plus platinum. In total, 128 patients are part of these three clinical trials, of which 105 patients are in the experimental arm with iPARP and 23 patients in the control arm. All three studies showed that in terms of safety, the combination of radiotherapy with platinum and radiotherapy is well tolerated with an acceptable adverse event rate for its combination in clinical practice.

At the efficacy level, all three studies showed favourable results, although only two of them present the assessment of survival or response as a primary objective. Notably, the study by Kozono *et al.* (24), shows an objective response rate (ORR) of 73% with a median PFS of 19.6 months with no control group. The other study by Argiris *et al.* (25), has a similar response and survival rate between the veliparib *vs.* placebo group, although at the OS level it shows a 1-year survival rate of 89% for the iPARP arm *vs.* 54% in the placebo arm (not statistically significant). At the response rate level, there was no statistical difference between the veliparib *vs.* placebo group (56% *vs.* 69%).

Efficacy analysis of iPARP in metastatic stages

Among the studies that evaluated iPARPs in metastatic stages, six of them do so in combination with chemotherapy +/– immunotherapy, two the action of iPARPs without combinations, one study the combination of iPARPs with immunotherapy, another the action of NSCLC with target mutations (*EGFR*) and finally another study the action of iPARPs in the treatment of central nervous system metastases (*Table 2*). Among the combination studies with chemotherapy, the studies by Ramalingam *et al.* (26) and Govindan *et al.* (27), overall, did not show greater efficacy of combination treatments with veliparib *vs.* placebo, however, in patients with LP52$^+$, greater efficacy was observed. The first study showed an OS in the LP52$^+$ NSCLC subgroup of 14 months for veliparib *vs.* 9.6 months for placebo [hazard ratio (HR) =0.66; 95% confidence interval (CI): 0.49–0.89] The second study, with similar results, shows a lack of efficacy in the overall analysis, but with a trend towards a better OS in LP52$^+$ tumours of 11.2 months for veliparib *vs.* 9.2 months for placebo (HR =0.64; 95% CI: 0.40–1.05).

Given the current standard of care for advanced or metastatic NSCLC with chemo-immunotherapy in programmed death-ligand 1 (PD-L1) <50% without target mutations, the study by Clarke *et al.* (28) is of particular interest. This clinical trial shows a partial response rate as best response of 64.0%, with an ORR of 40.0% for the overall population. In the remaining three studies evaluating the combination of chemotherapy plus iPARP, a trend towards increased response and survival was observed for the combination *vs.* the platinum doublet, although not statistically significantly.

Table 1 General characteristics of the clinical trials included in the systematic review

Study	Year	Phase	N	Stage	Study design	No. of Pts, experimental arm	No. of Pts, control arm	iPARP	Treatments	Primary endpoints	Secondary endpoints
Kozono *et al.* (24)	2021	I	48	III	Single-arm study	48	–	Veliparib	Radiotherapy + carboplatin + paclitaxel + veliparib	RP2D	PFS, OS, ORR, DOR
Argiris *et al.* (25)	2021	II	52	IIIA, IIIB	Randomized two-arm study	39	13	Veliparib	Radiotherapy + carboplatin + paclitaxel + veliparib *vs.* radiotherapy + carboplatin + paclitaxel + placebo	PFS	OS
Ramalingam *et al.* (26)	2021	III	970	IV	Randomized two-arm study	486	484	Veliparib	Carboplatin + paclitaxel + veliparib *vs.* carboplatin + paclitaxel + placebo	OS in current smokers	OS in ITT, PFS
Govindan *et al.* (27)	2022	III	595 ($LP52^+$ 80)	IV	Randomized two-arm study	298 ($LP52^+$ 40)	297 ($LP52^+$ 40)	Veliparib	Carboplatin + paclitaxel + veliparib *vs.* investigator's choice (carboplatin/paclitaxel, cisplatin/pemetrexed or carboplatin/pemetrexed)	OS in the $LP52^+$	OS, PFS in $LP52^+$, ORR in $LP52^+$
Clarke *et al.* (28)	2021	I	25	IIIB, IV	Two-arm study	19	6	Veliparib	Carboplatin + pemetrexed + nivolumab + veliparib or carboplatin + paclitaxel + nivolumab + veliparib	Safety	ORR
Ramalingam *et al.* (29)	2022	II	38	IIIB, IV	Randomized two-arm study	17	21	Niraparib	Niraparib + pembrolizumab	ORR	DOR, PFS, OS
Garcia-Campelo *et al.* (30)	2020	II	182	IV	Randomized two-arm study	91	91	Olaparib	Gefitinib *vs.* gefitinib + olaparib	PFS	Safety, OS
Novello *et al.* (31)	2014	II	119	IV	Randomized two-arm study	80	39	Iniparib	Gemcitabine + cisplatin *vs.* gemcitabine + cisplatin + iniparib	ORR	PFS, OS
de Hann *et al.* (32)	2021	I	28	II, III, IV	Randomized two-arm study	18	10	Olaparib	Olaparib + radiotherapy + cisplatin *vs.* olaparib + radiotherapy	Safety, tolerability	PFS
Fennell *et al.* (33)	2022	II	70	IIIB, IV	Randomized two-arm study	38	32	Olaparib	Olaparib maintenance *vs.* placebo	PFS	OS
Owonikoko *et al.* (34)	2021	II	47	IV	Single-arm study	47	–	Talazoparib	Talazoparib	ORR	PFS, OS
Mizugaki *et al.* (35)	2015	I	12	IV	Single-arm study	12	–	Veliparib	Carboplatin + paclitaxel + veliparib	Safety, tolerability	ORR
Ramalingam *et al.* (36)	2017	II	158	IV	Randomized two-arm study	105	53	Veliparib	Carboplatin + paclitaxel + veliparib *vs.* carboplatin + paclitaxel + placebo	PFS	OS, ORR, DOR
Chabot *et al.* (37)	2017	II	307	IV	Randomized three-arm study	205	102	Veliparib	Placebo + WBRT *vs.* veliparib 50 mg + WBRT *vs.* veliparib 200 mg + WBRT	OS	ORR, PFS

N, number of patients; Pts, patients; iPARP, poly (ADP ribose) polymerase inhibitor; $LP52^+$, lung panel 52-gene positive; RP2D, recommended phase II dose; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of overall response; ITT, intention-to-treat; WBRT, whole-brain radiation therapy.

Table 2 Summary of the main results of clinical trials showing data on OS, PFS and ORR in the use of iPARP in NSCLC

Study	OS			PFS			ORR	Primary endpoints	Secondary endpoints
	HR	95% CI	P	HR	95% CI	P			
Novello *et al.* (31)	0.78	0.48–1.27	–	0.89	0.56–1.40	–	25.6% *vs.* 20.0%	ORR	PFS, OS
Garcia-Campelo *et al.* (30)	0.82	0.53–1.22	0.345	1.38	1.00–1.92	0.124	67% *vs.* 71%	PFS	Safety, OS
Fennell *et al.* (33)	0.68	0.37–1.26	0.22	0.83	0–1.03	0.23	–	PFS	OS
Ramalingam *et al.* (36)	0.80	0.54–1.18	0.27	0.72	0.45–1.15	0.17	32.4% *vs.* 32.1%	PFS	OS, ORR, DOR
Chabot *et al.* (37)	0.98	0.71–1.36	0.9	–	–	–	41.2% *vs.* 42.2%	OS	ORR
Argiris *et al.* (25)	0.65	0.24–1.75	0.19	1.47	0.59–3.66	0.2	–	PFS	OS
Ramalingam *et al.* (26)	0.9	0.74–1.10	0.26	0.89	0.77–1.03	0.1	37% *vs.* 37%	OS in current smokers	PFS, ORR
Govindan *et al.* (27)	0.64	0.40–1.05	0.84	0.647	0.39–1.08	0.26	23% *vs.* 30%	OS in the LP52$^+$	PFS in LP52$^+$, ORR in LP52$^+$

OS, overall survival; PFS, progression-free survival; ORR, objective response rate; iPARP, poly (ADP ribose) polymerase inhibitor; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; DOR, duration of overall response; LP52$^+$, lung panel 52-gene positive.

Of the remaining studies, particularly significant is the clinical trial by Ramalingam *et al.* (29), which shows that the combination of nivolumab plus niraparib is effective in the treatment of advanced or metastatic NSCLC with higher response and survival rates than single immunotherapy treatment for tumours with PD-L1 values of 1–49% (median PFS 8.4 months and OS not reached). The other important study, being the only one to date that has evaluated the effectiveness of iPARPs in NSCLC with driver mutations, is that of Garcia-Campelo *et al.* (30). This study compares the combination of a first-generation *EGFR* inhibitor such as gefitinib with olaparib *vs.* treatment alone (standard at the time of the study). This study failed its primary endpoint of PFS, with a rate of 12.8 months for the combination *vs.* 10.9 months for gefitinib alone (HR =1.38, 95% CI: 1.00–1.92). Subsequently, a study published by Karachaliou *et al.* (38) subanalysed these patients according to *BRCA1* messenger ribonucleic acid (mRNA) expression. In these patients with high expression, PFS was 12.9 months for the olaparib arm *vs.* 9.2 months for placebo (P=0.0449).

Overall analysis of iPARP efficacy in NSCLC

A global analysis of the sample was performed by meta-analysis. The analysis included those studies that provided data in OS and PFS. The only one of the studies analysed that was in localised or locally advanced stages was Argiris *et al.* (25). In the OS analysis, the use of iPARPs is statistically significantly beneficial (HR =0.85, 95% CI: 0.74–0.97). The heterogeneity of the studies (I^2) was 0% (P=0.84), with a weight of 43.3% from the study by Ramalingam *et al.* (26). The forest plot is shown in *Figure 3A*.

For PFS, there is no statistically significant benefit for the use of iPARPs (HR =0.93, 95% CI: 0.74–1.17). The I^2 in this case was 51% (P=0.07). The weight of the studies showed a main effect of the study by Ramalingam *et al.* (26) with 32.1% of the total. Forest plot in *Figure 3B*.

Safety of iPARP in NSCLC

Among the top five studies by number of patients [Garcia-Campelo *et al.* (30), Ramalingam *et al.* (26), Chabot *et al.* (37), Ramalingam *et al.* (36) and Govindan *et al.* (27)], toxicity was slightly higher in the iPARP arm *vs.* the control, primarily at the expense of grade ≥3 toxicity. Ramalingam's studies (26,36) combining platinum doublet therapy with veliparib show an overall toxicity of any grade of both studies of 95.9% (566/590 patients) for the veliparib arm *vs.* 95.1% (508/534 patients) in the placebo arm. For grade ≥3 toxicity in the veliparib arm the event rate was 61.7% (364/590 patients) *vs.* 58.2% (311/534 patients) in the placebo arm. In the study by Govindan *et al.* (27), also combining veliparib with platinum doublet, the toxicity of serious adverse events ≥3 was 11% higher in the veliparib arm *vs.* placebo. The rate of adverse events of any grade was similar between the two arms. In all three clinical trials, the main toxicity was

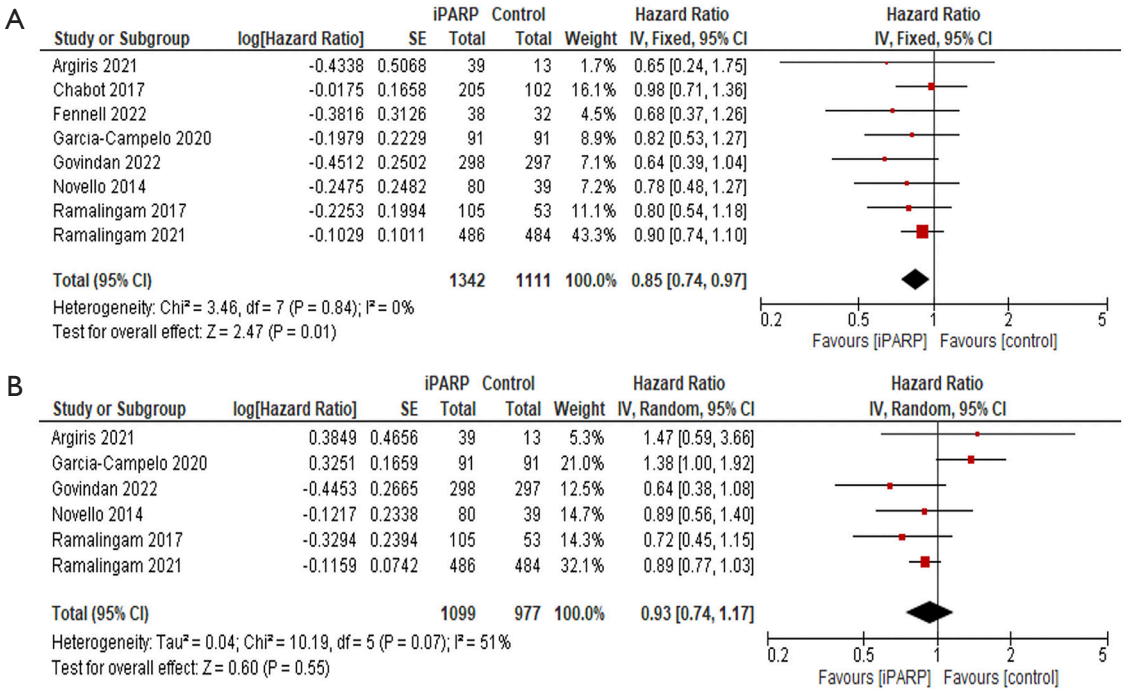

Figure 3 Forest plot summary of the main clinical trials with iPARP in NSCLC that showed data in OS (top forest plot) (A) and PFS (bottom forest plot) (B). iPARP, poly (ADP ribose) polymerase inhibitor; SE, standard error; IV, inverse variance; CI, confidence interval; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

haematological followed by digestive toxicity.

In the study by Chabot *et al.* (37) evaluating the combination of radiotherapy with veliparib, an adverse event rate of any grade was 98% in the iPARP arm *vs.* 90% in the placebo arm. In grade ≥3 toxicity, the event rate was 25% for veliparib *vs.* 43% for placebo. Finally, in the study by Garcia-Campelo *et al.* (30) the rate of grade ≥3 adverse events were equal between both arms (61.54% *vs.* 61.54%). All patients in both arms (100%) had some type of toxicity. In this study, the occurrence of grade ≥3 anaemia was statistically significantly higher in the veliparib arm (16.5%) *vs.* placebo (2.2%). In both studies, as in the previous three, the most important toxicity was haematological toxicity followed by digestive toxicity.

Discussion

The treatment of NSCLC has changed dramatically in the last decade (39). The discovery and characterisation of different molecular targets has led to survival rates that were unimaginable more than a decade ago (40-42). HRD is one of the most promising targets in this field, with important studies having already evaluated the efficacy of iPARPs in NSCLC (43). In this systematic review, we found a total of 14 clinical trials in different phases that have evaluated this efficacy. An overall analysis of the different clinical trials shows that the results of iPARPs as a potential new treatment in NSCLC are limited. Most of the clinical trials failed in their primary endpoints, failing to demonstrate that the addition of an iPARP to standard therapy increases response rate or survival, regardless of the line of therapy initiated. Nevertheless, there are several data supporting new clinical trials in patients selected for biomarkers predictive of response to iPARPs such as HRD and somatic or germline mutations in *BRCA1* and *BRCA2* genes (44,45).

Clinical trials in iPARP without HRD biomarkers or driver mutations

The two main clinical trials conducted were those of Govindan *et al.* (27) and Ramalingam *et al.* (26). Both phase III studies compared the combination of platinum-based chemotherapy with veliparib *vs.* placebo in non-squamous NSCLC histology in the former and in squamous NSCLC

in the latter. Both studies failed in their primary objectives of showing OS benefit in the veliparib arm, however, both showed the importance of patient selection for these treatments in NSCLC. In these cases, the use of a genomic platform known as LP52 was shown to be a possible clinical tool for the use of iPARPs in NSCLC (46,47), although these results will need to be assessed in independent studies. Therefore, this opens a way to assess the need for HRD or *BRCA1/2* status in NSCLC, as is done for other molecular alterations such as *EGFR*, *ALK*, *ROS1* or *K-RAS* (48).

Furthermore, these studies did not compare current treatment standards with chemo-immunotherapy at PD-L1 <50% (49) or immunotherapy at PD-L1 ≥50% (50). Preclinical investigations suggest the hypothesis of an increased response to immunotherapy in patients with HRD$^+$ tumours, particularly NSCLC (51). Therefore, the results of both clinical trials are likely to be affected by the lack of immunotherapy treatment in either arm. Of all the clinical trials conducted with iPARP in NSCLC, there are two that jointly assessed immunotherapy together with iPARP. These two clinical trials [Ramalingam *et al.* (29) and Clarke *et al.* (28)] phase I and II, showed similar results in response rates to the pivotal drug approval clinical trials. Most notably, the Clarke *et al.* phase I trial assessed the response rate of the combination of chemotherapy plus nivolumab and veliparib in 25 patients with advanced-stage NSCLC. The ORR of these patients was 64.0%, which was similar to the response rate of the KEYNOTE-189 (47.6%) (52) and KEYNOTE-407 (57.9%) (53) studies that assessed the chemo-immunotherapy combination. Therefore, this also opens a new avenue to evaluate new phase III clinical trials assessing the combination treatment of chemo-immunotherapy plus iPARP in advanced NSCLC and PD-L1 <50% and of immunotherapy plus iPARP with PD-L1 ≥50%.

Clinical trials in iPARP with HRD biomarkers or driver mutations

A key study that expands the knowledge on iPARPs in NSCLC is the one conducted by Garcia-Campelo *et al.* (30). This phase II clinical trial evaluated the efficacy of iPARPs in *EGFR*-mutated tumours. Data on both survival and response were unfavourable for the olaparib arm with no difference between the anti-*EGFR* drug alone or in combination. Furthermore, these results were consistent regardless of *EGFR* mutation type. It is likely that *EGFR*-mutated NSCLCs are HRD$^-$ tumours and have a lower accumulation of mutations, so that the action of iPARPs is more deficient than in tumours without target mutations. As in the previous cases, patient selection is key to understanding the poor results in all the clinical trials that have been done in this field. Of particular importance in understanding this point is the study by Karachaliou *et al.* (38), which demonstrated the superiority of the combination of *EGFR* with iPARP in NSCLC with high mRNA expression of the *BRCA1* gene.

One aspect on which there is consensus in most studies in the literature, both in *EGFR*-mutated and naïve tumours, is the importance of the presence of co-mutations to those existing in HRD-associated genes (*BRCA1*, *BRCA2*, *RAD51C*, *PALB2*, etc.) (54). The presence of *TP53* mutations in NSCLC (50–65%) is suspected to confer worse response to anti-EGFR, so their existence may condition unfavourable response to iPARPs even in HRD$^+$ tumours (55). However, the involvement of *TP53* mutations in the response to immunotherapy is doubtful, with some studies indicating a greater response to immune checkpoint inhibitors. Therefore, in selected patients with HRD$^+$ NSCLC and mutated *TP53*, a combination of iPARP with immunotherapy (in addition to chemotherapy depending on PD-L1 values) could be a highly recommended option. Along with *TP53* mutations, other mutations such as *PTEN* or *RB1* are also suspected to influence the efficacy of iPARPs, which shows the importance of proper patient selection for clinical trials with iPARPs (56).

Global efficacy of iPARP in NSCLC

In the overall analysis of the efficacy of iPARPs in NSCLC, a statistically significant benefit is observed for OS with a HR of 0.85. In the fixed-effect statistical analysis, a high homogeneity of the studies was noted. However, in the PFS no statistically significant final value was found in the forest plot with an intermediate heterogeneity for the clinical trials (random-effect). The finding of these results highlights the importance of the primary objective sought in clinical trials. Most studies have PFS or response as this objective, without looking for OS. It is likely that the effect of iPARPs in NSCLC is more long-term and their effect on tumour biology is more durable than classical chemotherapy through changes in the tumour genome or microenvironment.

It is important to consider the relative weight of the studies. In the case of our study, the clinical trial by Ramalingam *et al.* in 2021 (26) has a weight of 43.3% in OS and 32.1% in

PFS. This may significantly influence the results because it is the largest clinical trial of iPARP in NSCLC. However, as previously indicated, this study may mark the beginning of the benefit of iPARPs in clinical practice using genomic platforms or biomarkers that allow for proper patient selection. In addition, when evaluating the results, it is also important to consider in the meta-analysis the presence of the study by Argiris *et al.* (25) which was performed in localised and locally advanced stages. The weight of this study was 1.7% in OS and 5.3% in PFS and this may have conditioned part of the results, especially for PFS.

Side effects of iPARP in NSCLC

Overall, clinical trials have shown a similar rate of adverse events of any grade between the iPARP *vs.* placebo combination arms. Serious adverse event rates were slightly higher in the iPARP groups, with rates 0–12% higher than the placebo groups. However, rates of minor adverse events were similar between the two groups. This higher percentage of grade ≥3 toxicity in the iPARP arms was mainly due to the combination of iPARP with anti-EGFR, with no such association observed in the iPARP with chemotherapy combination. The rates of grade 5 adverse events were similar in both groups. Therefore, iPARP combinations in NSCLC appear to be safe in their different modalities.

In summary, it would be important to consider standardised HRD status for patients with advanced NSCLC in the future, as in other tumours such as ovarian cancer. In these patients, just as PD-L1, *EGFR*, *ALK*, *ROS* or *K-RAS* determination is routinely performed (57), HRD status could also be considered for a better understanding of the patients and their correct selection. Future clinical trials in this field should certainly optimise the section of patients to obtain correct results.

Conclusions

Studies to date on iPARP treatment in NSCLC have failed in terms of response and survival. The correct selection of patients, through predictive biomarkers of response to iPARPs, appears to be the right way forward for future clinical trials. Undoubtedly, iPARPs are opening a very promising path in the treatment of NSCLC, which in the future could be standardised in properly selected patient tumours.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-58/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-58/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-58/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018;553:446-54.
2. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. Arch Pathol Lab Med 2013;137:1191-8.
3. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc 2019;94:1623-40.
4. Alexander M, Kim SY, Cheng H. Update 2020: Management of Non-Small Cell Lung Cancer. Lung

2020;198:897-907.
5. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. J Clin Oncol 2022;40:611-25.
6. Shea M, Costa DB, Rangachari D. Management of advanced non-small cell lung cancers with known mutations or rearrangements: latest evidence and treatment approaches. Ther Adv Respir Dis 2016;10:113-29.
7. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev 2020;34:360-94.
8. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst) 2018;71:172-6.
9. Wang Y, Luo W, Wang Y. PARP-1 and its associated nucleases in DNA damage response. DNA Repair (Amst) 2019;81:102651.
10. Dantzer F, Amé JC, Schreiber V, et al. Poly(ADP-ribose) polymerase-1 activation during DNA damage and repair. Methods Enzymol 2006;409:493-510.
11. Huber A, Bai P, de Murcia JM, et al. PARP-1, PARP-2 and ATM in the DNA damage response: functional synergy in mouse development. DNA Repair (Amst) 2004;3:1103-8.
12. Levra MG, Olaussen KA, Novello S, et al. PARP inhibitors: an interesting pathway also for non-small cell lung cancer? Curr Pharm Des 2014;20:3875-82.
13. Fugger K, Hewitt G, West SC, et al. Tackling PARP inhibitor resistance. Trends Cancer 2021;7:1102-18.
14. Liu FW, Tewari KS. New Targeted Agents in Gynecologic Cancers: Synthetic Lethality, Homologous Recombination Deficiency, and PARP Inhibitors. Curr Treat Options Oncol 2016;17:12.
15. Nesic K, Kondrashova O, Hurley RM, et al. Acquired RAD51C Promoter Methylation Loss Causes PARP Inhibitor Resistance in High-Grade Serous Ovarian Carcinoma. Cancer Res 2021;81:4709-22.
16. Rivera B, Di Iorio M, Frankum J, et al. Functionally Null RAD51D Missense Mutation Associates Strongly with Ovarian Carcinoma. Cancer Res 2017;77:4517-29.
17. Carreira S, Porta N, Arce-Gallego S, et al. Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial. Cancer Discov 2021;11:2812-27.
18. Tarsounas M, Sung P. The antitumorigenic roles of BRCA1-BARD1 in DNA repair and replication. Nat Rev Mol Cell Biol 2020;21:284-99.
19. Mekonnen N, Yang H, Shin YK. Homologous Recombination Deficiency in Ovarian, Breast, Colorectal, Pancreatic, Non-Small Cell Lung and Prostate Cancers, and the Mechanisms of Resistance to PARP Inhibitors. Front Oncol 2022;12:880643.
20. Pacheco-Barcia V, Muñoz A, Castro E, et al. The Homologous Recombination Deficiency Scar in Advanced Cancer: Agnostic Targeting of Damaged DNA Repair. Cancers (Basel) 2022;14:2950.
21. Revythis A, Limbu A, Mikropoulos C, et al. Recent Insights into PARP and Immuno-Checkpoint Inhibitors in Epithelial Ovarian Cancer. Int J Environ Res Public Health 2022;19:8577.
22. Chabanon RM, Muirhead G, Krastev DB, et al. PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer. J Clin Invest 2019;129:1211-28.
23. Paul I, Savage KI, Blayney JK, et al. PARP inhibition induces BAX/BAK-independent synthetic lethality of BRCA1-deficient non-small cell lung cancer. J Pathol 2011;224:564-74.
24. Kozono DE, Stinchcombe TE, Salama JK, et al. Veliparib in combination with carboplatin/paclitaxel-based chemoradiotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 2021;159:56-65.
25. Argiris A, Miao J, Cristea MC, et al. A Dose-finding Study Followed by a Phase II Randomized, Placebo-controlled Trial of Chemoradiotherapy With or Without Veliparib in Stage III Non-small-cell Lung Cancer: SWOG 1206 (8811). Clin Lung Cancer 2021;22:313-323.e1.
26. Ramalingam SS, Novello S, Guclu SZ, et al. Veliparib in Combination With Platinum-Based Chemotherapy for First-Line Treatment of Advanced Squamous Cell Lung Cancer: A Randomized, Multicenter Phase III Study. J Clin Oncol 2021;39:3633-44.
27. Govindan R, Lind M, Insa A, et al. Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer. Clin Lung Cancer 2022;23:214-25.
28. Clarke JM, Patel JD, Robert F, et al. Veliparib and nivolumab in combination with platinum doublet chemotherapy in patients with metastatic or advanced non-small cell lung cancer: A phase 1 dose escalation study. Lung Cancer 2021;161:180-8.
29. Ramalingam SS, Thara E, Awad MM, et al. JASPER: Phase 2 trial of first-line niraparib plus pembrolizumab in patients with advanced non-small cell lung cancer. Cancer 2022;128:65-74.
30. Garcia-Campelo R, Arrieta O, Massuti B, et al.

Combination of gefitinib and olaparib versus gefitinib alone in EGFR mutant non-small-cell lung cancer (NSCLC): A multicenter, randomized phase II study (GOAL). Lung Cancer 2020;150:62-9.
31. Novello S, Besse B, Felip E, et al. A phase II randomized study evaluating the addition of iniparib to gemcitabine plus cisplatin as first-line therapy for metastatic non-small-cell lung cancer. Ann Oncol 2014;25:2156-62.
32. de Haan R, van den Heuvel MM, van Diessen J, et al. Phase I and Pharmacologic Study of Olaparib in Combination with High-dose Radiotherapy with and without Concurrent Cisplatin for Non-Small Cell Lung Cancer. Clin Cancer Res 2021;27:1256-66.
33. Fennell DA, Porter C, Lester J, et al. Olaparib maintenance versus placebo monotherapy in patients with advanced non-small cell lung cancer (PIN): A multicentre, randomised, controlled, phase 2 trial. EClinicalMedicine 2022;52:101595.
34. Owonikoko TK, Redman MW, Byers LA, et al. Phase 2 Study of Talazoparib in Patients With Homologous Recombination Repair-Deficient Squamous Cell Lung Cancer: Lung-MAP Substudy S1400G. Clin Lung Cancer 2021;22:187-194.e1.
35. Mizugaki H, Yamamoto N, Nokihara H, et al. A phase 1 study evaluating the pharmacokinetics and preliminary efficacy of veliparib (ABT-888) in combination with carboplatin/paclitaxel in Japanese subjects with non-small cell lung cancer (NSCLC). Cancer Chemother Pharmacol 2015;76:1063-72.
36. Ramalingam SS, Blais N, Mazieres J, et al. Randomized, Placebo-Controlled, Phase II Study of Veliparib in Combination with Carboplatin and Paclitaxel for Advanced/Metastatic Non-Small Cell Lung Cancer. Clin Cancer Res 2017;23:1937-44.
37. Chabot P, Hsia TC, Ryu JS, et al. Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: results of a randomized, global, placebo-controlled study. J Neurooncol 2017;131:105-15.
38. Karachaliou N, Arrieta O, Giménez-Capitán A, et al. BRCA1 Expression and Outcome in Patients With EGFR-Mutant NSCLC Treated With Gefitinib Alone or in Combination With Olaparib. JTO Clin Res Rep 2020;2:100113.
39. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192-237.
40. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv1-iv21.
41. Passaro A, Leighl N, Blackhall F, et al. ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer. Ann Oncol 2022;33:466-87.
42. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:358-76.
43. Jiang M, Jia K, Wang L, et al. Alterations of DNA damage response pathway: Biomarker and therapeutic strategy for cancer immunotherapy. Acta Pharm Sin B 2021;11:2983-94.
44. Ji W, Weng X, Xu D, et al. Non-small cell lung cancer cells with deficiencies in homologous recombination genes are sensitive to PARP inhibitors. Biochem Biophys Res Commun 2020;522:121-6.
45. Wu C, Fan M, Hu Y. Response to olaparib in metastatic lung adenocarcinoma with germline BRCA2 mutation: a case report. Anticancer Drugs 2022;33:e734-7.
46. Wilkerson MD, Schallheim JM, Hayes DN, et al. Prediction of lung cancer histological types by RT-qPCR gene expression in FFPE specimens. J Mol Diagn 2013;15:485-97.
47. Faruki H, Mayhew GM, Fan C, et al. Validation of the Lung Subtyping Panel in Multiple Fresh-Frozen and Formalin-Fixed, Paraffin-Embedded Lung Tumor Gene Expression Data Sets. Arch Pathol Lab Med 2016;140:536-42.
48. Wen S, Dai L, Wang L, et al. Genomic Signature of Driver Genes Identified by Target Next-Generation Sequencing in Chinese Non-Small Cell Lung Cancer. Oncologist 2019;24:e1070-81.
49. Jiang J, Wang Y, Gao Y, et al. Neoadjuvant immunotherapy or chemoimmunotherapy in non-small cell lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res 2022;11:277-94.
50. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:586-97.
51. Zhou Z, Ding Z, Yuan J, et al. Homologous recombination deficiency (HRD) can predict the therapeutic outcomes of immuno-neoadjuvant therapy in NSCLC patients. J Hematol Oncol 2022;15:62.
52. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al.

Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
53. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
54. Molina-Vila MA, Bertran-Alamillo J, Gascó A, et al. Nondisruptive p53 mutations are associated with shorter survival in patients with advanced non-small cell lung cancer. Clin Cancer Res 2014;20:4647-59.
55. Canale M, Petracci E, Delmonte A, et al. Impact of TP53 Mutations on Outcome in EGFR-Mutated Patients Treated with First-Line Tyrosine Kinase Inhibitors. Clin Cancer Res 2017;23:2195-202.
56. Harper JW, Elledge SJ. The DNA damage response: ten years after. Mol Cell 2007;28:739-45.
57. Viñal D, Martínez D, Higuera O, et al. Genomic profiling in non-small-cell lung cancer in young patients. A systematic review. ESMO Open 2021;6:100045.

Cite this article as: Olivares-Hernández A, Roldán-Ruiz J, Miramontes-González JP, Toribio-García I, García-Hernández JL, Posado-Domínguez L, Bellido-Hernández L, Cruz-Hernández JJ, Fonseca-Sánchez E, del Barco-Morillo E. Efficacy and safety of PARP inhibitor in non-small cell lung cancer: a systematic review with meta-analysis. Chin Clin Oncol 2023;12(6):62. doi: 10.21037/cco-23-58