UNIVERSITY OF BIRMINGHAM
University of Birmingham Research at Birmingham

Olaparib as maintenance treatment in patients with chemosensitive small cell lung cancer (STOMP)

Woll, Penella; Gaunt, Piers; Danson, Sarah; Steele, Nicola; Ahmed, Samreen; Mulatero, Clive; Shah, Riyaz; Bhosle, Jaishree; Hodgkinson, Elizabeth; Watkins, Ben; Billingham, Lucinda

DOI:
10.1016/j.lungcan.2022.07.007

License:
Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Woll, P, Gaunt, P, Danson, S, Steele, N, Ahmed, S, Mulatero, C, Shah, R, Bhosle, J, Hodgkinson, E, Watkins, B & Billingham, L 2022, 'Olaparib as maintenance treatment in patients with chemosensitive small cell lung cancer (STOMP): a randomised, double-blind, placebo-controlled phase II trial', *Lung Cancer*, vol. 171, pp. 26-33. https://doi.org/10.1016/j.lungcan.2022.07.007

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 02. May. 2024

Lung Cancer 171 (2022) 26–33

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Olaparib as maintenance treatment in patients with chemosensitive small cell lung cancer (STOMP): A randomised, double-blind, placebo-controlled phase II trial

Penella Woll [a,h], Piers Gaunt [b], Sarah Danson [a,h,*], Nicola Steele [c], Samreen Ahmed [d], Clive Mulatero [e], Riyaz Shah [f], Jaishree Bhosle [g], Elizabeth Hodgkinson [h], Ben Watkins [b], Lucinda Billingham [b]

[a] University of Sheffield, Sheffield, United Kingdom
[b] Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom
[c] Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom
[d] University Hospitals of Leicester, Leicester, United Kingdom
[e] St James's University Hospital, Leeds, United Kingdom
[f] Maidstone Hospital, Maidstone, United Kingdom
[g] Royal Marsden Hospitals Trust, Sutton, United Kingdom
[h] Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

ARTICLE INFO

Keywords:
Small cell lung cancer
Maintenance treatment
Olaparib
Clinical trial

ABSTRACT

Objectives: Small cell lung cancer (SCLC) responds well to chemoradiotherapy but frequently relapses. Here, we evaluate activity and safety of the poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitor olaparib as maintenance treatment for patients with chemoresponsive SCLC.

Materials and methods: Eligible patients had complete or partial response to first line chemotherapy or chemoradiotherapy for SCLC. Patients were randomised 2:2:1:1 to olaparib 300 mg twice a day (BD), olaparib 200 mg three times a day (TDS), placebo BD or placebo TDS. The primary outcome was progression-free survival time (PFS). The trial design had 80% power to detect a 3-month difference in median PFS based on a one-sided 5% significance level. Secondary outcome measures included overall survival time (OS), adverse events and quality of life.

ISRCTN 73164486, EudraCT 2010-021165-76.

Results: 220 patients were randomised: 74 placebo, 73 olaparib BD, 73 olaparib TDS. Median PFS (90% confidence interval (CI)) was 2·5 (1·8, 3·7), 3·7 (3·1, 4·6) and 3·6 (2·8, 4·7) months in the placebo, olaparib BD and TDS arms, respectively. There was no significant difference in PFS between olaparib and placebo for either BD (Hazard Ratio (HR) (90%CI) 0·76 (0·57, 1·02), $P = 0·125$ or TDS 0·86, (0·64, 1·15), $P = 0·402$. Common adverse events on olaparib were fatigue, nausea, anaemia, vomiting and anorexia. Of 214 patients who discontinued treatment before 24 months, toxicity was the reason cited for 66 (18 placebo, 24 olaparib BD, 24 olaparib TDS).

Conclusion: This trial does not provide sufficient evidence that either the BD or TDS regimen for maintenance olaparib monotherapy improves PFS or OS in an unselected SCLC population to warrant further research. Toxicity for olaparib was similar to other studies.

1. Introduction

For over thirty years, the preferred first line treatment for small cell lung cancer (SCLC) has been chemotherapy, with or without radiotherapy. Although the initial objective response rate is up to 80%, the majority of patients will relapse and die from chemoresistant disease. In large UK studies, the median survival time from diagnosis in a mixed population was only 10·3 months[1] while even among the best

* Corresponding author at: Sheffield Experimental Cancer Medicine Centre, University of Sheffield & Sheffield Teaching Hospitals NHS Foundation Trust, Weston Park Hospital, Sheffield S10 2SJ, United Kingdom.
E-mail address: s.danson@sheffield.ac.uk (S. Danson).

https://doi.org/10.1016/j.lungcan.2022.07.007
Received 14 March 2022; Received in revised form 6 July 2022; Accepted 8 July 2022
Available online 15 July 2022
0169-5002/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

prognostic group, treated with concurrent chemoradiotherapy, only 54% survive 24 months.[2] Treatment with a platinum-based compound (cis- or carbo-platin) and etoposide has been the standard initial chemotherapy for three decades, and the only improvements in survival over this period were attributable to the addition of radiotherapy. More recently, immunotherapy has been incorporated into standard care for some patients with extensive stage SCLC.[3] However, it is likely that a significant proportion of SCLC patients will not receive immunotherapy, through having better prognosis limited disease or extensive disease with poor performance status and co-morbidities, with the incremental improvement in efficacy having to be balanced against potential immune-mediated toxicities. There is therefore intense interest in the incorporation of oral, well-tolerated biologically targeted agents into treatment regimens that could improve outcomes for SCLC patients.

Genomic instability is a hallmark of cancer and SCLC is one of the most highly mutated malignancies.[4] SCLC typically has loss of function alterations in the tumour suppressor genes *TP53*, *RB1*, *FHIT* and *PTEN*.[5] These lead to the accumulation of multiple genetic abnormalities, resulting in increased cell proliferation and ultimately chemoresistance. These include many defects in DNA repair pathways, including poly-(ADP-ribose), *NBS1*, *ATM*, *RAD51*, Chk1/2, *MDC1, ERCC1* and *PTEN* which make SCLC cells susceptible to DNA damage.[6–8]

Poly (ADP-ribose) polymerases (PARPs) are critical components in the detection and repair of single-strand DNA breaks through the base excision repair pathway. Double-strand DNA damage repair relies upon homologous recombination. In cells with inherited or acquired abnormalities of homologous recombination pathways, loss or inhibition of PARP activity leads to synthetic lethality.[9–11] PARP1 is highly expressed at the mRNA and protein levels in SCLC. A study of 318 cell lines from 30 cancer types found that SCLC cells showed the highest median PARP1 expression of any solid tumour cells.[7] Furthermore, *in vitro* studies showed significant growth inhibition in SCLC cells treated with PARP inhibitors and SCLC cells were as sensitive to PARP inhibition as *BRCA1*-mutated breast cancer.[7,12] We therefore hypothesised that the accumulated defects in DNA repair genes in SCLC make it susceptible to treatment with a PARP inhibitor and that this could be tested in the maintenance setting, after patients had achieved a response to primary chemotherapy.

Olaparib (Lynparza, AstraZeneca) is a potent and orally bioavailable PARP inhibitor, with good tolerability, well suited to use in a maintenance setting. The key objectives of the "SCLC Trial of Olaparib as Maintenance Programme" (STOMP) randomised phase II trial were to evaluate the safety and efficacy of olaparib as a maintenance treatment in patients with chemoresponsive SCLC to determine whether there is sufficient evidence of benefit to warrant further research. We used a new formulation of olaparib, so two different dose schedules were compared against placebo to assess their acceptability.

2. Methods

2.1. Study design and participants

In this randomised, double-blind, placebo-controlled, phase II trial, we recruited patients from 36 hospitals in the UK National Cancer Research Network. Eligible patients were aged 18 years or older, with pathologically confirmed SCLC (including limited and extensive stage disease) and had achieved a complete or partial response after at least three cycles of first line chemotherapy with etoposide and either cisplatin or carboplatin. Patients had an Eastern Co-operative Oncology Group (ECOG) performance status of 0–2, a life expectancy of greater than 12 weeks and adequate renal, hepatic and bone marrow function. Concurrent and sequential radiotherapy were permitted. The maintenance study treatment had to start promptly after completion of primary therapy. Where the last primary treatment was radiotherapy, radiotherapy had to start within 35 days from the start of the last chemotherapy cycle, and patients were ineligible if the interval between the start of trial treatment and last radiation fraction was more than 21 days. Where the last primary treatment was chemotherapy, patients were ineligible if the interval between the start of trial treatment and the start of the last chemotherapy cycle was more than 42 days. Patients were ineligible if they had symptomatic uncontrolled brain metastases, interstitial lung disease, malabsorption or major gastrointestinal tract resection likely to affect trial drug absorption, prior treatment with a PARP inhibitor or previous malignancy within 3 years.

The trial protocol was approved by the Yorkshire & The Humber (Leeds East) Research Ethics Committee (REC reference 11/YH/0290) and local institutional review boards and ethical committees in accordance with national and international guidelines. It was carried out in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice produced by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). All patients provided written informed consent.

2.2. Randomisation and masking

Eligible patients were randomly assigned 2:2:1:1 to receive maintenance treatment with olaparib 300 mg BD, olaparib 200 mg TDS, placebo 300 mg BD or placebo 200 mg TDS. Treatment allocation was by telephone to the central randomisation service at the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham. Randomisation was stratified by disease extent (M0 vs M1a/b with any T or N stage, according to the AJCC TNM staging for lung cancer, 7th edition) and prior radiotherapy (concurrent vs sequential vs none). A treatment pack number was allocated to patients sequentially using a block randomisation scheme with block size 6 that was generated in-house, loaded onto the Cenduit Interactive Web Recognition System (IWRS) database and accessed by CRCTU on behalf of randomising sites. For all subsequent clinic visits the IWRS was used by the site research team to record visits and dispense required medication. Active treatments and placebo were manufactured by AstraZeneca (UK) and packaged by Fisher Clinical Services (UK). The matching tablets were presented in identical packaging and were available in 100 mg and 150 mg strengths. Patients, clinicians and pharmacists were blinded to whether the treatment pack contained olaparib or placebo.

2.3. Procedures

Patients received oral olaparib 300 mg BD or 200 mg TDS or matching placebo in continuous 28 day cycles for two years or until disease progression, death, unacceptable toxicity, or withdrawal of patient consent. Protocol drugs were dispensed in an outpatient setting and patients were instructed that tablets should be swallowed whole at the same times each day with a glass of water. Dose interruptions and reductions for toxicity were permitted according to protocol, at the investigators' discretion. Grade 3 or 4 toxicity required dose interruption (until recovery to grade 1) and dose decrements of 50 mg per dose thereafter. Treatment was discontinued if the toxicity had not resolved to grade 1 within 28 days.

Pre-treatment evaluation included: medical history (including cancer history and concomitant medications), clinical examination to assess fitness (including ECOG performance status and blood pressure), laboratory analyses (complete blood count and coagulation tests, blood chemistry) and peripheral blood smear to test for myelodysplastic syndrome and acute myelogenous leukaemia. CT scan of chest and upper abdomen (to include liver and adrenals) was performed within 28 days before randomisation and then after every even number of cycles. Chest x-ray was performed within 7 days before starting treatment and then after every odd number of cycles. For those patients who discontinued treatment for reasons other than death or disease progression, tumour assessment using CT scans continued every 8 weeks until progression. Response was assessed locally with RECIST 1.1.[13] Adverse events

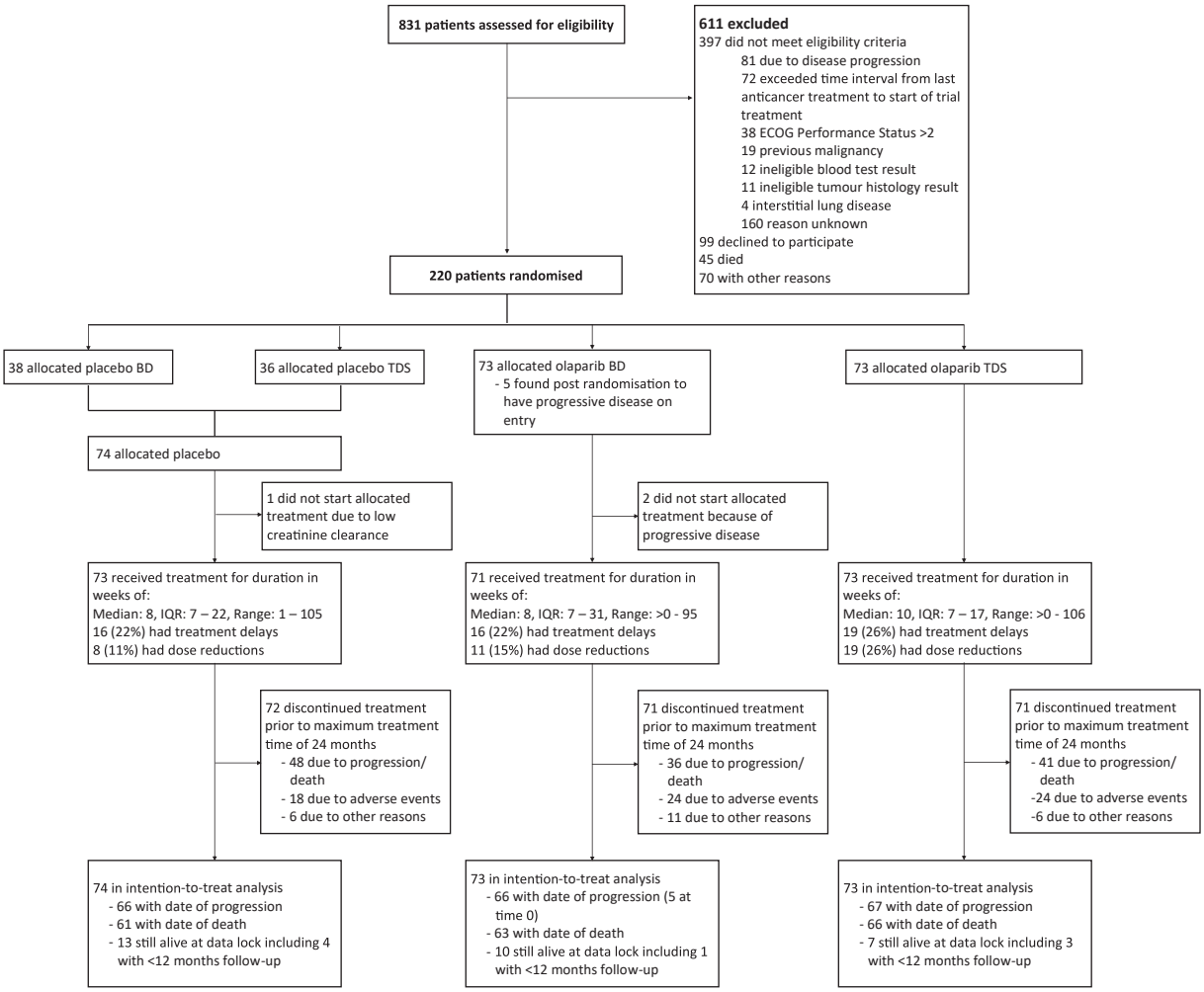

Fig. 1. STOMP trial profile. BD, twice daily; IQR, interquartile range; TDS, three times a day.

were assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0) at every clinic visit. Follow-up data were collected at standard post-treatment clinic visits at approximately 3-monthly intervals. Quality of life was assessed using the EuroQol EQ-5D-3L questionnaires,[14] which were completed independently by patients at baseline and each study visit. Blood biomarker and tumour analysis will be reported separately.

2.4. Outcomes

The primary outcome measure was progression-free survival time (PFS) defined as the interval between date of randomisation and the earliest date of detection of disease progression or date of death from any cause for those without recorded progression. For those patients alive and with no recorded progression at the time of database lock, PFS was censored at the date when they were last known to be alive and free of progression.

Secondary outcome measures were PFS at 4 months, overall survival time (OS, defined as time from date of randomisation to date of death from any cause, with those alive at database lock censored at date last seen alive), overall survival at 6 months, changes in ECOG performance status, quality of life (utility measure and visual analogue score) and adverse events.

2.5. Statistical analysis

The aim was to compare each of the olaparib schedules to the pooled placebo arm, subject to the placebo arms being sufficiently comparable to be combined.

For the primary outcome measure of PFS, the survivor function for each treatment arm was estimated using Kaplan-Meier method from which medians are reported with Greenwood's formula used for 90% confidence intervals (in line with the planned one-sided 5% significance level). For each olaparib regimen, the primary analysis tests the null hypothesis of no difference between olaparib and placebo using a stratified log-rank test (stratifying for M−status and prior radiotherapy). In addition, a Cox regression model adjusting for the stratification factors was applied. Regression coefficients from the model provided estimates of hazard ratios (HR) with two-sided 90% confidence intervals (CI) to compare treatment arms. All analyses of the primary outcome measure were based on an intention-to-treat principle (ITT). Sensitivity analysis was performed including an analysis with pooling of the olaparib arms and a per-protocol population (i.e., all those that received at least one dose of study drug). In addition, a further sensitivity analysis was undertaken removing ineligible patients who had progressive disease after primary therapy and were randomised in error.

OS was analysed using the same approach as PFS. PFS rates at 4 months and OS rates at 6 months were estimated from Kaplan-Meier with 90% confidence intervals. Changes in ECOG performance status and quality of life were analysed descriptively and restricted to the 6 month period from randomisation to incorporate the most clinically relevant survival period. In addition, the utility measures were used in a quality-adjusted survival analysis to report the quality-adjusted life months restricted to 6 months (QALM6) using an area under the curve

Table 1
Baseline patient characteristics.

	Placebo *N* = 74	Olaparib BD *N* = 73	Olaparib TDS *N* = 73
Age, years			
Median	64	66	63
Inter-quartile range	58 – 68	58 – 70	55 – 69
Range	43 – 86	43 – 89	42 – 82
Sex, number (percent)			
Male	34 (46%)	36 (49%)	31 (42%)
Female	40 (54%)	37 (51%)	42 (58%)
Time from diagnosis to randomisation weeks, median (range)	22 (15, 34)	25 (16, 38)	24 (15, 32)
Disease extent at diagnosis			
M0	21 (28%)	22 (30%)	23 (32%)
M1a	6 (8%)	6 (8%)	5 (7%)
M1b	47 (64%)	45 (62%)	45 (62%)
Chemotherapy regimen			
Carboplatin, etoposide	52 (70%)	56 (77%)	54 (74%)
Cisplatin, etoposide	18 (24%)	16 (22%)	13 (18%)
Cisplatin, carboplatin, etoposide	4 (5%)	1 (1%)	6 (8%)
Chemotherapy, number of cycles			
3	1 (1%)	0	2 (3%)
4	31 (42%)	27 (37%)	23 (32%)
5	5 (7%)	3 (4%)	4 (5%)
6	37 (50%)	43 (59%)	44 (60%)
Radiotherapy schedule			
Concurrent	10 (14%)	6 (8%)	4 (5%)
Sequential	57 (77%)	57 (78%)	61 (84%)
None	7 (9%)	10 (14%)	8 (11%)
Radiotherapy sites			
Thoracic & cranial	40 (54%)	33 (45%)	36 (49%)
Thoracic only	2 (3%)	5 (7%)	5 (7%)
Cranial only	25 (34%)	25 (34%)	24 (33%)
None	7 (9%)	10 (14%)	8 (11%)
Response to primary treatment			
Complete response	5 (7%)	4 (5%)	7 (10%)
Partial response	69 (93%)	64 (88%)	66 (90%)
Progression	0	5 (7%)	0
ECOG performance status			
0	18 (24%)	17 (23%)	25 (34%)
1	48 (65%)	51 (70%)	44 (60%)
2	8 (11%)	5 (7%)	3 (4%)
Not known	0	0	1 (1%)

BD, twice daily; ECOG, Eastern Cooperative Oncology Group; TDS, three times a day.

approach.[15] Incidence of common adverse events (i.e., recorded for ≥ 10% of trial patients) are reported together with any adverse events graded as 3 or more in >1 patient.

At the design stage, sample size determinations were based on the primary outcome measure of PFS. A median PFS of 4·8 months was assumed for the placebo arm based on relevant data shared from a large UK study in SCLC.[1] Our trial was designed to detect an improvement in median PFS to 7·8 months (equivalent to a HR of 0·62) for either of the two olaparib regimens. As a phase II trial, a relaxed one-sided significance level of 10% was selected, however, this was halved to a one-sided 5% significance level to adjust for multiplicity of comparing two

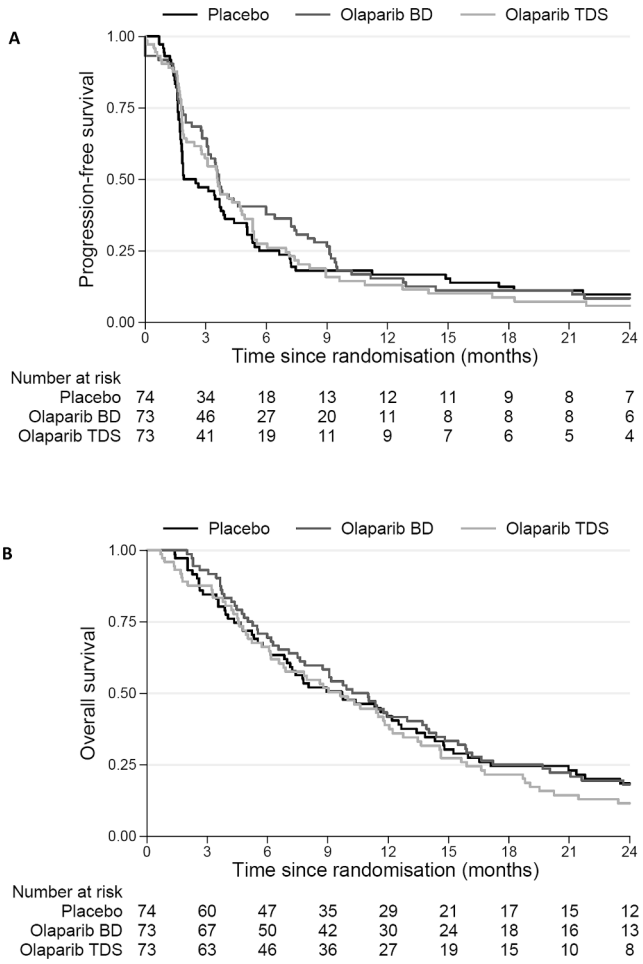

Fig. 2. Progression-free and overall survival time. Panel A shows progression-free survival time (PFS) defined as the interval between date of randomisation and the earliest date of detection of disease progression or date of death from any cause. Patients without progression were censored at the date when they were last known to be alive and progression-free. Panel B shows overall survival time defined as time from date of randomisation to date of death from any cause. Patients alive at database lock were censored at date last seen alive.

experimental arms separately to the pooled placebo arm. The trial required 105 events per comparison to ensure 80% power. Given the planned accrual time of 24 months and follow-up time of 6 months it was estimated that the trial needed approximately 75 patients per arm to observe this number of events.

An independent Data Monitoring Committee reviewed interim data annually to ensure patient safety. There were no formal stopping rules. The trial was registered on the EU Clinical Trials Register with EudraCT number 2010–021165-76 and on the International Standard Randomised Controlled Trials Number Register with ISRCTN number 73164486.

3. Results

Between 21 November 2013 and 11 December 2015, 220 patients were randomised into the trial. They were assigned to receive placebo BD (38), placebo TDS (36), olaparib BD (73) or olaparib TDS (73) (Fig. 1). Results are reported following a database lock on 31 January 2020. In total, 9383 Case Report Forms were returned out of 9386 expected (99·97%). Within these, more than 98% of data fields were complete at the time of the database lock. The two placebo arms were combined for the analysis in accordance with the pre-planned

Table 2
Progression-free, overall and quality-adjusted survival time outcomes measured from date of randomisation. For Table 2, can the table be formatted so that the 90% CIs stay on a single line? – in 3 rows of the table they split onto a second line

	Placebo *N* = 74	Olaparib BD *N* = 73	Olaparib TDS *N* = 73
Progression-free survival time (PFS)			
Median PFS, months (90% CI)	2.5 (1.8, 3.7)	3.7 (3.1, 4.6)	3.6 (2.8, 4.7)
PFS rate at 4 months (90% CI)	36% (27, 45)	45% (35, 54)	45% (35, 54)
Comparison to placebo			
Hazard Ratio (90% CI)		0.76 (0.57, 1.02)	0.86 (0.64, 1.15)
P-value from stratified log-rank test		0.180	0.164
P-value from adjusted Cox model		0.125	0.402
Overall survival time (OS)			
Median OS, months (90% CI)	9.7 (7.1, 12.2)	11.0 (7.9, 12.9)	9.6 (6.8, 11.8)
OS rate at 6 months (90% CI)	66% (56, 75)	69% (60, 77)	66% (56, 75)
Comparison to placebo			
Hazard ratio (90% CI)		0.85 (0.63, 1.15)	1.03 (0.77, 1.39)
P-value from stratified log-rank test		0.709	0.990
P-value from adjusted Cox model		0.376	0.850
Quality-adjusted life weeks within 6 months of trial entry (QALM6)			
Mean QALM6 (90% CI)	3.2 (2.8, 3.5)	3.0 (2.7, 3.3)	3.2 (2.9, 3.6)

BD, twice daily; CI, confidence intervals; TDS, three times a day.

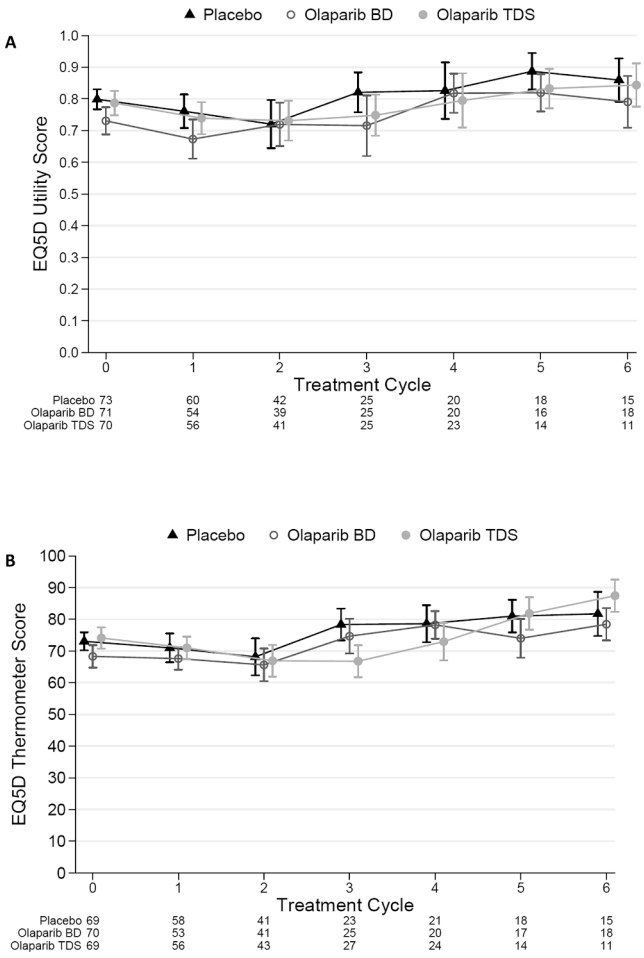

Fig. 3. Quality of life. Outcomes over time of EQ-5D-3L utility measures (A) and EQ-5D-3L visual analogue scores (B) are shown as the means with 90% confidence intervals (CI).

comparability assessment (Supplementary Appendix 1). At the time of analysis, 30 patients were still alive, with median follow-up for all patients being 37 months and comparable across treatment arms. Only 8 patients had less than 12 months follow-up.

The patient groups were well balanced and representative of a mixed population of limited and extensive stage SCLC (Table 1). Overall, 83 patients (38%) had limited disease (M0/M1a) and 137 patients (62%) had extensive disease (M1b). Median age was 64 years (range 42 to 89), 46% were male and only 16 (7%) patients were ECOG performance status 2. There were 58 patients (26%) with liver metastases and 2 patients (1%) with brain metastases. Only 11% of patients had no radiotherapy. The majority of patients (90%) had a partial rather than complete response to prior platinum-based chemotherapy and 5 patients (all on the olaparib BD arm) were found post-randomisation to be ineligible having progressed during primary therapy.

All patients received study treatment as allocated, except for three ineligible patients who did not commence study treatment (Fig. 1). Overall, the median treatment duration was 8 weeks (i.e., 2 treatment cycles) (interquartile range 7–21, range 0–106) and was similar in all the treatment arms (Fig. 1). Only 3 patients completed the planned 24 months of protocol treatment. Of the 214 who started treatment and discontinued early, the principal reasons were progression or death (58%), adverse events (31%) or other (11%). The proportion of patients requiring treatment delays or dose reductions was 24% and 18% respectively and was reasonably balanced across the three treatment arms (Fig. 1).

PFS from randomisation was better for patients on the olaparib arms compared to placebo with median PFS of 3·7 and 3·6 months for BD and TDS respectively compared to 2·5 for placebo (Fig. 2A, Table 2) with HRs for each olaparib arm compared to placebo of 0·76 (90%CI: 0·57-1·02) for BD and 0·86 (90%CI: 0·64, 1·15) for TDS. However, these observed differences were not statistically significant for olaparib BD (P = 0·180 and 0·125 from stratified log-rank and adjusted Cox model respectively) or for TDS (P = 0·164 and 0·402 from stratified log-rank and adjusted Cox model respectively). Sensitivity analysis with pooled olaparib arms and per-protocol population resulted in the same conclusions. However, the sensitivity analysis that excluded the 5 patients who were randomised despite being ineligible because of having progressive disease after primary therapy, showed a statistically significant benefit in PFS for olaparib BD compared to placebo (HR = 0·69, 95%CI (0·51, 0·93), P = 0·043).

PFS rate at 4 months from randomisation showed a benefit for the olaparib arms (45% for both) compared to placebo (36%) (Table 2). The trial did not show any clinically relevant benefit for olaparib compared to placebo in terms of OS (Fig. 2B and Table 2), with 6-month OS rates of 69% and 66% for olaparib BD and TDS respectively compared to 66% for placebo. Plots of the changing distribution of performance status for each treatment group over time (Supplementary Appendix 2) showed that performance status was maintained during the study with no apparent benefit in the olaparib arms. Mean quality of life scores for each treatment group over the 6 month period from randomisation (Fig. 3) demonstrated modest improvements in all three treatment groups for those who were alive and able to respond to the questionnaires at those time points. There were no apparent differences between the treatment groups in terms of the quality-adjusted life months within the first 6 months from randomisation (QALM6; Table 2).

Only six patients (3%) experienced no adverse events. 214 patients

Table 3
Key adverse events reported during the STOMP trial.

	Placebo $N = 74$		Olaparib BD $N = 73$		Olaparib TDS $N = 73$	
	All	G3+	All	G3+	All	G3+
At least one AE reported	72 (97%)	33 (45%)	70 (96%)	38 (53%)	72 (99%)	36 (49%)
Haematological						
Anaemia	15 (20%)	0	37 (51%)	4 (5%)	41 (56%)	11 (15%)
Leucopenia	0	0	3 (4%)	3 (4%)	1 (1%)	1 (1%)
Lymphopenia	0	0	8 (11%)	8 (11%)	9 (12%)	9 (12%)
Neutropenia	0	0	5 (7%)	5 (7%)	2 (3%)	2 (3%)
Thrombocytopenia	2 (3%)	2 (3%)	4 (5%)	4 (5%)	5 (7%)	5 (7%)
Non-Haematological						
Constipation	19 (26%)	0	16 (22%)	0	14 (19%)	1 (1%)
Diarrhoea	18 (24%)	3 (4%)	13 (18%)	1 (1%)	12 (16%)	2 (3%)
Dyspepsia	12 (18%)	0	11 (15%)	1 (1%)	6 (8%)	0
Nausea	44 (59%)	2 (3%)	47 (64%)	1 (1%)	51 (70%)	2 (3%)
Vomiting	21 (28%)	3 (4%)	25 (34%)	0	33 (45%)	2 (3%)
Fatigue	55 (74%)	10 (14%)	64 (88%)	16 (22%)	58 (79%)	7 (10%)
Chest Pain	9 (12%)	0	10 (14%)	0	3 (4%)	0
Respiratory infection	15 (20%)	5 (7%)	21 (29%)	2 (3%)	22 (30%)	6 (8%)
Anorexia	30 (41%)	0	34 (47%)	2 (3%)	28 (38%)	2 (3%)
Hypomagnesemia	5 (7%)	2 (3%)	2 (3%)	0	1 (1%)	0
Hyponatraemia	12 (16%)	7 (9%)	7 (10%)	3 (4%)	10 (14%)	4 (5%)
Arthralgia	17 (23%)	0	6 (8%)	0	9 (12%)	0
Back pain	18 (24%)	1 (1%)	13 (18%)	0	14 (19%)	2 (3%)
Dizziness	14 (19%)	0	16 (22%)	0	15 (21%)	0
Dysgeusia	12 (16%)	0	12 (16%)	1 (1%)	12 (16%)	0
Headache	18 (24%)	0	19 (26%)	0	17 (23%)	0
Insomnia	10 (14%)	0	8 (11%)	0	5 (7%)	1 (1%)
Cough	27 (36%)	0	25 (34%)	0	27 (37%)	0
Dyspnoea	21 (28%)	3 (4%)	26 (36%)	1 (1%)	28 (38%)	3 (4%)
Pneumonia	0	0	0	0	4 (5%)	2 (3%)
Alopecia	11 (15%)	0	13 (18%)	0	16 (22%)	0
Hypertension	8 (11%)	3 (4%)	5 (7%)	1 (1%)	4 (5%)	1 (1%)
Thromboembolic Event	3 (4%)	2 (3%)	3 (4%)	1 (1%)	6 (8%)	3 (4%)

AE, adverse event; BD, twice daily; G3+, grade 3 or above; TDS, three times a day.
Note: Events are included if their overall incidence in the trial is ≥ 10% and/or there was >1 patient experiencing the event at grade 3 or above. Data are shown as number (percentage) of patients who experienced the event at least once.

(97%) reported at least one adverse event with 107 (49%) reporting at least one adverse event of grade 3 or higher (Table 3). As expected in this patient population recovering from chemoradiotherapy for SCLC, anaemia, fatigue, nausea and respiratory symptoms were common, with more anaemia in the olaparib treatment groups. Other adverse effects reported more commonly with olaparib included nausea, vomiting, neutropenia and lymphopenia. A full listing of adverse events reported at grade 3 or higher, or by more than 10% of patients in any arm, is shown in the Supplementary Appendix 3.

98 serious adverse events (SAE) were reported for 73 patients: 29 on placebo, 26 on Olaparib BD and 43 on Olaparib TDS. However, only 33 (34%) were judged to be likely related to the study treatment: 3, 14 and 16 respectively.

Two patients (1%) developed second primary malignancies, one adenomatous non-SCLC, the other a squamous skin cancer, both in the placebo arm.

4. Discussion

This randomised phase II trial evaluated the efficacy and safety of oral olaparib as a maintenance treatment in patients who had completed first line treatment for SCLC with platinum-based chemotherapy. This strategy has proven beneficial in other solid tumour types. The study was appropriately powered and accrued well. In addition, olaparib was well tolerated. The observed data showed some benefit for olaparib but did not demonstrate a statistically significant difference in PFS or OS between the treatment arms. The treatment effect of olaparib BD, however, was potentially diluted by the pre-planned ITT analysis that included 5 ineligible patients (7%) who had progressed after primary therapy and were included in the analysis as events with zero PFS. When these were excluded in a sensitivity analysis, the PFS benefit became statistically significant.

Although platinum-based chemoradiotherapy has been the first line treatment of choice for SCLC for three decades, immune checkpoint inhibitors are now incorporated into treatment for some patients with extensive stage SCLC.[3] However, a significant proportion of SCLC patients are ineligible for treatment with immune checkpoint inhibitors and these agents were not available when our trial started. Our study was popular with both patients and clinicians, showing that an effective oral maintenance treatment would be an acceptable option, given the high relapse rate and poor outcome for relapsed SCLC.

In breast, ovarian, prostate and pancreatic cancers, *BRCA* mutations predict for sensitivity to PARP inhibitors, which have now entered clinical practice. *BRCA* mutations are not found in SCLC, but we hypothesised that abnormalities in other DNA repair genes such as *NBS1*, *ATM*, *RAD51*, Chk1/2, *MDC1, ERCC1* and *PTEN* might make SCLC susceptible to synthetic lethality with olaparib. The rationale that PARP inhibitors have a role in treating beyond *BRCA* mutant tumours is now widely accepted, especially for tumours associated with high levels of replication stress such as SCLC.[16,17] Our study concept was also supported by the finding that *PARP1* is overexpressed in SCLC and evidence of sensitivity to PARP inhibitors *in vitro* and *in vivo*.[7,12] However, more recent work suggests that expression of Schlafen-11 (SLFN-11) is a better predictor of sensitivity to PARP inhibitors in SCLC.[18,19] The targeting of DNA damage response in SCLC remains of much interest,[20] and inhibitors against novel targets, including DNA repair proteins, DNA damage signalling and DNA metabolism are in development.[21]

In our study, two dose schedules of olaparib were compared with placebo: 300 mg olaparib twice daily (BD arm) and 200 mg olaparib thrice daily (TDS arm). As expected, the efficacy of the two schedules was comparable. The adverse effect profile was also similar. Although more SAEs were recorded in the TDS arm, these were not judged to be treatment related. The number of patients requiring dose delays was similar in all three arms (22%, 22% and 25% for placebo, olaparib BD and olaparib TDS respectively), but more patients in the TDS arm required dose reductions (11%, 15% and 26% respectively). Importantly, performance status and quality of life were maintained in all three treatment groups. Both schedules are therefore acceptable, but we would recommend the BD schedule for patient convenience, consistent with other studies and the current data sheet.

Other clinical data are now available for PARP inhibitors in SCLC. Veliparib has been evaluated in first line treatment in combination with cisplatin-etoposide.[22] The primary endpoint of PFS was lengthened from 5·5 months to 6·1 months with the addition of veliparib but this small increase was not associated with a significant increase in response rate or OS and is of uncertain clinical significance. Olaparib has been combined with temozolomide as a second line treatment with a response rate of 42%, PFS of 4·2 months and OS of 8·5 months.[23] A randomised phase II study of veliparib combined with temozolomide as second line treatment for SCLC,[24] showed a response rate of 39% for the combination compared to 14% for temozolomide alone ($P = 0{\cdot}016$). However, there was no significant difference between the groups in PFS or OS, although both were improved in those on veliparib with SLFN-11 positive tumours. Talazoparib, a highly potent PARP trapping inhibitor, showed a clinical benefit rate of 26% (9% PR and 17% SD) in a phase I expansion of 23 SCLC patients.[25] Alternative strategies include olaparib in combination with Wee1 inhibition, Chk1 inhibition, reactivators of p53 and anti-angiogenics, all of which are currently under active investigation.

The advent of immunotherapy in SCLC introduces exciting opportunities to improve treatment outcomes. Immune checkpoint inhibitors given in combination with platinum agents are beneficial in some better prognosis patients with extensive stage SCLC. However, immunotherapy plus chemotherapy can have significant morbidity and is not appropriate for all SCLC patients. An alternative approach, as abnormalities of DNA repair lead to an increased tumour mutational burden, is to use PARP inhibition to sensitise cells to immune checkpoint inhibition.[26] Such combinations are now being tested in clinical trials.[27,28] In parallel, the mechanism of action is being sought: for example PARP inhibition, using olaparib and veliparib, enhances tumour cell-intrinsic immunity in ERCC1-deficient cells[29]; histone PARylation factor 1 (HPF1) interacts with PARP1 and increases its affinity to olaparib[30].

5. Conclusions

We conclude that olaparib monotherapy is well tolerated and the observed data showed some benefit but our trial did not reach the pre-planned level of evidence of improved efficacy when given as a maintenance treatment in SCLC in an unselected population to warrant further research. However, PARP inhibition may be effective in this tumour type when combined with other agents. Combinations of PARP inhibitors with immunotherapy should be investigated further.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

PJW and LJB conceived the study which they designed with help from PG, SJD and EH. All authors contributed to the acquisition and interpretation of the data, and preparation of the manuscript. All authors approved the final manuscript.

The authors are grateful to all the patients who participated in the trial and their families. We also acknowledge the support of all the participating clinicians and their local research teams. We thank all staff at Cancer Research UK Clinical Trials Unit (CRCTU) at University of Birmingham who contributed to this trial, particularly Peter Fletcher for statistical support.

Disclosures

S.A. reports honoraria and consulting fees from Amgen, AstraZeneca, BMS, Lilly, MSD, Novartis, Pfizer, Roche and Takeda. C.M. has been an employee of MSD since 2017. L.J.B. reports honoraria from AstraZeneca. All remaining authors have declared no conflicting interests.

Data sharing

Participant data and the associated supporting documentation will be available within 6 months after the publication of this manuscript. Details of our data request process is available on the CRCTU website. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the Chief Investigator, the trial steering committee, the Sponsor, consent arrangements, the practicality of anonymising the requested data and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgements and obligations for the responsible use of data. An anonymised encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on encryption of data sets.

Funding

This work was supported by Cancer Research UK [CRUK/10/037 to P.W.] and AstraZeneca [ISS22810017 to P.W.]. This trial was an investigator-initiated study supported by the collaboration between AstraZeneca and the UK National Cancer Research Network, for which AstraZeneca provided partial funding. This study was sponsored by Sheffield Teaching Hospitals NHS Foundation Trust (ISS22810017) and run by the Cancer Research UK Clinical Trials Unit, University of Birmingham. Staff at the CRCTU who contributed to the trial were supported by a core funding grant from Cancer Research UK (C22436/A25354).

The funder had no role in trial design, data collection, data analysis, data interpretation or writing of the report. The chief investigator and corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.07.007.

References

[1] S.M. Lee, P.J. Woll, R. Rudd, D. Ferry, M. O'Brien, G. Middleton, S. Spiro, L. James, K. Ali, M. Jitlal, A. Hackshaw, Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial, J Natl Cancer Inst. 101 (15) (2009) 1049–1057.

[2] C. Faivre-Finn, M. Snee, L. Ashcroft, W. Appel, F. Barlesi, A. Bhatnagar, A. Bezjak, F. Cardenal, P. Fournel, S. Harden, C. Le Pechoux, R. McMenemin, N. Mohammed, M. O'Brien, J. Pantarotto, V. Surmont, J.P. Van Meerbeeck, P.J. Woll, P. Lorigan, F. Blackhall, Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial, Lancet Oncol. 18 (8) (2017) 1116–1125.

[3] W.T. Iams, J. Porter, L. Horn, Immunotherapeutic approaches for small-cell lung cancer, Nat Rev Clin Oncol. 17 (5) (2020) 300–312.

[4] M. Peifer, L. Fernández-Cuesta, M.L. Sos, J. George, D. Seidel, L.H. Kasper, D. Plenker, F. Leenders, R. Sun, T. Zander, R. Menon, M. Koker, I. Dahmen, C. Müller, V. Di Cerbo, H.-U. Schildhaus, J. Altmüller, I. Baessmann, C. Becker, B. de Wilde, J.o. Vandesompele, D. Böhm, S. Ansén, F. Gabler, I. Wilkening, S. Heynck, J.M. Heuckmann, X. Lu, S.L. Carter, K. Cibulskis, S. Banerji, G. Getz, K.-S. Park, D. Rauh, C. Grütter, M. Fischer, L. Pasqualucci, G. Wright, Z. Wainer, P. Russell, I. Petersen, Y. Chen, E. Stoelben, C. Ludwig, P. Schnabel, H. Hoffmann, T. Muley, M. Brockmann, W. Engel-Riedel, L.A. Muscarella, V.M. Fazio, H. Groen, W. Timens, H. Sietsma, E. Thunnissen, E. Smit, D.A.M. Heideman, P.J.F. Snijders, F. Cappuzzo, C. Ligorio, S. Damiani, J. Field, S. Solberg, O.T. Brustugun, M. Lund-Iversen, J. Sänger, J.H. Clement, A. Soltermann, H. Moch, W. Weder, B. Solomon, J.-C. Soria, P. Validire, B. Besse, E. Brambilla, C. Brambilla, S. Lantuejoul, P. Lorimier, P.M. Schneider, M. Hallek, W. Pao, M. Meyerson, J. Sage, J. Shendure, R. Schneider, R. Büttner, J. Wolf, P. Nürnberg, S. Perner, L.C. Heukamp, P.

K. Brindle, S. Haas, R.K. Thomas, Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer, Nat Genet. 44 (10) (2012) 1104–1110.
[5] U. Testa, G. Castelli, E. Pelosi, Lung cancers: Molecular characterization, clonal heterogeneity and evolution, and cancer stem cells, Cancers (Basel) 10 (8) (2018) 248.
[6] J. Bartek, J. Bartkova, J. Lukas, DNA damage signalling guards against activated oncogenes and tumour progression, Oncogene. 26 (56) (2007) 7773–7779.
[7] Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov. 2012;2(9):798-811.
[8] D.M. Jackman, B.E. Johnson, Small-cell lung cancer, Lancet. 366 (9494) (2005) 1385–1396.
[9] McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res. 2006;66(16):8109-8115.
[10] C.J. Lord, A. Ashworth, PARP inhibitors: Synthetic lethality in the clinic, Science. 355 (6330) (2017) 1152–1158.
[11] J. Mateo, C.J. Lord, V. Serra, A. Tutt, J. Balmaña, M. Castroviejo-Bermejo, C. Cruz, A. Oaknin, S.B. Kaye, J.S. de Bono, A decade of clinical development of PARP inhibitors in perspective, Ann Oncol. 30 (9) (2019) 1437–1447.
[12] Cardnell RJ, Feng Y, Diao L, et al. Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. Clin Cancer Res. 2013;19(22):6322-6328.
[13] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur J Cancer. 45 (2) (2009) 228–247.
[14] EuroQol Research Foundation. EQ-5D user guides. Last accessed 07-Feb-2022. https://euroqol.org/publications/user-guides/.
[15] L.J. Billingham, K.R. Abrams, Simultaneous analysis of quality of life and survival data, Stat Methods Med Res. 11 (1) (2002) 25–48.
[16] Pilié PG, Gay CM, Byers LA, et al. PARP inhibitors: Extending benefit beyond BRCA-mutant cancers. Clin Cancer Res. 2019;25(13):3759-3771.
[17] M. Yi, B. Dong, S. Qin, Q. Chu, K. Wu, S. Luo, Advances and perspectives of PARP inhibitors, Exp Hematol Oncol. 8 (1) (2019).
[18] Lok BH, Gardner EE, Schneeberger VE, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. Clin Cancer Res. 2017;23(2):523-535.
[19] C.A. Stewart, P. Tong, R.J. Cardnell, T. Sen, L. Li, C.M. Gay, F. Masrorpour, Y. Fan, R.O. Bara, Y. Feng, Y. Ru, J. Fujimoto, S.T. Kundu, L.E. Post, K. Yu, Y. Shen, B. S. Glisson, I. Wistuba, J.V. Heymach, D.L. Gibbons, J. Wang, L.A. Byers, Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer, Oncotarget. 8 (17) (2017) 28575–28587.
[20] V. Foy, M.W. Schenk, K. Baker, F. Gomes, A. Lallo, K.K. Frese, M. Forster, C. Dive, F. Blackhall, Targeting DNA damage in SCLC, Lung Cancer. 114 (2017) 12–22.
[21] T.A. Yap, R. Plummer, N.S. Azad, T. Helleday, The DNA damaging revolution: PARP inhibitors and beyond, Am Soc Clin Oncol Educ Book. (39) (2019) 185–195.
[22] T.K. Owonikoko, S.E. Dahlberg, G.L. Sica, L.I. Wagner, J.L. Wade, G. Srkalovic, B. W. Lash, J.W. Leach, T.B. Leal, C. Aggarwal, S.S. Ramalingam, Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-ACRIN 2511 study, J Clin Oncol. 37 (3) (2019) 222–229.
[23] Farago AF, Yeap BY, Stanzione M, et al. Combination olaparib and temozolomide in relapsed small-cell lung cancer. Cancer Discov. 2019;9(10):1372-1387.
[24] M.C. Pietanza, S.N. Waqar, L.M. Krug, A. Dowlati, C.L. Hann, A. Chiappori, T. K. Owonikoko, K.M. Woo, R.J. Cardnell, J. Fujimoto, L. Long, L. Diao, J. Wang, Y. Bensman, B. Hurtado, P. de Groot, E.P. Sulman, I.I. Wistuba, A. Chen, M. Fleisher, J.V. Heymach, M.G. Kris, C.M. Rudin, L.A. Byers, Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer, J Clin Oncol. 36 (23) (2018) 2386–2394.
[25] de Bono J, Ramanathan RK, Mina L, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov. 2017;7(6):620-629.
[26] Sen T, Rodriguez BL, Chen L, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov. 2019;9(5):646-661.
[27] M. Friedlander, T. Meniawy, B. Markman, L. Mileshkin, P. Harnett, M. Millward, J. Lundy, A. Freimund, C. Norris, S. Mu, J. Wu, V. Paton, B.o. Gao, Pamiparib in combination with tislelizumab in patients with advanced solid tumours: results from the dose-escalation stage of a multicentre, open-label, phase 1a/b trial, Lancet Oncol. 20 (9) (2019) 1306–1315.
[28] A. Thomas, R. Vilimas, C. Trindade, R. Erwin-Cohen, N. Roper, L. Xi, V. Krishnasamy, E. Levy, A. Mammen, S. Nichols, Y. Chen, V. Velcheti, F. Yin, E. Szabo, Y. Pommier, S.M. Steinberg, J.B. Trepel, M. Raffeld, H.A. Young, J. Khan, S. Hewitt, J.-M. Lee, Durvalumab in combination with olaparib in patients with relapsed SCLC: Results from a phase II study, J Thorac Oncol. 14 (8) (2019) 1447–1457.
[29] R.M. Chabanon, G. Muirhead, D.B. Krastev, J. Adam, D. Morel, M. Garrido, A. Lamb, C. Hénon, N. Dorvault, M. Rouanne, R. Marlow, I. Bajrami, M. L. Cardeñosa, A. Konde, B. Besse, A. Ashworth, S.J. Pettitt, S. Haider, A. Marabelle, A.N.J. Tutt, J.-C. Soria, C.J. Lord, S. Postel-Vinay, PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer, J Clin Invest. 129 (3) (2019) 1211–1228.
[30] J. Rudolph, G. Roberts, K. Luger, Histone parylation factor 1 contributes to the inhibition of PARP1 by cancer drugs, Nat Commun. 12 (1) (2021) 736.