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Olaparib sebagai Terapi Metastatic-Castration Resistant Prostate Cancer (mCRPC): Systematic Review dan Meta-Analysis

Olaparib as Therapy for Metastatic-Castration Resistant Prostate Cancer (mCRPC): Systematic Review and Meta-Analysis

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Abstract
Prostate cancer is the second most prevalent cancer in men with approximately 1.4 million men worldwide. The main therapy for prostate cancer is androgen deprivation therapy (ADT), but patients who have received ADT may experience a condition of castration resistant prostate cancer (CRPC). More than 84% of patients have metastasized when diagnosed with CRPC (mCRPC) and median survival about 36 months. The Food & Drugs Association (FDA) has approved new therapy for mCRPC patients, an example is olaparib. The purpose of this systematic review and meta analysis is to assess the effectiveness (overall survival) and safety of olaparib in mCRPC. This research used randomized control trial's (RCT) articles. The literature searching process was carried out using the PubMed database. The quality of inclusion was assessed using the Critical Appraisal Skill Program (CASP) checklist and journal reputation. The results of the meta-analysis on the effectiveness of olaparib has showed that there was no significant difference in the patient's overall survival rate (RR=0.81; 95% CI=0.58-1.13). The results of the meta analysis on the safety level of olaparib has showed a significant difference, seen from the side effects such as anemia (RR=3.47; 95% CI=2.59-4.65), nausea (RR=2.05; 95% CI=1.62-2.60) and fatigue (RR=1.32; 95% CI=1.10-1.59). The conclusion is olaparib as mCRPC therapy does not show significant effectiveness in improving overall survival in mCRPC. In addition, the low safety level of olaparib in mCRPC patients were seen from side effects such as anemia, nausea and fatigue.

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men and affects an estimated 1.4 million men worldwide (Sung *et al.*, 2021). The prevalence of prostate cancer in men aged ≤ 30 years is 5%, while in men aged ≥ 79 years is 59% (48-71%) (Mottet *et al.*, 2021). The number of people with prostate cancer varies by geographical region, for example prostate cancer patients in Australia and Northern America are very high (age-standardized rates [ASR] per 100,000 of 111.6 and 97.2 respectively), while prostate cancer patients in Eastern and South-Central Asia are low, but have increased from year to year (Mottet *et al.*, 2021). There are several risk factors that can affect prostate cancer, include family history or genetics, metabolic syndrome, cholesterol, obesity, hormonal drugs, testosterone and dietary (Mottet *et al.*, 2021).

The main treatment of prostate cancer is androgen deprivation therapy (ADT). ADT therapy is divided into two types, i.e. based on surgery and based on pharmaceutical (Mottet *et al.*, 2021). Patients who have received ADT therapy (surgery or based on pharmaceuticals) are likely to experience castration resistant prostate cancer (CRPC) which has characterized by an increase intracellular androgen levels compared to androgen sensitive cells, as well as overexpression of androgen receptors which indicates an adaptive mechanism of androgen hormones (Mottet *et al.*, 2021). There are various causes of CRPC, including through intrinsic cellular mechanisms where there is a signal from androgen receptor (AR) so it produced from overexpression of AR due to AR gene amplification, AR structural changes due to mutations, overexpression of AR co-activator and androgen production in tumor tissue (Seruga, Ocana and Tannock, 2011). More than 84% of patients have already metastasized when diagnosed with CRPC (mCRPC), and patients who did not metastasize when diagnosed with CRPC will metastasize within 2 years of CRPC diagnosis (Kirby, Hirst and Crawford, 2011). mCRPC is an aggressive and fatal disease with an average survival of 36 months, make it as a special concern for medical personnel today (Levee *et al.*, 2021).

New therapies has been approved by the Food & Drugs Association (FDA) as mCRPC therapy, i.e. poly(ADP-ribose) polymerase (PARP) inhibitor (Levee *et al.*, 2021). PARPi has a mechanism of action by capturing the PARP1 and PARP2 enzymes in DNA damage. PARPi also binds to nicotinamide adenine dinucleotide in DNA, thus prevent the activation of PARP's binding to DNA (Levee *et al.*, 2021). When the PARP enzyme has inhibited in normal cells, the homologous recombination repair (HRR) pathway can repair double-stranded breaks (DSB) in DNA which will become single-stranded breaks (SSB). When PARP was inhibited in HRR-mutated cells, there was an accumulation of DSB (Levee *et al.*, 2021). This will result in DSB repair through the non-homologous end-joining (NHEJ) mechanism which is less accurate than DNA repair through the HRR mechanism, resulting increase of DNA damage that lead to apoptosis and inhibits tumor progression (Levee *et al.*, 2021). Examples of therapies that belong to the PARPi class are olaparib, rucaparib, niraparib, veliparib and talazoparib (Teyssonneau *et al.*, 2021).

Olaparib is the first generation of PARPi (Teyssonneau *et al.*, 2021). Olaparib has been approved by the FDA as therapy in mCRPC patients with one of 14 mutated HRR genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCI, PALB2, RAD51B, RAD51C, RAD51D, RAD54L), who previously received hormone therapy (Antonarakis, Gomella and Petrylak, 2020). The number of patients with HRR somatic or germline gene mutations are around 25%, while BRCA1 or BRCA2 somatic or germline gene mutations are 10%, so olaparib has included in the mCRPC therapy algorithm in Prostate Cancer NCCN Guideline (Antonarakis, Gomella and Petrylak, 2020). In previous randomized controlled trial (RCT) studies, which has examined the effectiveness of olaparib in mCRPC patients, the observation of overall survival (OS), the level of risk of death and the safety of therapy in each group was carried out. Overall survival (OS) of 19.1 months was obtained in the olaparib group compared to the control group with OS of 14.7 months. In addition, the risk of death was lower by 31% in the olaparib group compared to the control group (Hussain *et al.*, 2020). Olaparib has decreased the duration of pain and improves patient's quality of life (Teyssonneau *et al.*, 2021). However, the most common side effects of using PARPi are anemia, nausea and fatigue (Antonarakis, Gomella and Petrylak, 2020). The purpose of this systematic review and meta analysis was to assess the effectiveness of olaparib as a therapy for mCRPC and its side effects. In addition, this systematic review and meta analysis is expected to be able to update information on findings related to the effectiveness and safety of using olaparib in mCRPC patients.

METHOD

Data Source and Searching Strategy

This study was a systematic review and meta analysis which aims to examine the effectiveness and safety of olaparib as a therapy for metastatic-castration resistant prostate cancer (m-CRPC). A search of published literatures was conducted using the PubMed database with the keywords

("parp inhibitor" OR olaparib) AND (prostate cancer). Screening of articles and quality assessment were performed by both authors (IMRPG and FH) independently. We resolved disagreements by discussion. The quality of the articles was assessed using the Critical Appraisal Tools Program (CASP) checklist and journal reputation. Articles have good quality if the results of the CASP checklist assessment are good and are published in a reputable journal (Table 2). The CASP checklist contains several questions that are divided into 3 parts (parts A, B and C). Part A was used to assess the validity of the research results, part B was used to assess the research results and part C was used to assess whether the research results can be applied or used by readers. For the CASP checklist, articles were considered of good quality if there were at least ten "yes" answers. The search for articles in the database was conducted from June to July 2023. The outcomes looked at were overall survival (OS) and side effects such as anemia, nausea and fatigue.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were the patients population aged ≥ 18 years who were diagnosed with mCRPC (increased PSA levels > 2 ng/mL and RECIST radiological examination obtained the results of bone lesions or lesions in soft tissue) and research conducted in a randomized controlled trials (RCTs). Patients who had received taxane therapy were allowed. Exclusion criteria were observational studies, reviews, editorials, articles that were not open access or full text, case reports and articles that were not published in English. Flow of study search on PubMed Database can be seen in Figure 1.

Data Extraction

The results of data extraction conducted by the researchers are included in the following information: author's name, year of publication, country, method, study subject, intervention group, control group, total population, intervention population, control population, median age, median PSA baseline, outcome (OS) and side effects (anemia, nausea and fatigue). In addition, the authors included the hazard ratio (HR) and 95% confidence interval (CI) related to the treatment outcome (Table 1).

Risk of Bias Assessment

An evaluation of the risk of bias in each article was conducted based on the Cochrane Risk of Bias Tool (Table 3). The risk of bias in selected articles was assessed by looking at the parameters: randomization of sample order, allocation concealment, masking of participants and test personnel, masking of outcome assessments, incomplete outcome data and selective reporting.

Journal Reputation

Journal reputation was assessed by looking at journal quartiles according to Scopus. Scopus was chosen because it has an indicator that can assess an international journal, that is Scimago Journal Rank (SJR). SJR is a measure of scientific influence that considers two things, that is: (1) Number of referring articles (without considering self citations); (2) Popularity of other referring journals.

Journal categories based on Scopus are divided into four quartiles (Q1 to Q4). Journals accredited Q1-Q3 according to Scopus are considered good quality because before the journal is indexed in Scopus, an evaluation process is carried out and articles are selected transparently and reviewed independently. In addition to rigorous evaluation and selection, journals are also re-evaluated regularly to maintain the quality of the journal over the year.

Data Analysis

Data analysis was conducted using the meta analysis method using the Revman 5.4 program. The type of data used in the analysis was dichotomous data. The risk ratio (RR) and 95% confidence interval (CI) were used to measure differences between intervention and control groups. Heterogeneity was assessed with the I^2 statistic. An I^2 value ≥50% indicates significant heterogeneity between studies, while an I^2 value ≤50% indicates acceptable heterogeneity between studies. The results of the meta-analysis were presented in the form of a forest plot.

Table 1. Study Characteristics

Author	de Bono, *et al.*	Hussain, *et al.*	Clarke, *et al.*
Year of publication	2020	2020	2018
Country	England	England	United Kingdom, Poland, Russia, Spain, Czech Republic, Italy, USA, Canada
Method	Randomized, open label phase 3 trial	Randomized, open label phase 3 trial	Randomized double blind, placebo controlled phase 2 trial

Table 1. Study Characteristics (continuous)

Author	de Bono, *et al.*	Hussain, *et al.*	Clarke, *et al.*
Research subject	Patients aged ≥18 years diagnosed with mCRPC, gleason score ≥8, have gene abnormalities in one of the following genes BRCA1, BRCA2, ATM (Cohort A), have abnormalities in one of a total of 12 genes (Cohort B)	Patients diagnosed with mCRPC, have gene abnormalities in one of the following genes BRCA1, BRCA2, ATM (Cohort A), had an abnormality in one of a total of 12 genes (Cohort B)	Patients aged ≥18 years with confirmed mCRPC, serum testosterone ≤50 ng/dL, lesions on bone scan (CT-scan or MRI)
Intervention group	Olaparib 300 mg twice daily	Olaparib 300 mg twice daily	Olaparib 300 mg twice daily + abiraterone 1000 mg once daily in the morning + prednisolone 5 mg twice daily
Control group	Enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily + prednisone (5 mg twice daily)	Enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily + prednisone (5 mg twice daily)	Placebo + Abiraterone 1000 mg twice daily + prednisolone 5 mg twice daily.
The total number of population	387	387	142
Number of intervention population	256	256	71
Total control population	131	131	71
Median age	69 (47-91) vs. 69 (49-87)	-	70 (65-75) vs. 67 (62-74)
Median baseline PSA (µg/L)	68.2 (24.1-294.4) vs. 106.5 (37.2-326.6)	-	86 (23-194) vs. 47 (21-199)
OUTCOMES			
OS (month)	18.5 months (Cohort A) vs. 15.1 months (Control group) (HR 0.64: 95% CI, 0.43-0.97; P = 0.02). Overall population (Cohort A and B) 17.5 months vs 14.3 months (Control group) (HR 0.67; 95% CI 0.49-0.93)	19.1 (Cohort A) vs. 14.7 months (Control group) (HR 0.69; 95% CI 0.50-0.97; p=0.02). (Cohort B) 14.1 months vs. 11.5 months (Control group) (HR 0.96; 95% CI 0.63-1.49)	22.7 months on olaparib plus abiraterone (95% CI 17.4-29.4) vs 20.9 months on placebo plus abiraterone (95% CI 17.6-26.3)
Anemia	All grades 119 people (intervention group) vs 20 people (control group)	All grades 127 people (intervention group) vs 20 people (control group)	All grades 22 people (intervention group) vs 1 person (control group)
Nausea	All grades 106 people (intervention group) vs 25 people (control group)	All grades 110 people (intervention group) vs 27 people (control group)	All grades 27 people (intervention group) vs 15 people (control group)
Fatigue	All grades 105 people (intervention group) vs 42 people (control group)	All grades 107 people (intervention group) vs 43 people (control group)	All grades 31 people (intervention group) vs 19 people (control group)

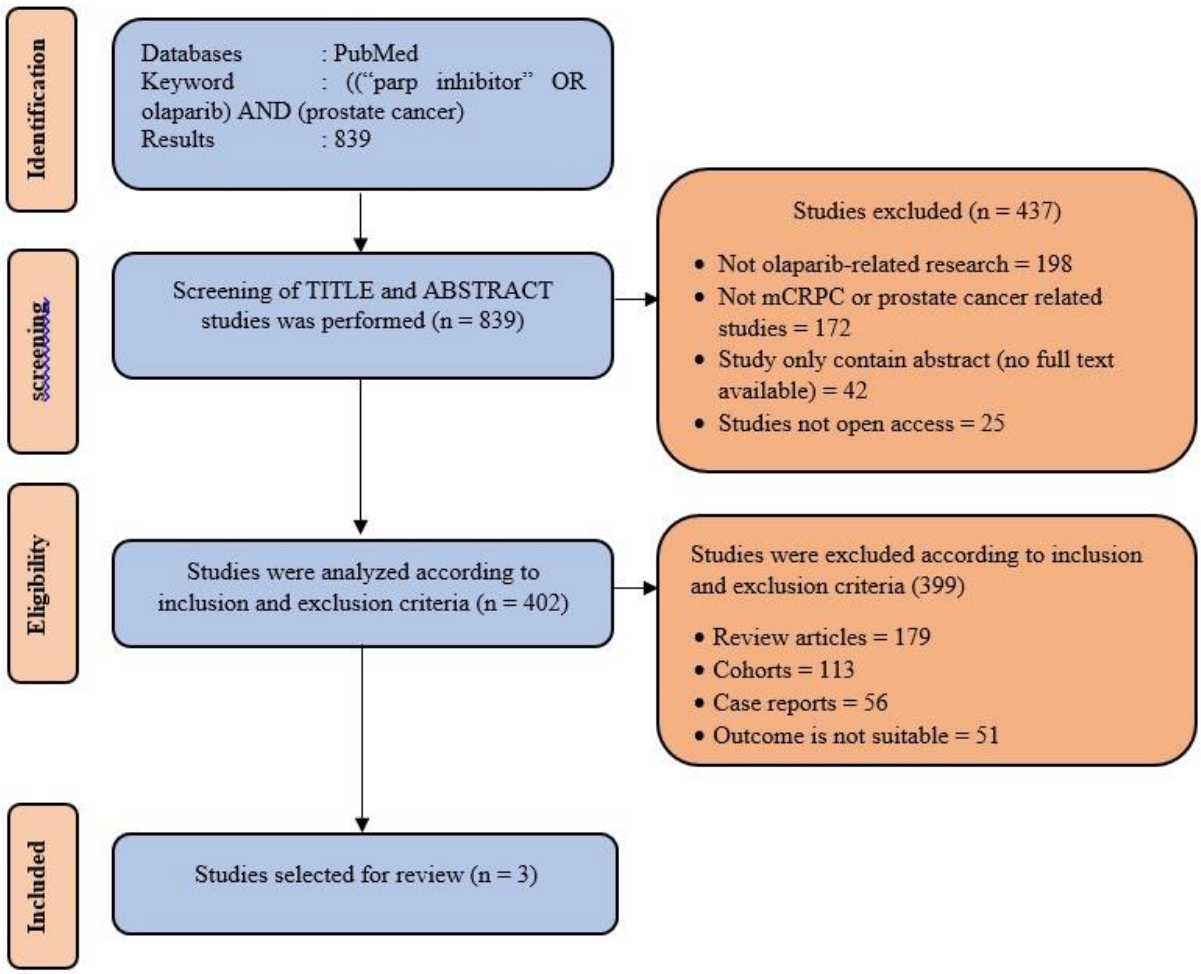

Figure 1. Flow of Study Search on PubMed Database

Table 2. Assessment of Study Quality with the CASP Checklist

Article Study	CASP Questions *												
	1	**2**	**3**	**4a**	**4b**	**4c**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
de Bono, *et al.*, 2020	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Hussain, *et al.*, 2020	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Clarke, *et al.*, 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

* Description : Y=Yes, N=No, (-)=Unclear

Table 3. Risk of bias assessment

	Randomi-zation of sample order (selection bias)	**Allocation concealment (selection bias)**	**Masking of participants and personnel (performance bias)**	**Masking of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**
de Bono, *et al.*, 2020	(+)	(+)	(-)	(-)	(+)	(+)
Hussain, *et al.*, 2020	(?)	(+)	(-)	(-)	(+)	(+)
Clarke, *et al.*, 2018	(+)	(+)	(+)	(+)	(+)	(+)

Remarks : low risk of bias : (+), unclear risk of bias : (?), high risk of bias : (-)

DISCUSSION

Overall Survival (OS)

As the first generation of PARPi, many studies have carried out comprehensive clinical evaluations of olaparib as a single or combination therapy for various malignant disease. Olaparib showed stable responses against diseases such as breast cancer, ovarian cancer, gastric cancer and showed beneficial effects in patients with BRCA tumor mutations (Bang *et al.*, 2017; Pujade-Lauraine *et al.*, 2017; Robson *et al.*, 2017; Guo *et al.*, 2018). In previous meta analysis, olaparib was able to increase overall survival (OS) in patients with prostate cancer but accompanied by side effects Grade 3 such as anemia, nausea and fatigue (Ratta *et al.*, 2020a; Keisner, 2022; Luo *et al.*, 2023; Warli *et al.*, 2023). In the systematic review and meta analysis that have been conducted, it was found that the use of olaparib as a therapeutic option in mCRPC patients showed positive results in OS although it showed negative results in other outcomes (anemia, nausea and fatigue). In the overall survival outcomes, two RCT studies reported a statistically significant difference between patients who received olaparib and patients who did not receive olaparib, while one RCT reported no statistical difference. The results of the meta analysis of overall survival (OS) outcome that have been carried out show no significant difference between the group that received olaparib compared to the control group (Figure 2). The results of this study are not in accordance with the results of a systematic review from Ratta *et al.* (2019) and Hatano and Nonomura (2023) who reported that patients who received olaparib showed positive results in overall survival and significant difference when compared to control (Ratta *et al.*, 2020a; Wu *et al.*, 2021; Iannantuono *et al.*, 2023) (Hatano and Nonomura, 2023). The difference in results reported by Ratta *et al.* (2019) and Hatano and Nonomura (2023) perhaps because this study involved RCT and observational research. This research also did not conduct meta analysis, while this study only involved RCT and conducted meta analysis.

Anemia

The use of olaparib in mCRPC patients in addition to providing benefits in the form of improving OS but the use of this therapy also causes unwanted outcomes such as anemia (Kim *et al.*, 2023). Three RCT studies used, the majority of studies mentioned that anemia is a side effect that often appears when using olaparib in mCRPC patients (Clarke *et al.*, 2018; de Bono *et al.*, 2020; Hussain *et al.*, 2020). The results of the meta-analysis that has been done show a significant differences between patients who received olaparib compared to patients who did not receive olaparib (Figure 3). These results indicate that patients who did not receive olaparib experienced a lower rate of anemia than patients who received olaparib. Patients are said to be anemic when the hemoglobin level are <12 g/dL (Dai *et al.*, 2018). These results are in line with the meta analysis conducted by Dai *et al.* (2018) and Schutz, *et al.* (2019) who reported that long-term using of olaparib can cause anemia (Dai *et al.*, 2018; Ruiz-Schutz *et al.*, 2019)(Maiorano *et al.*, 2023). This is because olaparib suppresses the hormone testosterone then it will interfere with the process of erythropoiesis (inhibits the formation of erythrocytes in the spinal cord) (Dai *et al.*, 2018).

Nausea

The results of the meta-analysis of the three studies showed a significant differences between mCRPC patients who received olaparib compared to patients who did not receive olaparib (Figure 4). mCRPC patients who did not receive olaparib experienced lower side effects of nausea than mCRPC patients who received olaparib. Although nausea is a frequent side effect in various ADTs, when using olaparib, nausea is the most common side effect that causes patients to stop taking olaparib (Roubaud *et al.*, 2022). This result is consistent with the systematic review of Ratta *et al.* (2019) who reported that mCRPC patients who received olaparib experienced higher nausea than mCRPC patients who did not receive olaparib (Ratta *et al.*, 2020b). Some neurotransmitters that play a role in inducing nausea are serotonin, dopamine, substance P and neurokinin-1 (NK1) when taking olaparib (Eakin *et al.*, 2020).

Fatigue

In the meta-analysis that has been conducted, in addition to causing anemia and nausea, the use of olaparib can also cause fatigue. The results of the meta-analysis of the three studies showed a significant differences between patients who received olaparib and patients who did not receive olaparib (Figure 5). These results indicate that patients who did not receive olaparib showed a lower rates of fatigue. This result is in line with the meta analysis of Schutz, *et al.* (2019), that mCRPC patients who received olaparib have a greater risk of fatigue than mCRPC patients who did not receive olaparib (Ruiz-Schutz *et al.*, 2019). This is because olaparib inhibits PARP which plays an important role during DNA repair in cells, thus causing biological deregulation which causes fatigue (Ruiz-Schutz *et al.*, 2019; Li and Zhang, 2021).

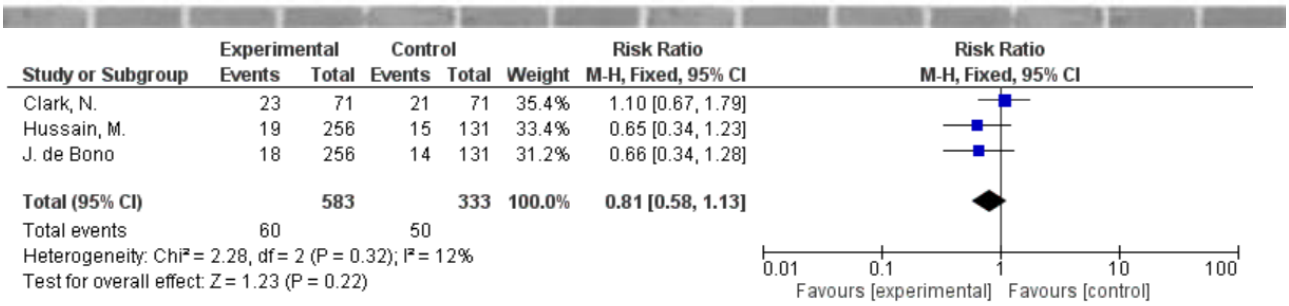

Figure 2. Forest Plot of Overall Survival (OS)

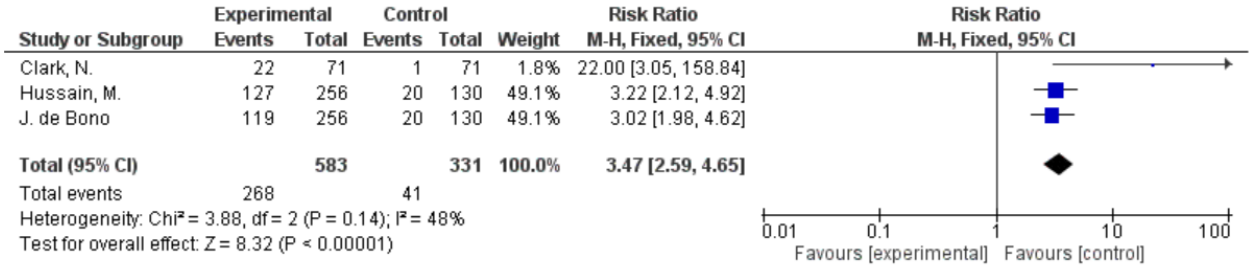

Figure 3. Forest Plot of Anemia

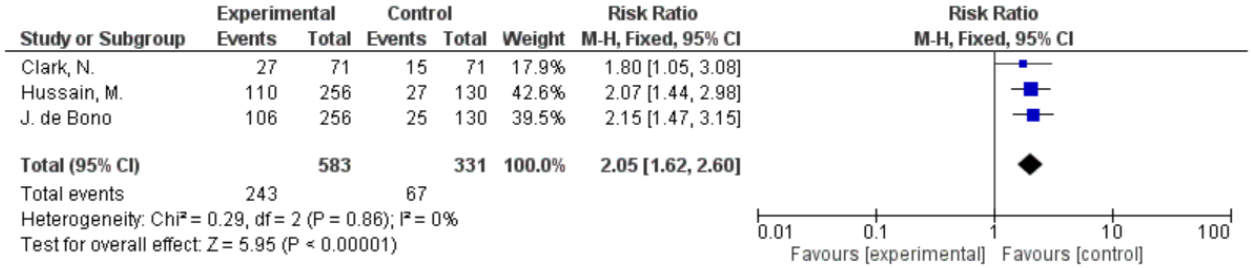

Figure 4. Forest Plot of Nausea

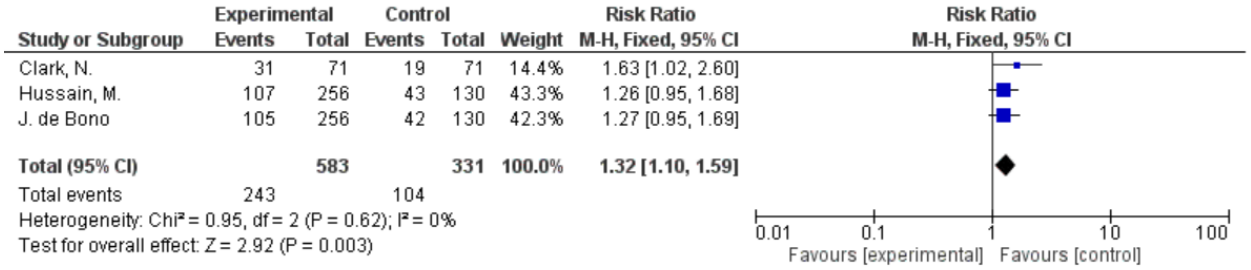

Figure 5. Forest Plot of Fatigue

CONCLUSION

The use of olaparib as mCRPC therapy did not show a significant effect in improving overall survival in mCRPC patients. In addition, the safety level of olaparib use in mCRPC patients is low judging from the side effects such as anemia, nausea and fatigue.

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