Poster 5051

Indirect treatment comparison of the efficacy of olaparib 300 mg tablets bid and cabazitaxel 25 mg/m² every 3 weeks plus daily prednisolone and granulocyte colony-stimulating factor in the treatment of patients with metastatic castration-resistant prostate cancer

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Objective

- To estimate the relative efficacy of olaparib vs cabazitaxel in the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) and a qualifying homologous recombination repair gene alteration (HRRm), using data from the PROfound and CARD studies.

Conclusions

- The results of the indirect treatment comparison suggest that olaparib is associated with significantly improved radiographic progression-free survival (rPFS) vs cabazitaxel in the treatment of patients with alterations in *BRCA1*-, *BRCA2*-, and/or *ATM* (BRCAm/*ATM*) who have progressed on prior taxane and next-generation hormonal agent (NHA) therapy.
- After adjusting for the effect of switching from NHA to olaparib in PROfound, olaparib is associated with a numerical overall survival (OS) improvement vs cabazitaxel in both populations.
- The results require confirmation in comparative studies. Analysis limitations include uncertainty over the efficacy of cabazitaxel vs NHA in HRRm mCRPC patients, and between-study heterogeneity.

Plain-language summary

Why did we perform this research?

- Olaparib and cabazitaxel are both effective treatments licenced for the treatment of metastatic castration-resistant prostate cancer, but they have not been compared directly in a clinical trial.
- Olaparib is a targeted treatment used to treat men with alterations in homologous recombination repair (HRR) genes such as *BRCA1*, *BRCA2* (BRCA) or *ATM*, and cabazitaxel is a type of chemotherapy.
- We performed an indirect treatment comparison of clinical trials for olaparib (PROfound) and cabazitaxel (CARD)[1,2] to help understand the effects of these drugs in men with mutations in BRCA and/or *ATM* genes.

How did we perform this research?

- We used results from the published studies and considered statistical modeling approaches to indirectly compare the effects of olaparib and cabazitaxel in men with prostate cancer.
- In contrast to the PROfound study, in which men were prospectively selected to have mutations in HRR genes such as BRCA and/or *ATM*, the CARD study did not examine gene mutations. Based on cabazitaxel's mode of action, the presence or absence of any gene mutations was not expected to affect the outcome of any comparison.
- The results of the CARD study were assumed to represent the effect of cabazitaxel in patients with mutations in HRR genes, as per the PROfound study.

What were the findings of this research and what are the implications?

- In the absence of head-to-head studies, we found that olaparib reduced the risk for cancer progression by 64%, compared with cabazitaxel, in men with BRCA mutations, and by 49% for men with BRCA and/or *ATM* mutations.
- Further studies of the effects of olaparib and cabazitaxel in this population are needed to confirm the results of the indirect treatment comparison.

Where can I access more information?

- PROfound study identifier: NCT02987543
- CARD study identifier: NCT02485691

Published papers

1. de Bono J *et al. N Engl J Med* 2020;382:2091–102.
2. de Wit R *et al. N Engl J Med* 2019;381:2506–18.

This study was funded by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing assistance was provided by Kristin Almond, PhD, from Mudskipper Business Ltd, funded by AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
References (click to access): [1]de Bono J *et al. N Engl J Med* 2020;382:2091–102; [2]de Wit R *et al. N Engl J Med* 2019;381:2506–18.
Poster presented at the virtual American Society for Clinical Oncology (ASCO) Annual Meeting, held on June 4–8, 2021 by Tim Reason.

Poster

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Presented at the virtual American Society for Clinical Oncology (ASCO) Annual Meeting, held on June 4–8, 2021.
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Mr Reason has no conflicts of interest to declare.

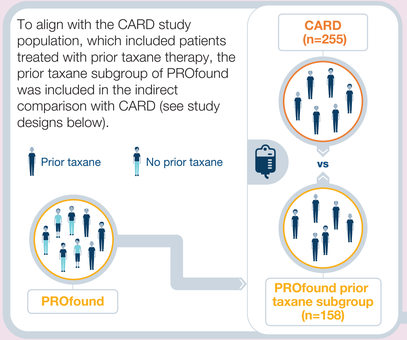
Introduction

- In the PROfound study (NCT02987543), olaparib demonstrated significantly improved rPFS, compared with a control of physician's choice NHA, in patients with previously treated mCRPC and alterations in HRR genes[1]
  - Olaparib was also associated with significantly improved OS vs control in mCRPC patients with BRCAm/*ATM*[3]
- Efficacy was observed across prespecified subgroups, including patients who had received prior taxane therapy and for whom intravenous cabazitaxel is an alternative treatment option.
- The relative efficacy of olaparib vs cabazitaxel has not been assessed directly in a clinical trial. An indirect treatment comparison (ITC) was performed to estimate the comparative efficacy of olaparib and cabazitaxel in patients with HRRm mCRPC after prior taxane and NHA.

Methods

A systematic literature review identified the cabazitaxel CARD study[2] (NCT02485691) as the most appropriate study to compare with olaparib in an NHA-treated mCRPC population. CARD and PROfound both share the same comparator arm (physician's choice NHA), enabling the indirect comparison of olaparib vs cabazitaxel.

To align with the CARD study population, which included patients treated with prior taxane therapy, the prior taxane subgroup of PROfound was included in the indirect comparison with CARD (see study designs below).



Efficacy analyses were performed on the hazard ratios (HRs) of rPFS by independent central review and OS using:
- published data from Phase IV CARD study and rPFS and OS* results from the prior taxane subgroup of PROfound.

*The OS analysis was performed using the final PROfound OS results, which included switching from NHA to olaparib after progression, and using results that were adjusted for switching.

In the absence of biomarker subgroup data, the efficacy results of the overall population in CARD were assumed generalizable to the BRCAm/*ATM* and BRCAm populations of PROfound.

Based on cabazitaxel's mode of action as a microtubule inhibitor, it was presumed that HRR gene mutation status is not a modifier of relative treatment effect for cabazitaxel vs NHA.

Following best practice guidance, we assessed the basic assumptions of indirect treatment comparisons in terms of **similarity**, **homogeneity** and **consistency** of included trials.

Statistical analysis was conducted following guidance from NICE DSU TSD 18.

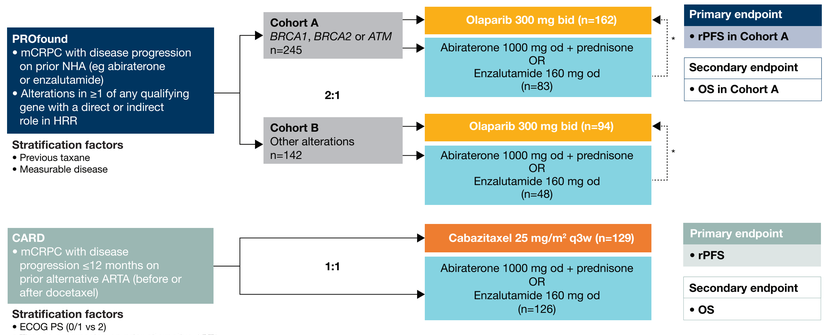
The **similarity** assumption was assessed by testing for the presence of relative effect modifiers in the prior taxane subgroup of PROfound.

Homogeneity was assessed qualitatively and is further discussed in the limitations section.

The assumption of **consistency** was not considered owing to a lack of head-to-head evidence for the comparison of interest.

Results presented here are for the comparison of olaparib with cabazitaxel in the BRCAm and BRCAm/*ATM* populations.

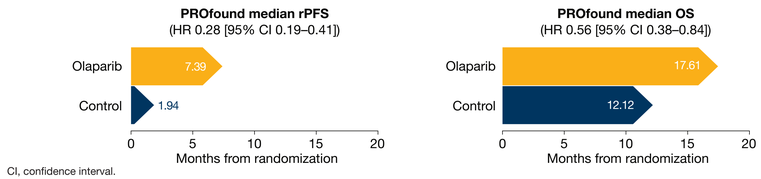
PROfound and CARD study designs



*Upon radiographic progression, patients in the control arm were given the option to switch to olaparib. ARTA, androgen receptor-targeted treatment; ECOG PS, Eastern Cooperative Oncology Group Performance Status; od, once daily; q3w, every 3 weeks.

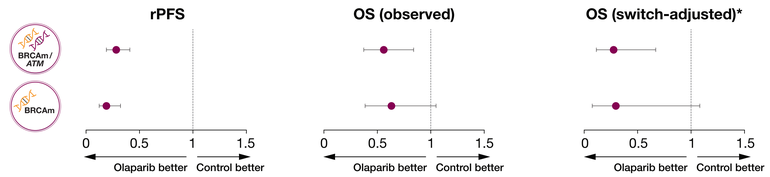
Results and interpretation

In the prior taxane subgroup of the PROfound BRCAm/*ATM* population (n=158), olaparib demonstrated a significant improvement in both rPFS and OS vs control.



CI, confidence interval.

For rPFS, OS and switch-adjusted OS, the HRs show the benefit of olaparib vs control in both the BRCAm/*ATM* and BRCAm patient populations.

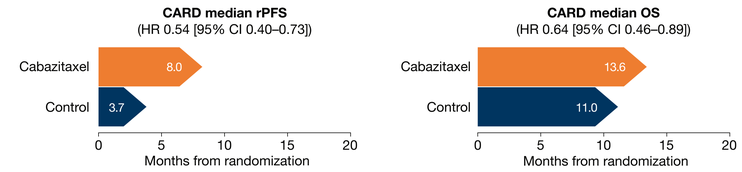


*OS results after adjustment for switching to olaparib using the rank-preserving structural failure time method.

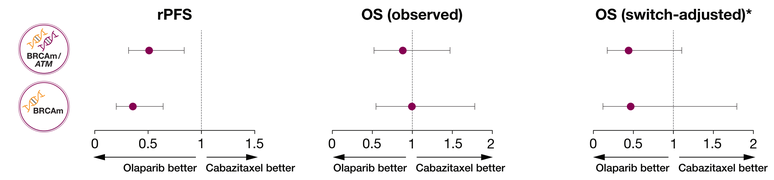
Post discontinuation of study treatment

11.8% of patients in the PROfound BRCAm/*ATM* population went on to receive cabazitaxel as subsequent anticancer therapy (11.7% from the olaparib arm and 12.0% from the control arm).

In the CARD trial (n=255), cabazitaxel was associated with improved rPFS and OS, compared with control, in patients who had prior taxane treatment.



ITC results for olaparib and cabazitaxel suggest that olaparib treatment significantly improved rPFS, compared with cabazitaxel, in both the BRCAm/*ATM* and BRCAm patient populations, who previously progressed on taxane and NHA therapy.



*OS results after adjustment for switching to olaparib using the rank-preserving structural failure time method.

After removing the effect of switching from control to olaparib in PROfound, olaparib appears to be associated with an OS improvement vs cabazitaxel in both populations.

ITC

- **Olaparib** reduced the risk of disease progression by **49% vs cabazitaxel** in the BRCAm/*ATM* population.
- **Olaparib** reduced the risk of death by **56% vs cabazitaxel** in the BRCAm/*ATM* population, when adjusted for treatment switching.

BRCAm /*ATM*

ITC

- **Olaparib** reduced the risk of disease progression by **64% vs cabazitaxel** in the BRCAm population.
- **Olaparib** reduced the risk of death by **53% vs cabazitaxel** in the BRCAm population, when adjusted for treatment switching.

BRCAm

Analysis limitations include uncertainty over the efficacy of cabazitaxel vs NHA in HRRm mCRPC patients, and between-study heterogeneity in prior taxane and NHA therapy. Results will require confirmation in comparative studies.

Acknowledgments

This study was funded by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing assistance was provided by Kristin Almond, PhD, from Mudskipper Business Ltd, funded by AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

References

1. de Bono J *et al. N Engl J Med* 2020;382:2091–102.
2. de Wit R *et al. N Engl J Med* 2019;381:2506–18.
3. Hussain M *et al. N Engl J Med* 2020;383:2345–57.