Thank you for your inquiry, please see the following page for the information you requested.

This content includes a QR code giving access to supportive information for the study.

Poster 624P

Tolerability of olaparib in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: PROfound

Guilhem Roubaud,[1] Mustafa Özgüroğlu,[2] Nicolas Penel,[3] Nobuaki Matsubara,[4] Niven Mehra,[5] Michael Kolinsky,[6] Giuseppe Procopio,[7] Susan Feyerabend,[8] Jae Young Joung,[9] Gwenaelle Gravis,[10] Kazuo Nishimura,[11] Craig Gedye,[12] Charles Padua,[13] Neal Shore,[14] Antoine Thiery-Vuillemin,[15] Chris Gresty,[16] Neil Brickel,[16] Joe Burgents,[17] Allison Allen,[18] Karim Fizazi[19]

[1]Dept. of Medical Oncology, Institut Bergonié, Bordeaux, France; [2]Dept. of Internal Medicine, Division of Medical Oncology, Cerrahpaşa School of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [3]Centre Oscar Lambret, Lille, France; [4]National Cancer Center Hospital East, Chiba, Japan; [5]Radboud University Medical Center, Nijmegen, The Netherlands; [6]Dept. of Medical Oncology, University of Alberta Cross Cancer Institute, Edmonton, Alberta, Canada; [7]Medical Oncology Dept., Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]Urologic Oncology, Studienpraxis Urologie, Nürtingen, Germany; [9]Center for Prostate Cancer, National Cancer Center, Goyang, South Korea; [10]Institut Paoli-Calmettes, Marseille, France; [11]Dept. of Urology, Osaka International Cancer Institute, Osaka, Japan; [12]Calvary Mater Newcastle, Waratah, Australia; [13]Cetus Medicina Oncológica, Betim, Brazil; [14]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [15]CU-PH Medical Oncology Unit, CHU Besançon, Besançon, France; [16]AstraZeneca, Cambridge, UK; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]AstraZeneca, Gaithersburg, MD, USA; [19]Institut Gustave Roussy, University of Paris Saclay, Villejuif, France

Objective

- The most common adverse events (AEs) in the PROfound trial have been reported previously. Here we describe further details on the tolerability assessments at the primary data cut-off (4 June 2019).

Conclusions

- In PROfound, the most common AEs in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations who were treated with olaparib were anaemia, nausea, decreased appetite, and fatigue/asthenia (experienced by >30% patients).
- These AEs typically occurred within the first 3 months of treatment and were generally manageable through supportive care, dose interruptions and dose reductions.
- Safety data from PROfound should be interpreted in the context of the longer duration of treatment in the olaparib arm compared with the control arm.
- Tolerability in patients with mCRPC was generally consistent with the tolerability profiles seen with olaparib monotherapy in other tumour types.

Scan to obtain the poster, narrated poster and supplementary material

https://www.astrazenecaoncology.com/zym5m2?utm_source=QR&utm_medium=Poster&utm_campaign=ESMO&utm_content=Roubaud-et-al.-PROfound-tolerability-ESMO-2020

Poster presented at the 2020 Annual Meeting of ESMO, held virtually on 19–21 September 2020.

Corresponding author email address: G.Roubaud@bordeaux.unicancer.fr.

Dr. Roubaud declares receiving advisory board fees from Astellas Pharma, AstraZeneca, Ipsen, Janssen, Sanofi; travel support from Astellas Pharma, Ipsen, Janssen and Sanofi; and research support from Bayer.

Introduction

- 1st positive Phase III open-label study of a PARP inhibitor in men with mCRPC.
- Olaparib significantly prolonged radiographic progression-free survival versus enzalutamide or abiraterone (control) in patients with HRR gene alterations whose disease had progressed on prior enzalutamide or abiraterone.[1]
- Olaparib activity was seen before and after chemotherapy.
- Safety in the overall population of patients was a key secondary endpoint.

Methods

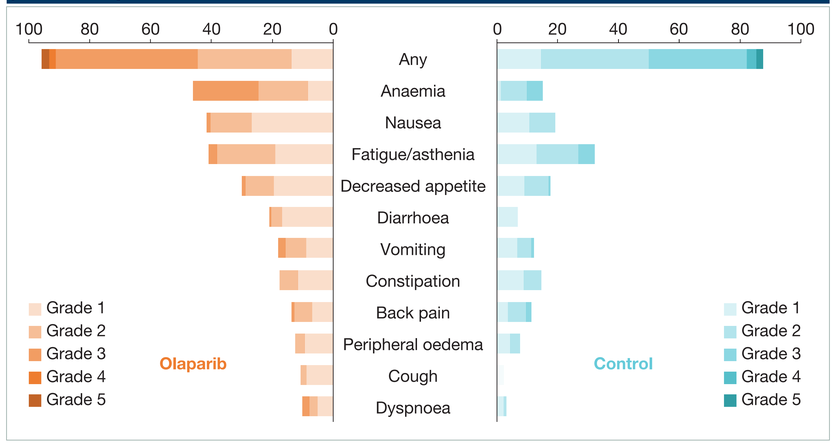
- Patients had alterations in at least one of 15* prespecified genes and were randomized (2:1) to receive olaparib or control until disease progression or unacceptable toxicity. Patients in the control arm who progressed had the option to cross over to olaparib.
- Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments.
- More information on methods, including management of AEs, is provided in the **Supplement** that can be accessed through the **QR code** at the bottom left of the poster.

*BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L.

Results and interpretation

Of the **387** patients randomized, **256** received **olaparib** and **130** received **control** treatment and were included in the safety analyses.

AEs that were experienced by ≥10% of patients in the olaparib and/or control arms were predominantly Grades 1 or 2



The most common AEs were managed with supportive treatment, dose interruptions and dose reductions, limiting the need for patients to discontinue

	Anaemia*		Nausea		Decreased appetite		Fatigue/asthenia	
	Olaparib	Control	Olaparib	Control	Olaparib	Control	Olaparib	Control
AE (all grades), n	119	20	106	25	77	23	105	42
Supportive therapy	61%	70%	57%	60%	29%	26%	5%	12%
Dose interruption	25%	1.5%	2%	2%	1%	1.5%	3%	3%
Dose reduction	16%	0%	2%	1%	0%	1%	2%	2%
Discontinued	7%	1%	1%	0%	<1%	0%	2%	2%
Resolved	37%	40%	70%	56%	42%	39%	33%	36%

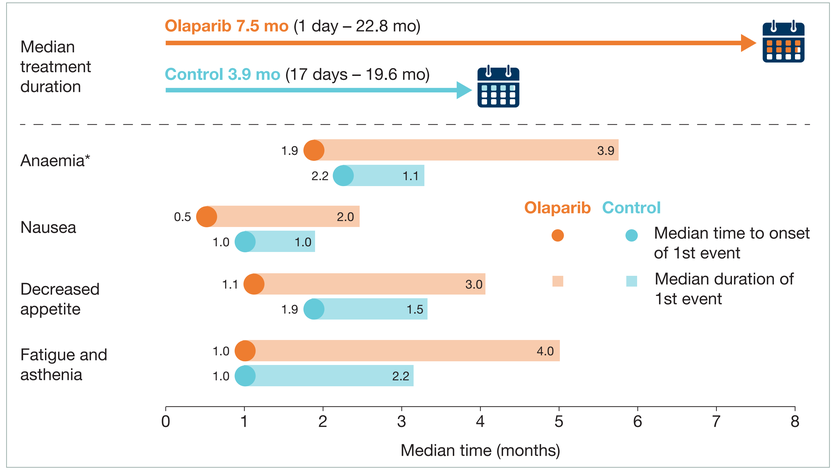
*Grouped term. Patients with multiple AEs leading to treatment reduction were counted once for each preferred term. More details on supportive therapy can be found in the supplement.

In the **olaparib** arm, **52%** of patients with anaemia had ≥1 blood transfusion and **11%** received erythropoiesis stimulating agent

There does not appear to be an increased risk of anaemia with olaparib in patients with more bone metastases or who have received prior taxane

Bone metastases	**<10** (n=163)	**≥10** (n=93)
Any grade anaemia	48%	44%
Grade ≥3 anaemia	21%	22%
Prior taxane	**Yes** (n=170)	**No** (n=86)
Any grade anaemia	44%	51%
Grade ≥3 anaemia	21%	23%

The median times to first onset of the most common AEs (all grades) were all within the first 3 months and were typically resolved within the first 6 months of treatment



*Grouped term (a full definition can be found in the **Supplement**). Duration is defined as time from onset to resolution.

The longer duration of treatment in the olaparib arm, and the lack of imbalance in venous thrombosis events, makes it difficult to interpret the small difference in pulmonary embolism (PE) between the study arms

Venous thromboembolism occurred in **7%** of **olaparib** patients and **3%** of **control** patients

PE occurred in **11 (4%) olaparib** patients and **one (1%) control** patient

PE in olaparib patients

	J	F	M	A	M	J	J	A	S	O	N
0.2 to 11.1 months to onset	●	●	●	●	●	●	●	●	●	●	●
Diagnosed by routine chest scan, n	●	●	●	●	●	●	●	●	●	●	●
CTCAE grade, n	1	●	●	2	●	3	●	●	●	●	4
Dose interruption, n	●	●	●	○	○	○	○	○	○	○	○
Discontinued, n	●	○	○	○	○	○	○	○	○	○	○

PE in control patient

Onset at 1.8 months of treatment, was Grade ≥3 and led to dose interruption

Advanced prostate cancer carries a significant risk of venous thromboembolic events, a risk that androgen deprivation therapy also contributes to.

The evidence from PROfound is insufficient to confirm or refute a causal association between PE and olaparib, and no imblance has been observed in olaparib trials in ovarian, breast and pancreatic cancer.

Fatal AEs (Related to study treatment)

- **Olaparib, 4%**: Lung infection and neutropaenia (n=1)
- **Control, 4%**: Pleural effusion (n=1)

Acknowledgements

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 Laura Smart, MChem, 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.

Supplementary materials to:

Tolerability of olaparib in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: PROfound

Guilhem Roubaud, Mustafa Özgüroğlu, Nicolas Penel, Nobuaki Matsubara, Niven Mehra, Michael Kolinsky, Giuseppe Procopio, Susan Feyerabend, Jae Young Joung, Gwenaelle Gravis, Kazuo Nishimura, Craig Gedye, Charles Padua, Neal Shore, Antoine Thiery-Vuillemin, Chris Gresty, Neil Brickel, Joe Burgents, Allison Allen, Karim Fizazi

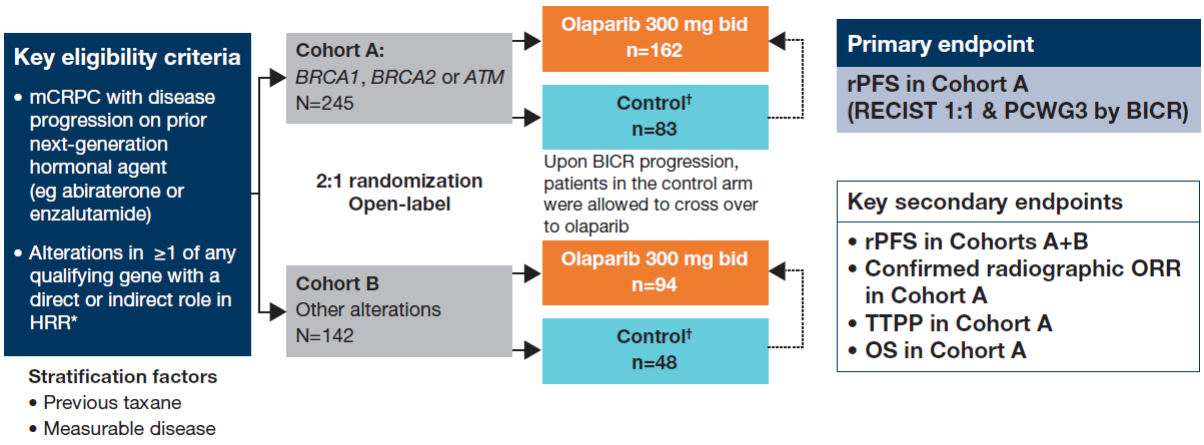
Presented at the 2020 Annual Meeting of the European Society for Medical Oncology (ESMO), held virtually on 19–21 September 2020. Abstract #3937. Poster number #624P.

This supplementary material has been provided by the study authors to give additional information about the tolerability of olaparib in the PROfound trial at the primary data cut-off (4 June 2019).

Supplementary methods

- Patients with metastatic castration-resistant prostate cancer and disease progression on a prior next-generation hormonal agent (eg enzalutamide or abiraterone) were randomized (2:1) to olaparib tablets (300 mg twice daily [bid]) or physician's choice (control) of enzalutamide (160 mg/day) or abiraterone (1000 mg/day plus prednisone at 5 mg bid) (Figure S1).
- Patients had alterations in *BRCA1*, *BRCA2* and/or *ATM* (Cohort A), or ≥1 of 12 other prespecified genes with a direct or indirect role in homologous recombination repair (HRR): *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and/or *RAD54L* (Cohort B).
- The primary endpoint of radiographic progression-free survival was assessed by blinded independent central review with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[1] and Prostate Cancer Working Group 3 criteria.[2]

Figure S1. PROfound study design



*An investigational Clinical Trial Assay, based on the FoundationOne CDx next-generation sequencing test, and developed in partnership with Foundation Medicine Inc., was used to prospectively select patients harbouring alterations in the following genes in their tumour tissue: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L*.

†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]).

BICR, blinded independent central review; bid, twice daily; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3 criteria; qd, each day; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; rPFS, radiographic progression-free survival; TTPP, time to pain progression.

Management of adverse events (AEs) related to olaparib

- AEs could be managed by dose interruptions and dose reductions.
- Dose interruptions were for a maximum of 4 weeks on each occasion.
  - If the interruption was longer than 4 weeks, then the study team was informed.
- Dose was reduced to 250 mg bid and then to 200 mg bid if further dose reduction was allowed.
  - If the reduced dose of 200 mg bid was not tolerable, no further dose reduction was allowed, and study treatment was discontinued.

Management of anaemia

- If a patient had a first instance of Common Terminology Criteria for Adverse Event (CTCAE) Grade 2 anaemia (haemoglobin [Hb] level <10 but ≥8 g/dL), they could continue olaparib with or without supportive treatment, or with a dose interruption for a maximum of 4 weeks.

- If a patient had a repeat incidence of CTCAE Grade 2 anaemia (Hb level <10 but ≥9 g/dL), they could continue with supportive treatment or with a dose interruption for a maximum of 4 weeks.
  - Upon recovery, a dose reduction could be considered.
- If a patient had a repeat incidence of CTCAE Grade 2 anaemia (Hb level <9 but ≥8 g/dL), the dose was interrupted for a maximum of 4 weeks until Hb level ≥9 g/dL.
  - Upon recovery, a dose reduction could be considered.
- If a patient had CTCAE Grade 3 anaemia (Hb level <8 g/dL), they were given supportive treatment, monitored, and causality was investigated. Olaparib dose was interrupted for a maximum of 4 weeks until Hb level improved to ≥9 g/dL, and then the dose was reduced following recovery.

Management of nausea and vomiting

- Patients were given anti-emetic treatment at the first onset of nausea or vomiting and as required afterwards, in accordance with local treatment practice.
- Alternatively, patients could also take olaparib tablets with a light meal or snack, such as two pieces of toast or two biscuits.

Grouped term

Anaemia is reported as a ‘grouped term’ and included: anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, and red blood cell count decreased.

Supplementary references

1. Eisenhauer EA *et al. Eur J Cancer* 2009;45:228–47.
2. Scher HI *et al. J Clin Oncol* 2016;34:1402–18.