Talazoparib (Talzenna®) in combination with enzalutamide for the treatment of metastatic castration-resistant prostate cancer (mCRPC)

General information

Drug description [1]

Talazoparib (Talzenna®) is a potent PARP inhibitor and traps PARP on single-strand DNA breaks, preventing DNA repair.

Indication [2]

Talazoparib (Talzenna®) is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Incidence

In Austria, in 2020, a total of 6126 men were newly diagnosed with prostate cancer. The age-standardised[1] incidence rate was 149.9/100,000 men [3].
The median age at disease onset is 60 years; approximately 30% of men have metastatic disease at the time of diagnosis [4].

Current treatment[2]

For the treatment of mCRPC, the ESMO recommends:

- External beam radiotherapy plus ADT-abiraterone-prednisone is recommended for men with very high-risk M0 prostate cancer (defined by N1 disease or at least two risk factors among T3-T4, PSA >40 ng/ml, Gleason score 8-10) (I, B).
- Men receiving radical radiotherapy for very high-risk disease should have long-course ADT (24-36 months) plus abiraterone-prednisone (24 months) (I, B).
- ADT-docetaxel-abiraterone-prednisone is recommended as first-line treatment for fit men with de novo metastatic hormone-sensitive prostate cancer (mHSPC), especially in those with multiple bone metastases (>3) or visceral metastases (I, B; ESMO-MCBS v1.1 score: 4).
- ADT-docetaxel-darolutamide is also recommended as first-line treatment of mHSPC, including patients with de novo mHSPC and those who have progressed to metastatic disease (I, B; ESMO-MCBS v1.1 score: 4).
- The other treatment option for men with mHSPC is a novel hormone agent (NHA) plus ADT (ADT-abiraterone-prednisone; ESMO-MCBS v1.1 score: 4), ADT-apalutamide (ESMO-MCBS v1.1 score: 4) or ADT-enzalutamide (ESMO-MCBS v1.1 score: 4), which is recommended for first-line treatment (I, A). Both strategies (NHA-ADT vs. triplet therapy) have not been directly compared.
- In men with mHSPC, ADT alone should be used only in vulnerable men who cannot tolerate treatment intensification (III, C).
- Olaparib should be considered after novel androgen receptor axis inhibitors (with or without prior taxane treatment) for patients with mCRPC and BRCA1/2 alterations (I, B; ESMO-MCBS v1.1 score: 3).
- In patients with mCRPC who have received a novel androgen receptor axis inhibitor (abiraterone, apalutamide, darolutamide or enzalutamide) and docetaxel, the following treatments should be used in patients who are considered fit enough to receive these treatments:
  - 177Lu-PSMA-617 in men with cancer expressing PSMA on positron emission tomography-PSMA and without PSMA non-expressing lesions (I, A; ESMO-MCBS v1.1 score: 4).
  - Cabazitaxel (I, A; ESMO-MCBS v1.1 score: 3).

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On 9 November 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Talzenna®. The CHMP adopted a new indication as follows: ❖ Talzenna® is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.	**Approval status for this indication**: not approved On 20 June 2023, the FDA approved talazoparib (Talzenna®) with enzalutamide for homologous recombination repair (HRR) gene-mutated mCRPC. **Other indications**: Talzenna® is indicated:

[1] European Standard Population 2013.
[2] Currently, there is no Onkopedia Guideline available for prostate cancer.

Other indications:

- ❖ Talzenna® is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy.

✓ **Medicine under additional monitoring**

- ❖ As a single agent, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for Talzenna®.

Manufacturer

Talzenna® is manufactured by Pfizer®.

Posology [7]

- ❖ Talzenna® in combination with enzalutamide (prostate cancer)
  - The recommended dose is 0.5 mg talazoparib in combination with 160 mg enzalutamide once daily.
  - Patients should be treated until disease progression or unacceptable toxicity occurs.
- ❖ Medical castration with luteinising hormone releasing hormone analogue should be continued during treatment in patients not surgically castrated. Please refer to the full enzalutamide product information for the recommended posology.
- ❖ Talzenna® when used in combination with enzalutamide (prostate cancer)
  - The effect of co-administration of P-gp inhibitors on talazoparib exposure when talazoparib is given in combination with enzalutamide has not been studied. Therefore, concomitant use of P-gp inhibitors during treatment with talazoparib should be avoided.

Special warnings and precautions for use [7]

- ❖ Myelosuppression
  - Myelosuppression consisting of anaemia, leukopenia/neutropenia, and/or thrombocytopenia, have been reported in patients treated with talazoparib. Talazoparib should not be started until patients have recovered from haematological toxicity caused by previous therapy (≤ Grade 1).
  - Precautions should be taken to routinely monitor haematology parameters and signs and symptoms associated with anaemia, leukopenia/neutropenia, and/or thrombocytopenia in patients receiving talazoparib. If such events occur, dose modifications (reduction or interruption) are recommended. Supportive care with or without blood and/or platelet transfusions and/or administration of colony stimulating factors may be used as appropriate.
- ❖ Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)
  - MDS/AML have been reported in patients who received PARP inhibitors, including talazoparib. Overall, MDS/AML has been reported in < 1% of solid tumour patients treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy. Complete blood counts should be obtained at baseline and monitored monthly for signs of haematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.
- ❖ Venous thromboembolic events
  - In patients with mCRPC a higher incidence of venous thromboembolic events was observed with Talzenna® in combination with enzalutamide compared with enzalutamide alone. Patients should be monitored for clinical signs and symptoms of deep venous thrombosis and pulmonary embolism and treated as medically appropriate.
- ❖ Contraception in women of childbearing potential
  - Talazoparib was clastogenic in an in vitro chromosomal aberration assay in human peripheral blood lymphocytes and in an in vivo bone marrow micronucleus assay in rats but not mutagenic in Ames assay and may cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus. Women of childbearing potential should not become pregnant while receiving Talzenna® and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. A highly effective method of contraception is required for female patients during treatment with Talzenna®, and for at least 7 months after completing therapy.

- Since the use of hormonal contraception is not recommended in patients with breast cancer, two non-hormonal and complementary contraception methods should be used.
- Male patients with female partners of reproductive potential or pregnant partners should be advised to use effective contraception (even after vasectomy), during treatment with Talzenna® and for at least4 months after the final dose.

Costs

30 Talzenna® hard capsules 0.25 mg = € 1,506.09 (ex-factory price) [8]

Study characteristics [1, 9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
TALAPRO-2 NCT03395197	805 (1:1)	talazoparib 0.5 mg + enzalutamide 160 mg, administered orally once daily	placebo + enzalutamide 160 mg, administered orally once daily	rPFS by BICR in the ITT population	24.9 months (IQR 21.9–30.2) vs. 24.6 months (IQR 14.4–30.2)	**ongoing**[3], randomised, double-blind, phase 3 trial	-	Pfizer	TALAPRO-2 trial [1]

Inclusion criteria[4]

- ≥18 years of age (≥20 years in Japan).
- Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features.
- Asymptomatic or mildly symptomatic mCRPC.
- Assessment of HRR mutation status by prospective analysis of blood, or tissue, or historical analysis of most recent tumour tissue per FoundationOne® testing.
- Biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the oesophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.
- Unless prohibited by local regulations or ethics committee decision, consent to a saliva sample collection for retrospective sequencing of the same HRR genes tested on tumour tissue and blood (liquid biopsy), or a subset thereof, and to serve as a germline control in identifying tumour mutations.
- Surgically or medically castrated, with serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening. Ongoing ADT with a gonadotropin-releasing hormone agonist or antagonist for patients who have not undergone bilateral orchiectomy must be initiated at

Exclusion criteria

- Any prior systemic cancer treatment initiated in the non-metastatic CRPC or mCRPC disease state.
- Patients whose only evidence of metastasis is adenopathy below the aortic bifurcation.
- Prior treatment with second-generation androgen receptor inhibitors (enzalutamide, apalutamide, and darolutamide), a PARP inhibitor, cyclophosphamide, or mitoxantrone for prostate cancer.
- Prior treatment with platinum-based chemotherapy within 6 months (from the last dose) prior to randomisation, or any history of disease progression on platinum-based therapy within 6 months (from the last dose). Prior docetaxel for mCSPC allowed if more than 4 weeks elapsed from the last dose of docetaxel.
- Treatment with cytotoxic chemotherapy which includes but is not limited to docetaxel, biologic therapy including sipuleucel-T, or radionuclide therapy received in the castration-sensitive prostate cancer is NOT exclusionary if discontinued in the 28 days prior to randomisation. Prior treatment with abiraterone in the castration-sensitive settings not exclusionary if discontinued prior to randomisation. Hormonal therapy not exclusionary if discontinued prior to randomisation. Prednisone >10 mg/day (or equivalents) is exclusionary.
- Treatment with any investigational agent within 4 weeks before randomisation.

Patient characteristics at baseline (I vs. C, n=402 vs. n=403)

- Median age: 71 years (IQR 66–76) vs. 71 years (IQR, 65–76)
- Race
  - White: 60% vs. 63%
  - Black or African American: 3% vs. 1%
  - Asian: 32% vs. 30%
  - Multiracial: 0 vs. <1%
  - Other: <1% vs. <1%
  - Not reported: 5% vs. 5%
- Renal impairment
  - None or mild: 86% vs. 86%
  - Moderate: 10% vs. 10%
- Baseline serum PSA, µg/L: 18.2 (6.9–59.4) vs. 16.2 (6.4–53.4)
- Baseline circulating tumour cell count, cells per 7.5 mL of blood: 1 (0–7) vs. 1 (0–6)
- Gleason score
  - <8: 29% vs. 28%
  - ≥8: 70% vs. 70%
- Disease site

[3] TALAPRO-2 trial is currently ongoing; the estimated study completion date is 12/2025.
[4] For detailed in- and exclusion criteria, please see Supplementary Appendix.

least 4 weeks before randomisation and must continue throughout the study. ❖ Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan. Scans obtained as part of standard of care in the 6 weeks (42 days) prior to randomisation can be used if they meet study requirements. ❖ Progressive disease at study entry in the setting of medical or surgical castration as defined by 1 or more of the following 3 criteria: • PSA progression defined by rising PSA of at least 2 consecutive rises in most recent PSA to be documented over a reference value (measure 1) taken at least 7 days apart within the last 12 months. If the third PSA measure is not greater than the second measure, a fourth PSA measure is required to be taken and be greater than the second measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomisation. The third (or the fourth) PSA value, obtained before randomisation must be ≥1 µg/L if qualifying only by PSA progression. • Soft tissue disease progression as defined by RECIST 1.1. • Bone disease progression defined by PCWG3 with 2 or more new metastatic bone lesions on a whole-body radionuclide bone scan. ❖ Ongoing bisphosphonate or denosumab use prior to randomisation is allowed but not mandatory. ❖ ECOG PS ≤1. ❖ Life expectancy ≥12 months as assessed by the investigator. ❖ Able to swallow the study treatment and have no known intolerance to study treatments or excipients. ❖ Sexually active participants that in the opinion of the investigator are capable of ejaculating, must agree to use a condom when having sex with a partner from the time of the first dose of study treatment through 4	❖ Prior treatment with opioids for pain related to either primary prostate cancer or metastasis within 28 days prior to randomisation. ❖ Current use of potent P-gp inhibitors within 7 days prior to randomisation. Potent P-gp inhibitors, and other medications exclusionary because of interaction with either talazoparib or enzalutamide. ❖ Major surgery within 2 weeks before randomisation, or palliative localised radiation therapy within 3 weeks before randomisation. ❖ Clinically significant cardiovascular disease, including any of the following: • Myocardial infarction or symptomatic cardiac ischaemia within 6 months before randomisation; congestive heart failure NYHA class III or IV; history of clinically significant ventricular arrhythmias within 1 year before screening; history of Mobitz II second degree or third-degree heart block unless a permanent pacemaker is in place; hypotension as indicated by systolic blood pressure <86 mm Hg at screening; bradycardia as indicated by a heart rate of <45 beats per minute on the screening ECG; uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening. ❖ Significant renal dysfunction as defined by eGFR <30 mL/min/1.73 m^2 by the MDRD equation. ❖ Significant hepatic dysfunction as defined by any of the following laboratory abnormalities on screening labs: • Total serum bilirubin >1.5 times the ULN • AST or ALT >2.5 times ULN • Albumin <2.8 g/dL. ❖ ANC <1500/µL, platelets <100,000/µL, or haemoglobin <9 g/dL. ❖ Known or suspected brain metastasis or active leptomeningeal disease. ❖ Symptomatic or impending spinal cord compression or cauda equina syndrome. ❖ Any history of myelodysplastic syndrome, acute myeloid leukaemia, or prior malignancy[5]. ❖ Any clinically significant gastrointestinal disorder affecting absorption. ❖ Fertile male participants who are unwilling or unable to use a condom and highly effective methods of contraception as appropriate for the duration of the study and for 4 months after the last dose of investigational product. ❖ Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised	• Bone (including with soft tissue component): 87% vs. 85% • Lymph node: 37% vs. 41% • Visceral (lung): 11% vs. 15% • Visceral (liver): 3% vs. 4% • Other soft tissue: 9% vs. 8% ❖ ECOG performance status • 0: 64% vs. 67% • 1: 36% vs. 33% ❖ Previous taxane-based chemotherapy: 21% vs. 23% ❖ Previous treatment with novel hormonal therapy: 6% vs. 7% • Abiraterone: 5% vs. 6% • Orteronel: <1% vs. <1% ❖ HRR gene alteration status by randomisation stratification: • Deficient: 21% vs. 21% • Non-deficient or unknown: 79% vs. 79% ❖ HRR gene alteration status by prospective tumour tissue testing: • Deficient: 21% vs. 20% • Non-deficient: 51% vs. 54% • Unknown: 27% vs. 25% ❖ BRCA1/2 alteration: 7% vs. 8%

[5] Except for any of the following: Carcinoma in situ or non-melanoma skin cancer; any prior malignancies ≥3 years before randomisation with no subsequent evidence of recurrence or progression regardless of the stage; Stage 0 or Stage 1 cancer <3 years before randomisation that has a remote probability of recurrence or progression in the opinion of the investigator.

months after last dose of study treatment. Must also agree for female partner of childbearing potential to use an additional highly effective form of contraception from the time of the first dose of study treatment through 4 months after last dose of study treatment when having sex with a non-pregnant female partner of childbearing potential. ❖ Must agree not to donate sperm from the first dose of study treatment to 4 months after the last dose of study treatment. ❖ Evidence of a personally signed and dated informed consent document. ❖ Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.	by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study. ❖ Other acute or chronic medical or psychiatric condition including recent or active suicidal ideation or behaviour or laboratory abnormality that interferes with ability to participate in the study, may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the patient inappropriate for entry into this study. ❖ History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of randomisation.	

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Data cutoff: 16 August 2022:</u> **HR for disease progression or death by BICR**: 0.63 (95% CI, 0.51–0.78; p<0.0001) **Median rPFS**: NR (95% CI, 27.5 months–NR) vs. 21.9 months (95% CI, 16.6–25.1) **HR for rPFS in subgroup analysis by HRR gene alteration status**: 0.46 (95% CI, 0.30–0.70; p=0.0003) in patients with a status of deficient and 0.70 (95% CI, 0.54–0.89; p=0.0039) in patients with a status of non-deficient or unknown in favour of I vs. C **HR for disease progression or death patients with HRR gene alteration status of non-deficient by prospective tumour tissue testing**: 0.66 (96% CI, 0.49–0.91); p=0.0092 **HR for rPFS or death in patients in the talazoparib group whose tumours had BRCA gene alterations**: 0.23 (95% CI, 0.10–0.53; p=0.0002) **HR for rPFS or death in patients in the talazoparib group with non-BRCA HRR gene alterations**: 0.66 (95% CI, 0.39–1.12); p=0.12 **HR for rPFS among patients (n=219) who had received previous treatment with docetaxel or a novel hormonal therapy for castration-sensitive disease:** 0.56 (95% CI, 0.38–0.83); p=0.0038 **HR for rPFS among patients who had received docetaxel (n=179**): 0.51 (95% CI, 0.32–0.81); p=0.0034 **HR for rPFS among patients who had received a novel hormonal agent (n=50):** 0.57 (95% CI, 0.28–1.16); p=0.12 **OS data**: immature; 31% vs. 32% of patients had died at data cutoff; HR for death: 0.89 (95% CI, 0.69–1.14); p=0.35 **Confirmed ORR in patients with measurable disease at baseline by BICR:** 62% (95% CI, 52.4–70.4) vs. 44% (95% CI, 35.3–52.8) CR: 38% vs. 18% **Median time to PSA progression**: 26.7 months vs. 17.5 months; HR 0.72 (95% CI, 0.58–0.89); p=0.0020 **Median time to initiation of cytotoxic chemotherapy**: NR vs. NR; HR 0.49 (95% CI, 0.38–0.65); p<0.0001 **Median time to progression or death on first subsequent antineoplastic therapy**: 36.4 months vs. 35.3 months; HR 0.77 (95%CI, 0.61–0.98; p=0.036)	**Any AE grade ≥3**: 75% vs. 45% **TRAE grade ≥3**: 59% vs. 18% **Serious AE grade ≥3**: 36% vs. 23% **Serious and TRAE grade ≥3**: 17% vs. 3% **Drug discontinuation due to AEs (talazoparib or placebo):** 19% v. 12% **Discontinuation rates of enzalutamide due to AEs**: 11% vs. 11% **Venous embolic and thrombotic events**: 4% vs. 1% **Treatment-related deaths:** 0 vs. <1%

Patient-reported outcomes (abstract data) [11]

- ❖ PROs were assessed at day 1 (baseline) and at scheduled visits until radiographic progression (every 4 weeks until week 53, and then every 8 weeks) using the EORTC QLQ-C30 and its prostate cancer module, QLQ-PR25.
- ❖ Prespecified PRO analyses included overall mean change from baseline (per longitudinal repeated measures mixed-effects model) and time to definitive clinically meaningful (≥10-point change) deterioration (TTD).

- Between-arm comparisons of TTD were made using a stratified log-rank test and a Cox proportional hazards model.
- Of the 805 men randomized and treated, 793 had a baseline score followed by at least 1 post-baseline score (n=395 vs. n=398).
- The treatment effect on GHS/QoL significantly favoured placebo + enzalutamide, the predefined threshold of clinical meaningfulness was not met; no significant differences between the arms were observed in any functioning scales.
- A significantly longer TTD in GHS/QoL was observed for talazoparib + enzalutamide; HR=0.780 (95% CI, 0.62-0.99), p=0.038; median: 30.8 months vs. 25.0 months.
- A numerical greater delay in TTD in urinary symptoms was longer for talazoparib + enzalutamide; HR=0.759 (95% CI, 0.543-1.061), p=0.105; median not reached vs. 35.9 months.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	< 6 months	rPFS: +12.9 months	0.63 (0.57-0.78)	HR≤0.65 AND gain ≥3 months	3	+14% serious TRAEs	maintained	-1[6]	2
Adapted	nc	2B	< 6 months	rPFS: +12.9 months	0.63 (0.57-0.78)	HR≤0.65 AND gain ≥3 months	3	+14% serious TRAEs	maintained	-1[7]	2

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes[8] low risk	unclear[9] unclear risk	yes[10] high risk	unclear

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT03395197/ TALAPRO-2	Please see above.	07/2024

Available assessments

- According to NICE, the appraisal "Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer" was suspended in August 2023 [15].
- In September 2021, NIHR published a Health Technology Briefing "Talazoparib in addition to enzalutamide for metastatic castration-resistant prostate cancer" [16].
- No assessments were identified via CADTH, ICER and G-BA.

Other aspects and conclusions

- In November 2023, the **CHMP adopted a new indication for Talzenna®,** indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. This indication is **not approved** by **the FDA**. However, in June 2023, the FDA approved Talzenna® with enzalutamide for HRR gene-mutated mCRPC.
- **TALAPRO-2** (NCT03395197) is an **ongoing, randomised, double-blind, phase 3 trial** of talazoparib plus enzalutamide vs. placebo plus enzalutamide as first-line therapy in men with asymptomatic or mildly symptomatic mCRPC receiving ongoing ADT. Eligible patients were adult men who had asymptomatic or mildly symptomatic mCRPC, had an ECOG PS of 0 or 1, had progressive disease at study entry, had adequate bone marrow function and had not received previous life-prolonging systemic therapy for CRPC or mCRPC. Patients whose only evidence of metastasis is adenopathy below the aortic bifurcation, who had prior treatment with second-generation androgen receptor inhibitors or prior treatment with platinum-based chemotherapy within 6 months prior to randomisation, or any history of disease progression on platinum-based therapy within 6 months, were excluded.
- The **primary endpoint was rPFS by BICR in the ITT** population. At the planned primary analysis, **median rPFS was not reached** (95% CI, 27.5 months–NR) vs. 21.9 months (95% CI, 16.6–25.1); HR 0.63 (95% CI, 0.51–0.78); p<0.0001.

[6] Toxicity adjustment (downgrade 1 level).
[7] Toxicity adjustment (downgrade 1 level).
[8] Of note, the sponsor, patients and investigators were blinded to talazoparib or matching placebo; enzalutamide was open-label.
[9] TALAPRO-2 trial is ongoing.
[10] The sponsor was involved in the trial design (together with the academic steering committee), data analysis, and data interpretation, and funded medical writing support. Astellas Pharma provided enzalutamide. All authors, including those employed by the sponsor, contributed to data interpretation as well as development, writing, and approval of the manuscript.

- **PROs were assessed** in TALAPRO-2 trial, showing that the treatment effect on GHS/QoL significantly favoured placebo + enzalutamide, the predefined threshold of clinical meaningfulness was not met and no significant differences between the arms were observed in any functioning scales. For talazoparib + enzalutamide, a significantly longer TTD in GHS/QoL and a numerical greater delay in TTD in urinary symptoms was observed.
- Both the **original and adapted ESMO-MCBS** were applied, resulting in an **adjusted magnitude of clinical benefit grade 2 in both scales**.
- Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, it **is increased** by the involvement of the sponsor in trial design, data analysis, and data interpretation.
- Beside the TALAPRO-2 trial, **no further ongoing phase 3 trials** were identified.
- **Final analysis** of TALAPRO-2 trial data and **long-term data** for the assessed indication are required to determine the role of talazoparib in patients with mCRCP.

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Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AML=acute myeloid leukaemia, AST=aspartate aminotransferase, BICR=blinded independent central review, BRCA=breast cancer gene, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CRPC=castration-resistant prostate cancer, CT=computed tomography, DNA=desoxyribonucleic acid, ECG=electrocardiogram ECOG, PS=Eastern Cooperative Oncology Group performance status, eGFR=estimated glomerular filtration rate, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health status, HR=hazard ratio, HRR=homologous recombination repair, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IQR=interquartile range, ITT=intention-to-treat,, mCRPC=metastatic castration-resistant prostate cancer, mCSPC=metastatic castration-sensitive prostate cancer, MDRD=Modification of Diet in Renal Disease, MDS=myelodysplastic syndrome, MG=median gain, mHSPC=metastatic hormone-sensitive prostate cancer, MRI=magnetic resonance imaging, n=number of patients, NHA=novel hormone agent, NICE=National Institute for Health Care Excellence, NR=not reached, NYHA=New York Heart Association, ORR=objective response rate, OS=overall survival, P-gp=P-glycoprotein, PARP=poly(ADP-ribose) polymerase, PCWG3=Prostate Cancer Clinical Trials Working Group 3, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PSA=prostate-specific antigen, PSMA=prostate-specific membrane antigen, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, rPFS=radiographic progression-free survival, SAE=serious adverse event, ST=standard treatment, TTD=time to deterioration, ULN=upper limit of normal

References:

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