IQWiG Reports – Commission No. A20-115

Olaparib (pancreatic cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Olaparib (Pankraskarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Olaparib (pancreatic cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
3 December 2020

Internal Commission No.
A20-115

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Christoph F. Dietrich, Hirslanden Clinics, Bern, Switzerland

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment

- Selver Altin
- Katharina Hirsch
- Florina Kerekes
- Stefan Kobza
- Inga Overesch
- Ulrike Seay
- Corinna ten Thoren
- Volker Vervölgyi

Keywords: Olaparib, Pancreatic Neoplasms, Adenocarcinoma, Benefit Assessment, NCT02184195

Table of contents

List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
gBRCA	germline breast cancer associated gene
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-PAN26	Quality of Life Questionnaire and Pancreatic Cancer Module
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
RKI	Robert Koch Institute
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of olaparib as maintenance treatment in comparison with watchful waiting as appropriate comparator therapy (ACT) in adult patients with germline breast cancer associated gene 1/2 (gBRCA1/2)-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after at least 16 weeks of platinum-containing treatment as part of first-line chemotherapy.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of olaparib

Subindication	ACT[a]
Maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	Watchful waiting[b]

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed that the first-line chemotherapy has been completed or that a continuation of the first-line chemotherapy is not indicated at the time point of the therapeutic decision for olaparib.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; gBRCA: germline mutation of the breast cancer associated gene

The company named watchful waiting as ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Study pool

The POLO study was included for the assessment of the added benefit.

Study characteristics

The POLO study was a randomized, double-blind, multicentre study on the comparison of olaparib with placebo. The study included adult patients with metastatic adenocarcinoma of the pancreas and a deleterious or presumably deleterious gBRCA1 or/and gBRCA2-mutation who had previously received first-line platinum-containing chemotherapy for at least 16 weeks (without interruption) and who, in the opinion of the investigator, had not progressed. Patients who had discontinued the platinum component due to toxicity after at least 16 weeks of platinum-containing treatment could also be included in the POLO study, provided that treatment with all other drugs comprised in the respective treatment regimen was continued and there was no indication of progression within 4 weeks after the last dose of the first-line chemotherapy. The general condition of the patients had to correspond to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The POLO study included 154 patients who were assigned in a 3:2 ratio either to treatment with olaparib (92 patients) or placebo (62 patients).

In the POLO study, treatment with olaparib was in compliance with the Summary of Product Characteristics (SPC). Moreover, patients in both study arms received any medication deemed necessary for their well-being that did not interact with the study intervention. Study treatment was continued until radiological progression according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1, unacceptable toxicity or death. Treatment with the study medication could be continued after radiological progression if the investigator considered the patients to benefit from this treatment.

Primary outcome of the POLO study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and AEs.

The POLO study is still ongoing.

Risk of bias

The risk of bias across outcomes was rated as low. The outcome-specific risk of bias for all outcomes except for "overall survival" and "discontinuation due to AEs" was rated as high. The certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Symptoms (recorded with the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-C30])

Nausea and vomiting

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome "nausea and vomiting". This resulted in a hint of lesser benefit of olaparib in comparison with watchful waiting.

Fatigue, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea

No statistically significant difference between the treatment groups was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "insomnia", "loss of appetite", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Symptoms (recorded with the EORTC Quality of Life Questionnaire and Pancreatic Cancer Module [QLQ-PAN26])

Pancreatic pain, digestive restrictions, altered bowel habits, hepatic symptoms, bloating, indigestion, flatulence, weight loss, muscle weakness in arms and legs, impairment due to side effects, dry mouth, altered sense of taste

There was no statistically significant difference between the treatment groups for each of the outcomes "pancreatic pain", "digestive restrictions", "altered bowel habits", "hepatic symptoms", "bloating", "indigestion", "flatulence", "weight loss", "muscle weakness in arms and legs", "impairment due to side effects", "dry mouth" and "altered sense of taste". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Health status (recorded with the visual analogue scale [VAS] of the European Quality of Life Questionnaire 5 Dimensions [EQ-5D])

There was no statistically significant difference between the treatment groups for the outcome "health status measured using the EQ-5D VAS". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status, role functioning, cognitive functioning, emotional functioning, social functioning

No statistically significant difference between the treatment groups was shown for the outcomes "global health status", "role functioning", "cognitive functioning", "emotional functioning", and "social functioning". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Physical functioning

There was no statistically significant difference between the treatment groups for the outcome "physical functioning". There was an effect modification by the characteristic "age", however. This resulted in a hint of lesser benefit of olaparib in comparison with watchful waiting for patients ≥ 65 years. For patients < 65 years of age, there was no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

EORTC QLQ-PAN26

Satisfaction with medical care, sexuality, body image, worries about the future, restriction in the planning of activities

For the outcomes "satisfaction with medical care", "sexuality", "body image", "worries about the future" and "restriction in the planning of activities", there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Side effects

Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from olaparib in comparison with watchful waiting in each case; greater or lesser harm is therefore not proven.

Specific AEs

Myelodysplastic syndrome (preferred term [PT], AE), acute myeloid leukaemia (PT, AE) and pneumonitis (PT, AE)

Module 4 A provides no usable data for the specific AEs "myelodysplastic syndrome (PT, AE)", "acute myeloid leukaemia (PT, AE)" and "pneumonitis (PT, AE)". Hence, there was no hint of greater or lesser harm from olaparib in comparison with watchful waiting in each case; greater or lesser harm is therefore not proven.

Decreased appetite (PT, AE)

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome "decreased appetite (PT, AE)". This resulted in a hint of greater harm from olaparib in comparison with watchful waiting.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug olaparib in comparison with the ACT are assessed as follows:

In the overall consideration, there were only negative effects of olaparib versus watchful waiting, each with the probability "hint" and up to the extent "considerable".

In summary, there is a hint of lesser benefit of olaparib in comparison with the ACT watchful waiting for the maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after at least 16 weeks of platinum-containing treatment as part of first-line chemotherapy.

Table 3 shows a summary of probability and extent of the added benefit of olaparib.

Table 3: Olaparib – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	Watchful waiting[b]	Hint of lesser benefit[c]
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that the first-line chemotherapy has been completed or that a continuation of the first-line chemotherapy is not indicated at the time point of the therapeutic decision for olaparib. c. Only patients with an ECOG PS of 0 or 1 were included in the POLO study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; gBRCA: human epidermal growth factor receptor		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of olaparib as maintenance treatment in comparison with watchful waiting as ACT in adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after at least 16 weeks of platinum-containing treatment as part of first-line chemotherapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of olaparib

Subindication	**ACT**[a]
Maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	Watchful waiting[b]
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that the first-line chemotherapy has been completed or that a continuation of the first-line chemotherapy is not indicated at the time point of the therapeutic decision for olaparib. G-BA: Federal Joint Committee; gBRCA: germline mutation of the breast cancer associated gene	

The company named watchful waiting as ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on olaparib (status: 30 September 2020)
- bibliographical literature search on olaparib (last search on 22 September 2020)
- search in trial registries/trial results databases for studies on olaparib (last search on 30 September 2020)
- search on the G-BA website for olaparib (last search on 30 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 7 December 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: olaparib vs. watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
D081FC00001 (POLO[d])	Yes	Yes	No	No[e]	Yes [3,4]	Yes [5-7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; EPAR: European Public Assessment Report; RCT: randomized controlled trial; vs.: versus

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: olaparib vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLO	RCT, double-blind, parallel	Adults with metastatic adenocarcinoma of the pancreas and with documented gBRCA1/2-mutation[b] whose disease has not progressed after at least 16 weeks of first-line platinum-containing chemotherapy, with ECOG-PS 0 or 1	Olaparib (N = 92) placebo (N = 62)	Screening: until 28 days before start of treatment treatment[c]: until disease progression[d], unacceptable toxicity, patient's decision, death or as long as the investigator considered the patient to benefit from this treatment observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	59 centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, South Korea, Spain, United Kingdom, USA 12/2014–ongoing first data cut-off: 15 January 2019	Primary: PFS secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Before randomization, the gBRCA mutation status had to be confirmed by a central test procedure (Myriad BRACAnalysis CDx Test [8]). Patients with deleterious or presumably deleterious gBRCA mutations were included.
c. Randomization within 6 weeks and start of treatment at least 4 and at most 8 weeks after the last dose of first-line platinum-containing chemotherapy.
d. Recorded using imaging techniques based on modified RECIST criteria (version 1.1).
e. Outcome-specific information is provided in Table 8.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; gBRCA: germline BRCA mutation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: olaparib vs. placebo

Study	Intervention	Comparison
POLO	▪ Olaparib 600 mg/day (2 film-coated tablets of 150 mg twice daily), orally, at the same time of the day, at 12-hour intervals	▪ Placebo (2 film-coated tablets twice daily), orally, at the same time of the day, at 12-hour intervals
	Treatment interruptions[a] and dose reduction[b] due to toxicity due to toxicity were possible	
	Pretreatment required: ▪ ≥ 16-week first line platinum-containing (cisplatin, carboplatin, oxaliplatin) chemotherapy[c] for metastatic adenocarcinoma of the pancreas without evidence of disease progression allowed: ▪ curative platinum therapy for prior cancer or as part of adjuvant/neoadjuvant treatment of the adenocarcinoma of the pancreas completed ≥ 12 months prior to first-line platinum-containing chemotherapy ▪ palliative radiotherapy completed ≥ 14 days before start of treatment (cycle 1, day 1) not allowed: ▪ cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days before start of treatment (cycle 1, day 1) ▪ investigational products within 30 days or 5 half-lives (whichever is longer) before randomization ▪ PARP inhibitors (including olaparib) **Concomitant treatment** allowed: ▪ any medication considered necessary for the patient's wellbeing and not interacting with the study intervention could be administered at the investigator's discretion not allowed: ▪ other anticancer therapies (chemotherapy, immunotherapy, hormonal therapy [hormone replacement therapy acceptable], radiotherapy or biological therapy or other novel drugs) or investigational products ▪ potent CYP3A4/5 inhibitors and CYP inducers ▪ live vaccines	

a. Treatment interruptions as needed for a maximum of 4 weeks; longer interruptions had to be reported.
b. Dose reduction to 200 mg, twice daily; escalation after dose reduction was not allowed.
c. Patients who discontinued the platinum component due to toxicity after at least 16 weeks of first-line chemotherapy and continued the remaining components of the chemotherapy were included in the POLO study if there was no evidence of disease progression within 4 weeks of the last dose of chemotherapy.

CYP: cytochrome P450; PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial

The POLO study was a randomized, double-blind, multicentre study on the comparison of olaparib with placebo. The study included adult patients with metastatic adenocarcinoma of the pancreas and a deleterious or presumably deleterious gBRCA1 or/and gBRCA2-mutation who had previously received first-line platinum-containing chemotherapy for at least 16 weeks (without interruption) and who, in the opinion of the investigator, had not progressed. Patients who had discontinued the platinum component due to toxicity after at least 16 weeks of platinum-containing treatment could also be included in the POLO study, provided that treatment with all other drugs comprised in the respective treatment regimen was continued and

there was no indication of progression within 4 weeks after the last dose of the first-line chemotherapy. The general condition of the patients had to correspond to an ECOG PS of 0 or 1.

The POLO study included 154 patients who were assigned in a 3:2 ratio either to treatment with olaparib (92 patients) or placebo (62 patients). Randomization was unstratified. Randomization had to take place within 6 weeks, and the study treatment had to be initiated at least 4 and at most 8 weeks after the last dose of first-line platinum-containing chemotherapy. The median time span between first-line chemotherapy and the start of study treatment was approx. 5 weeks.

In the POLO study, treatment with olaparib was in compliance with the SPC [9]. Moreover, patients in both study arms received any medication deemed necessary for their well-being that did not interact with the study intervention. Study treatment was continued until radiological progression according to RECIST criteria version 1.1, unacceptable toxicity or death. Treatment with the study medication could be continued after radiological progression if the investigator considered the patients to benefit from this treatment.

Primary outcome of the POLO study was PFS. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and AEs.

Treatment duration of first-line platinum-containing chemotherapy

The POLO study included patients who had previously been treated with first-line platinum-containing chemotherapy for at least 16 weeks. In accordance with the guidelines [10-13], a large proportion of the study population received FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, oxaliplatin) as palliative chemotherapy in the first-line setting (olaparib arm: 85.9%; placebo arm: 80.6%). The guidelines provide no information on the duration of treatment with FOLFIRINOX [10,13]. The guideline of the German Society for Haematology and Medical Oncology (DGHO) [11] recommends treatment until progression or, for patients with a very good response, as interval therapy. The guideline of the European Society for Medical Oncology (ESMO) [12] also recommends treatment until disease progression (according to RECIST criteria). In the study by Conroy 2011 [14], patients with response were to be treated with FOLFIRINOX for 6 months.

The majority (approx. 65%) of patients in the POLO study were treated with first-line chemotherapy for ≤ 6 months (in relation to the total population, the median treatment time was approx. 5 months). Information on whether the respective first-line chemotherapy had been completed or prematurely discontinued, e.g. due to toxicity, are completely missing in Module 4 A. Overall, it cannot be excluded that continuation of the first-line chemotherapy was still indicated for the patients in the POLO study at the time of randomization. In its comments on the ACT, the G-BA also assumed that the first-line chemotherapy in the present indication had been completed or that a continuation of the first-line chemotherapy was not indicated at the time point of the therapeutic decision for olaparib. Therefore, the certainty of conclusions of

the POLO study is limited; only hints, e.g. of an added benefit, can be derived on the basis of this study.

Data cut-offs

A total of 2 data cut-offs were preplanned:

- 15 January 2019 (first data cut-off): primary analysis after about 87 PFS events
- Final analysis of overall survival: planned after 106 deaths

The POLO study is still ongoing. In the benefit assessment, study results on the first data cut-off are analysed.

Implementation of the ACT in the POLO study

The G-BA specified watchful waiting as ACT in the present therapeutic indication. In the POLO study, watchful waiting was operationalized as a follow-up strategy that comprised regular examinations with the help of imaging techniques for the diagnosis of disease progression (at 8-week intervals until study week 40, followed by 12-week intervals). This is in line with the approach recommended in the ESMO [12] and American Society of Clinical Oncology (ASCO) [13] guidelines, which both recommend regular computed tomography (CT) scans at 2-month intervals to evaluate the efficacy in the treatment of metastatic pancreatic cancer.

Moreover, patients in the POLO study received any medically required intervention, which was specified by the investigator based on the symptoms for each individual patient. This procedure represents an adequate approximation to supportive therapy, which is recommended according to the S3 guideline on exocrine pancreatic carcinoma [10].

In summary, the approach used in the POLO study is considered an adequate implementation of the ACT.

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: olaparib vs. placebo

Study **outcome category** **outcome**	**Planned follow-up observation**
POLO	
Mortality	
Overall survival	Until death or final analysis
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-PAN26 symptom scales)	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30 and EORTC QLQ-PAN26 (functional scales)	Until 30 days after the last dose of the study medication
Side effects	
All outcomes in the category of side effects	Until 30 days after the last dose of the study medication

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib vs. placebo (multipage table)

Study characteristic category	**Olaparib N[a] = 92**	**Placebo N[a] = 62**
POLO[b]		
Age [years], mean (SD)	58 (10)	56 (9)
Sex [F/M], %	42/58	50/50
Family origin, n (%)		
Caucasian	82 (89)	59 (95)
Other[c]	10 (11[d])	3 (5[d])
Duration from original diagnosis to randomization [months], MW (SD)	10.3 (7.5)	8.8 (5.4)
Distant metastases, n (%)		
M0[e]	14 (15)	7 (11)
M1	72 (78)	48 (77)
NX	5 (5)	4 (7)
Missing	1 (1)	3 (5)
BRCA status according to Myriad[f], n (%)		
BRCA1	29 (32)	16 (26)
BRCA2	59 (64)	45 (73)
Both	1 (1)	0 (0)
Missing[g]	3 (3)	1 (2)
ECOG PS, n (%)		
0	65 (71)	38 (61)
1	25 (27)	23 (37)
Missing	2 (2)	1 (2)
Prior chemotherapy, n (%)		
FOLFIRINOX	79 (86)	50 (81)
Gemcitabine/cisplatin	2 (2)	3 (5)
Other	10 (11)	8 (13)
Missing	1 (1)	1 (2)
Duration of first-line treatment before randomization [months], n (%)		
≤ 6 months	61 (66)	40 (65)
> 6 months	30 (33)	21 (34)
Missing	1 (1)	1 (2)
Best response to first-line treatment, n (%)		
Stable disease state	45 (49)	31 (50)
Partial/complete response	46 (50)	30 (48)
Missing	1 (1)	1 (2)
Treatment discontinuation, n (%)	60 (65.2[d])	53 (85.5[d])
Study discontinuation, n (%)	43 (46.7[d])	35 (56.5[d])

Table 9: Characteristics of the study population – RCT, direct comparison: olaparib vs. placebo (multipage table)

Study characteristic category	Olaparib N[a] = 92	Placebo N[a] = 62

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. All data refer to the start of the POLO study.
c. Includes "black or African American", "Asian", "Native Indian or Native Alaskan" and "other".
d. Institute's calculation.
e. The M0 status at baseline is due to the effect of the first-line chemotherapy.
f. Before randomization, the gBRCA mutation status was determined by a central test procedure with the Myriad BRACAnalysis CDx test [8].
g. 4 patients did not give a blood sample for central testing with the Myriad BRACAnalysis CDx test, however, a gBRCA2 mutation status could be determined based on existing local test results. 2 of these test results had also been obtained by Myriad at an earlier date.

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; F: female; gBRCA: germline mutation of the breast cancer associated gene; M: male; max: maximum; min: minimum; n: Number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the included study population were predominantly comparable between both treatment arms. The mean age of the patients was 57 years and most were of Caucasian family origin (92%). 29% of the patients in the study population had a gBRCA1 mutation and two thirds had a gBRCA2 mutation. Before being included in the POLO study, 84% of the patients had been treated with the FOLFIRINOX regimen in the first-line setting. About 2 thirds of the study population were treated with first-line chemotherapy for ≤ 6 months. During first-line chemotherapy, approx. 50% of the study population achieved partial or complete response, and approx. 50% achieved a stable disease state as best response to platinum-containing chemotherapy.

Treatment duration and observation period

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: olaparib vs. placebo

Study **duration of the study phase** **outcome category**	**Olaparib** **N[a] = 92**	**Placebo** **N[a] = 62**
POLO		
Treatment duration [months]		
Median [min; max]	5.98 [0.8; 45.3][b]	3.71 [0.1; 30.1][b]
Observation period[c] [months]		
Overall survival		
Median [min; max]	12.09 [0.3; 45.3]	11.07 [0.3; 45.7]
Morbidity, health-related quality of life		
EORTC QLQ-C30, EQ-5D		
Median [min; max]	6.08 [0; 45.3]	4.45 [0; 30.1]
EORTC QLQ-PAN26		
Median [min; max]	6.18 [0; 45.3]	4.45 [0; 30.1]
Side effects		
Median [min; max]	6.51 [1.1; 45.3]	4.70 [0.3; 30.1]

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. The company did not provide any information on the determination of observation periods.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; max.: maximum; min: minimum; N: number of randomized patients; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; RCT: randomized controlled trial; vs.: versus

In the POLO study, the median treatment duration was slightly more than 2 months longer in the olaparib arm than in the placebo arm (approximately 6 months vs. 3.7 months). This difference is mainly due to earlier disease progression and subsequent treatment discontinuation in the placebo arm.

As the observation period for the outcomes of the category "morbidity", "health-related quality of life" and "side effects" depends on the duration of treatment with the study medication (plus 30 days after the end of treatment), the observation periods for each outcome are longer in the olaparib arm than in the placebo arm.

Subsequent therapies

In the POLO study, any decision on subsequent therapies after the end of the study medication was at the discretion of the investigator. According to the study protocol, the resumption of platinum-containing chemotherapy after disease progression was to be expected for most patients.

At the present data cut-off, approx. 49% of patients in the olaparib arm and approx. 74% of patients in the placebo arm had received a first subsequent therapy (see Appendix B of the full dossier assessment). The most common first subsequent therapy received by patients in both study arms was FOLFIRINOX (approx. 47% in the olaparib arm and approx. 35% in the placebo arm). At the present data cut-off, approx. 28% of the participants in the olaparib arm and approx. 44% of the participants in the placebo arm had already received a second subsequent therapy. Thereby, differences were shown between the treatment groups. The most common second subsequent therapy (approx. 39%) administered in the olaparib arm was gemcitabine/paclitaxel; in the placebo arm, other similar therapy regimens such as the FOLFIRI regimen (approx. 15%) were used in addition to the FOLFIRINOX regimen (approx. 11%).

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: olaparib vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
POLO	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the POLO study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company describes that the German and European guidelines provide no recommendations on the maintenance treatment for patients in the target population [10-12], and an established standard of care for this therapy situation was thus lacking in the European centres.

The company concluded that the results of the POLO study were transferable to the German healthcare context as the study fulfilled the requirements of the ACT, the dosage of olaparib corresponded to the current SPC, the study included predominantly patients of Caucasian origin and approx. 84% of the patients had received first-line platinum-containing chemotherapy in accordance with the FOLFIRINOX regimen before study inclusion in line with the German and European standard of recommendation [10-12]. The company pointed out that men and women were equally affected by pancreatic cancer [11,15,16] and that this gender ratio was reflected in the POLO study. Moreover, the company explained that gBRCA2 mutations occur 3 times

more often than gBRCA1 mutations in patients with pancreatic cancer [17] and that gBRCA2 mutations also occurred more often in the POLO study.

Using cancer registry data of the Robert Koch Institute (RKI), the company demonstrated that the median age of disease onset in the study population (57 years) was significantly younger than the median age of disease onset in Germany (men/women: 72/76 years) [15] and explained that this discrepancy was due to the selection of patients with a gBRCA mutation.

Finally, the company pointed out that the POLO study was conducted in accordance with the requirements of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP).

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms recorded with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-PAN26
  - Health status measured with the EQ-5D VAS
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30 as well as the scales the EORTC QLQ-PAN26
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Myelodysplastic syndrome (PT, AE)
  - Acute myeloid leukaemia (PT, AE)
  - Pneumonitis (PT, AE)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: olaparib vs. placebo

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-PAN26)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-PAN26)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelodysplastic syndrome (PT, AE)	Acute myeloid leukaemia (PT, AE)	Pneumonitis (PT, AE)	Decreased appetite (PT, AE)
POLO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire-Core 5 Dimensions; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on analyses of the outcome categories "morbidity" and "health-related quality of life"

- Symptoms and health-related quality of life: The company presented responder analyses up to a confirmed deterioration by 10 points for the outcomes recorded with the symptom and functional scales of the EORTC QLQ-C30 and the EORTC QLQ-PAN26. As explained in the *General Methods* of the Institute [1,18], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). This is not the case with the response criteria presented. The responder analyses submitted by the company were nevertheless used for the benefit assessment, because in the specific situation of the EORTC, the analysis with a response threshold of 10 points was considered a sufficient approximation to an analysis with a 15% threshold (15 points). An explanation can be found in benefit assessment A20-97 [19].
- Health status: The outcome "health status" was recorded with the EQ-5D VAS. The responder analyses are not used for the dossier assessment because the response criteria

used (7 or 10 points) do not correspond to at least 15% of the scale range on a predefined basis, nor to exactly 15% of the scale range on a post hoc basis. The continuous analyses (mixed-effects model with repeated measures [MMRM]) on the mean change until cycle 6 were used for the present benefit assessment. The responder analyses used by the company are presented as supplementary information in Appendix D of the full dossier assessment.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: olaparib vs. placebo

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-PAN26)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-PAN26)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Myelodysplastic syndrome (AE, UE)	Acute myeloid leukaemia (PT, AE)	Pneumonitis (PT, AE)	Decreased appetite (PT, AE)
POLO	L	L	H[b, c]	H[b, c]	H[b]	H[b, c]	H[b, c]	H[c]	H[c]	L[d]	H[c]	H[c]	H[c]	H[c]

a. Operationalized as CTCAE grade ≥ 3.
b. Strong decrease in response rates over the course of the study, which differ notably between the treatment arms (> 10% points)
c. Incomplete observations for potentially informative reasons; differences in the observation periods between the treatment groups.
d. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Concurring with the company, the risk of bias of the results on overall survival was rated as low.

Due to the strongly decreasing response rates of the questionnaires on the patient-reported outcomes as well as different observation periods between the treatment groups (for potentially informative reasons), the risk of bias of the results on "symptoms", "health status" and "health-

related quality of life" was rated as high. This deviates from the assessment of the company, which rated the risk of bias of these outcomes as low.

The risk of bias of the results on the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "specific AEs" is also rated as high, because the observations of outcomes were incomplete for potentially informative reasons (largely determined by discontinuation of observation after disease progression). The certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome "discontinuation due to AEs" to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns. This assessment of the risk of bias for outcomes in the category "side effects" differs from that of the company, which assessed the risk of bias for these outcomes as low.

2.4.3 Results

Table 14 and Table 15 summarize the results of the comparison of olaparib with placebo in patients with metastatic pancreatic cancer and gBRCA1/2 mutation whose disease was not progressive after at least 16 weeks of first-line platinum-containing chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs are presented in Appendix A of the full dossier assessment. Kaplan-Meier curves on event time analyses are presented in Appendix C of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib vs. placebo

Study outcome category outcome	Olaparib N	Olaparib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Olaparib vs. placebo HR [95% CI]; p-value[a]
POLO					
Mortality					
Overall survival	92	18.9 [14.9; 26.2] 41 (44.6)	62	18.1 [12.6; 26.1] 30 (48.4)	0.91 [0.56; 1.46]; 0.683
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales, time to confirmed clinically relevant deterioration[b])					
Fatigue	89	12.0 [4.6; NA] 37 (41.6)	58	NA 17 (29.3)	1.36 [0.79; 2.36]; 0.267
Nausea and vomiting	89	NA 35 (39.3)	58	NA 8 (13.8)	2.60 [1.42; 4.77]; 0.002
Pain	89	7.4 [3.7; 14.1] 42 (47.2)	58	4.6 [2.9; 6.0] 30 (51.7)	0.69 [0.42; 1.13]; 0.144
Dyspnoea	89	NA 20 (22.5)	58	NA 7 (12.1)	1.54 [0.70; 3.39]; 0.284
Insomnia	89	NA 24 (27.0)	58	12.1 [5.7; NA] 16 (27.6)	0.73 [0.38; 1.42]; 0.351
Appetite loss	89	NA 28 (31.5)	58	NA 9 (15.5)	1.74 [0.89; 3.40]; 0.103
Constipation	89	NA 25 (28.1)	58	20.3 [12.5; NA] 8 (13.8)	1.77 [0.87; 3.59]; 0.112
Diarrhoea	89	30.4 [30.4; NA] 14 (15.7)	57	NA 6 (10.5)	1.10 [0.42; 2.90]; 0.840
EORTC QLQ-PAN26 (symptom scales, time to confirmed clinically relevant deterioration[b])					
Pancreatic pain	88	13.0 [7.4; NA] 33 (37.5)	58	6.0 [4.6; NA] 23 (39.7)	0.70 [0.40; 1.23]; 0.214
Digestive restrictions	88	NA 27 (30.7)	58	NA 11 (19.0)	1.32 [0.68; 2.58]; 0.413
Altered bowel habits	88	NA 18 (20.5)	58	NA 7 (12.1)	1.43 [0.63; 3.26]; 0.391
Hepatic symptoms	88	22.1 [16.6; NA] 19 (21.6)	58	NA 10 (17.2)	0.82 [0.37; 1.84]; 0.628
Bloating	88	15.7 [10.4; NA] 29 (33.0)	58	12.1 [5.6; NA] 18 (31.0)	0.91 [0.50; 1.66]; 0.760
Indigestion	88	NA 19 (21.6)	58	NA 10 (17.2)	1.03 [0.48; 2.21]; 0.946
Flatulence	88	NA 22 (25.0)	58	NA 10 (17.2)	1.29 [0.63; 2.66]; 0.483

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib vs. placebo

Study outcome category outcome	Olaparib N	Olaparib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Olaparib vs. placebo HR [95% CI]; p-value[a]
Weight loss	88	NA 14 (15.9)	58	NA 3 (5.2)	2.11 [0.76; 5.85]; 0.153
Muscle weakness in arms and legs	88	NA 20 (22.7)	58	NA 7 (12.1)	1.59 [0.73; 3.50]; 0.245
Impairment due to side effects	87	NA 20 (23.0)	57	NA 8 (14.0)	1.47 [0.68; 3.17]; 0.325
Dry mouth	88	NA 13 (14.8)	58	NA 12 (20.7)	0.55 [0.24; 1.25]; 0.154
Altered sense of taste	87	NA 8 (9.2)	58	NA 3 (5.2)	1.37 [0.39; 4.82]; 0.624
Health-related quality of life					
EORTC QLQ-C30 (functional scales; time to confirmed clinically relevant deterioration[c])					
Global health status	89	34.3 [21.2; NA] 25 (28.1)	58	NA 19 (32.8)	0.66 [0.35; 1.24]; 0.199
Physical functioning	89	NA 22 (24.7)	58	NA 10 (17.2)	1.36 [0.66; 2.77]; 0.403
Role functioning	89	19.4 [13.8; NA] 32 (36.0)	58	NA 16 (27.6)	1.16 [0.64; 2.09]; 0.631
Cognitive functioning	89	NA 23 (25.8)	58	NA 14 (24.1)	0.97 [0.49; 1.89]; 0.921
Emotional functioning	89	16.6 [12.2; NA] 24 (27.0)	58	8.3 [5.7; NA] 18 (31.0)	0.66 [0.35; 1.26]; 0.204
Social functioning	89	26.9 [11.9; NA] 26 (29.2)	58	NA 9 (15.5)	1.52 [0.75; 3.06]; 0.241
EORTC QLQ-PAN26 (time to confirmed clinically relevant deterioration)					
Satisfaction with medical care[c]	88	NA 26 (29.5)	57	NA 10 (17.5)	1.43 [0.72; 2.84]; 0.303
Sexuality[c]	84	NA 17 (20.2)	56	NA 8 (14.3)	1.21 [0.53; 2.73]; 0.654
Body image[b]	88	NA 19 (21.6)	57	NA 9 (15.8)	1.17 [0.54; 2.55]; 0.687
Worries about the future[b]	87	NA 13 (14.9)	57	NA 5 (8.8)	1.42 [0.54; 3.76]; 0.477
Restrictions in the planning of activities[b]	88	26.9 [21.2; NA] 22 (25.0)	56	NA 6 (10.7)	1.78 [0.81; 3.93]; 0.153
Side effects					
AEs (supplementary information)	91	0.2 [0.1; 0.3] 87 (95.6)	60	0.3 [0.1; 0.3] 56 (93.3)	-

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: olaparib vs. placebo

Study outcome category outcome	Olaparib N	Olaparib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Olaparib vs. placebo HR [95% CI]; p-value[a]
SAEs	91	38.7 [15.6; NA] 22 (24.2)	60	NA 9 (15.0)	1.24 [0.58; 2.65]; 0.582
Severe AEs[d]	91	11.9 [7.2; NA] 36 (39.6)	60	19.4 [12.9; NA] 14 (23.3)	1.38 [0.77; 2.48]; 0.280
Discontinuation due to AEs	91	NA 5 (5.5)	60	NA 1 (1.7)	2.29 [0.41; 12.64]; 0.342
Myelodysplastic syndrome[e] (AE, UE)				No usable data	
Acute myeloid leukaemia[e] (PT, AE)				No usable data	
Pneumonitis[e] (PT, AE)				No usable data	
Decreased appetite (PT, AE)	91	NA 23 (25.3)	60	NA 4 (6.7)	2.93 [1.36; 6.32]; 0.006

a. HR and CI: log-rank test statistics; p-value: log-rank test; each without stratification.
b. Confirmed clinically relevant deterioration is defined as an increase by ≥ 10 points on 2 consecutive visits. Patients who died before a confirmed clinically relevant deterioration were censored.
c. Confirmed clinically relevant deterioration is defined as a decrease by ≥ 10 points on 2 consecutive visits. Patients who died before a confirmed clinically relevant deterioration were censored.
d. Operationalized as CTCAE grade ≥ 3.
e. In Module 4 A, the company declares to provide analyses based on the AEs of particular interest for MDS/AML and pneumonitis, although it does not comment on the respective operationalization. Analyses on pneumonitis presented by the company show that one patient in the olaparib arm and no patient in the comparator arm had such an event. Results on MDS/AML did not occur in either study arm.

AE: adverse event; AML: acute myeloid leukaemia; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MDS: myelodysplastic syndrome; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; RCT: randomized controlled trial; SAE: serious adverse event

Table 15: Results (morbidity, continuous) – RCT, direct comparison: olaparib vs. placebo

Study outcome category outcome	Olaparib			Placebo			Olaparib vs. placebo
	N[a]	Values at baseline mean (SD)	Change until cycle 6 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change until cycle 6 mean (SE)[b]	MD [95% CI]; p-value[b, c]
POLO							
Morbidity							
Health status							
EQ-5D VAS[d]	84	75.90 (15.89)	−0.65 (1.07)	53	77.50 (18.16)	−1.01 (1.47)	0.37 [-3.23; 3.96]; 0.840

a. Number of patients considered in the analysis for the calculation of the effect estimation, the values at baseline are based on all patients for whom a measurement at baseline and at least one subsequent measurement were available.
b. MMRM model adjusted for treatment, visit and value at baseline as well as interaction terms for treatment and visit, value at baseline and visit.
c. "Effect" presents the difference between the treatment groups of the changes from the start of the study until cycle 6.
d. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited certainty of conclusions of the POLO study.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

The company did not perform an outcome-specific derivation of the added benefit for the outcomes of the category "morbidity", but considered the added benefit as not proven across all outcomes. Hence, the company's outcome-specific assessment is not described below.

Symptoms

EORTC QLQ-C30

Nausea and vomiting

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome "nausea and vomiting". This resulted in a hint of lesser benefit of olaparib in comparison with watchful waiting.

Fatigue, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea

No statistically significant difference between the treatment groups was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "insomnia", "loss of appetite", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

EORTC QLQ-PAN26

Pancreatic pain, digestive restrictions, altered bowel habits, hepatic symptoms, bloating, indigestion, flatulence, weight loss, muscle weakness in arms and legs, impairment due to side effects, dry mouth, altered sense of taste

There was no statistically significant difference between the treatment groups for each of the outcomes "pancreatic pain", "digestive restrictions", "altered bowel habits", "hepatic symptoms", "bloating", "indigestion", "flatulence", "weight loss", "muscle weakness in arms and legs", "impairment due to side effects", "dry mouth" and "altered sense of taste". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status measured using the EQ-5D VAS" up to and including cycle 6. This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

The company did not perform an outcome-specific derivation of the added benefit for the outcome category "health-related quality of life", but derived an indication of a minor added benefit across all outcomes. Hence, the company's outcome-specific assessment is not described below.

EORTC QLQ-C30

Global health status, role functioning, cognitive functioning, "motional functioning, social functioning

No statistically significant difference between the treatment groups was shown for the outcomes "global health status", "role functioning", "cognitive functioning", "emotional functioning",

and "social functioning". This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Physical functioning

There was no statistically significant difference between the treatment groups for the outcome "physical functioning". However, there was an effect modification by the characteristic "age" (see Section 2.4.4). This resulted in a hint of lesser benefit of olaparib in comparison with watchful waiting for the outcome "physical functioning" in patients ≥ 65 years. For patients < 65 years of age, there was no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven.

EORTC QLQ-PAN26

Satisfaction with medical care, sexuality, body image, worries about the future, restriction in the planning of activities

For the outcomes "satisfaction with medical care", "sexuality", "body image", "worries about the future" and "restriction in the planning of activities", there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of olaparib in comparison with watchful waiting; an added benefit is therefore not proven for any of the outcomes.

Side effects

The company did not perform an outcome-specific derivation of the added benefit for the outcomes of the category "side effects", but considered the added benefit as not proven across all AE outcomes. Moreover, the company did not consider any specific AE outcomes for the derivation of the added benefit. Hence, the company's outcome-specific assessment is not described below.

According to the study protocol, AEs that are clearly due to a progression of the underlying disease should not be reported as AEs.

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from olaparib in comparison with watchful waiting in each case; greater or lesser harm is therefore not proven.

Specific AEs

Myelodysplastic syndrome (PT, AE), acute myeloid leukaemia (PT, AE) and pneumonitis (PT, AE)

Module 4 A provides no usable data for the specific AEs "myelodysplastic syndrome (PT, AE)", "acute myeloid leukaemia (PT, AE)" and "pneumonitis (PT, AE)". Hence, there was no

hint of greater or lesser harm from olaparib in comparison with watchful waiting in each case; greater or lesser harm is therefore not proven.

Decreased appetite (PT, AE)

A statistically significant difference to the disadvantage of olaparib compared with placebo was shown for the outcome "decreased appetite (PT, AE)". This resulted in a hint of greater harm from olaparib in comparison with watchful waiting.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- Sex (female/male)
- Age (< 65 years/≥ 65 years)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results on the comparison of olaparib with placebo. Kaplan-Meier curves on the event time analyses are presented in Appendix C.5 of the full dossier assessment.

Table 16: Subgroups (health-related quality of life) – RCT, direct comparison: olaparib vs. placebo

Study outcome characteristic subgroup	Olaparib L	Olaparib median time to event in months [95 % CI] patients with event n (%)	Placebo L	Placebo median time to event in months [95 % CI] patients with event n (%)	Olaparib vs. placebo HR [95% CI][a]	Olaparib vs. placebo p-value[a]
POLO						
Health-related quality of life						
EORTC QLQ-C30 (functional scales; time to confirmed clinically relevant deterioration[b])						
Physical functioning						
Age						
< 65 years	61	NA 10 (16.4)	47	NA 9 (19.1)	0.76 [0.31; 1.91]	0.551
≥ 65 years	28	NA 12 (42.9)	11	NA 1 (9.1)	5.65 [1.11; 102.84]	0.034
Total					Interaction:	0.037[c]

a. HR, CI and p-value: Cox proportional hazards model, unstratified.
b. Confirmed clinically relevant deterioration is defined as a decrease by ≥ 10 points on 2 consecutive visits. Patients who died before a confirmed clinically relevant deterioration were censored.
c. Likelihood ratio test from Cox proportional hazards model with corresponding interaction term; unstratified.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Physical functioning

For the outcome "physical function (recorded with the function scales of the EORTC QLQ-C30)", there was an effect modification by the characteristic "age".

For patients ≥ 65 years of age, a statistically significant difference was shown to the disadvantage of olaparib in comparison with placebo. This resulted in a hint of lesser benefit of olaparib in comparison with watchful waiting for patients ≥ 65 years.

There was no statistically significant difference between the treatment groups for patients < 65 years. This resulted in no hint of a lesser benefit or an added benefit of olaparib in comparison with watchful waiting; a lesser benefit or an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below. Taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Nausea and vomiting (EORTC QLQ-C30 symptom scale)

Module 4 A did not provide any information on the classification of the severity category for the outcome "nausea and vomiting", recorded with the EORTC QLQ-C30 symptom scales. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms.

Decreased appetite (PT, AEs)

It can be inferred from the information in Module 4 A that the majority of events of the outcome "decreased appetite (PT, AE)" were non-serious or non-severe (CTCAE - grade< 3). The specific AE "decreased appetite" was therefore assigned to the outcome category "non-serious/non-severe side effects".

Table 17: Extent of added benefit at outcome level: olaparib vs. placebo (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib vs. placebo** **median time to event (months) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 18.9 vs. 18.1 months HR: 0.91 [0.56; 1.46]; p = 0.683	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales		
Fatigue	Median: 12.0 vs. NA months HR: 1.36 [0.79; 2.36]; p =0.267	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. NA HR: 2.60 [1.42; 4.77]; HR: 0.38 [0.21; 0.70][c]; p = 0.002 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: “considerable”
Pain	Median: 7.4 vs. 4.6 months HR: 0.69 [0.42; 1.13]; p = 0.144	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 1.54 [0.70; 3.39]; p = 0.284	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. 12.1 months HR: 0.73 [0.38; 1.42]; p = 0.351	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 1.74 [0.89; 3.40]; p = 0.103	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. 20.3 months HR: 1.77 [0.87; 3.59]; p = 0.112	Lesser benefit/added benefit not proven
Diarrhoea	Median: 30.4 vs. NA months HR: 1.10 [0.42; 2.90]; p = 0.840	Lesser benefit/added benefit not proven
EORTC QLQ-PAN26 symptom scales		
Pancreatic pain	Median: 13.0 vs. 6.0 months HR: 0.70 [0.40; 1.23]; p = 0.214	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: olaparib vs. placebo (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib vs. placebo** **median time to event (months) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Digestive restrictions	Median: NA vs. NA HR: 1.32 [0.68; 2.58]; p = 0.413	Lesser benefit/added benefit not proven
Altered bowel habits	Median: NA vs. NA HR: 1.43 [0.63; 3.26]; p = 0.391	Lesser benefit/added benefit not proven
Hepatic symptoms	Median: 22.1 vs. NA months HR: 0.82 [0.37; 1.84]; p = 0.628	Lesser benefit/added benefit not proven
Bloating	Median: 15.7 vs. 12.1 months HR: 0.91 [0.50; 1.66]; p = 0.760	Lesser benefit/added benefit not proven
Indigestion	Median: NA vs. NA HR: 1.03 [0.48; 2.21]; p = 0.946	Lesser benefit/added benefit not proven
Flatulence	Median: NA vs. NA HR: 1.29 [0.63; 2.66]; p = 0.483	Lesser benefit/added benefit not proven
Weight loss	Median: NA vs. NA HR: 2.11 [0.76; 5.85]; p = 0.153	Lesser benefit/added benefit not proven
Muscle weakness in arms and legs	Median: NA vs. NA HR: 1.59 [0.73; 3.50]; p = 0.245	Lesser benefit/added benefit not proven
Impairment due to Side effects	Median: NA vs. NA HR: 1.47 [0.68; 3.17]; p = 0.325	Lesser benefit/added benefit not proven
Dry mouth	Median: NA vs. NA HR: 0.55 [0.24; 1.25]; p = 0.154	Lesser benefit/added benefit not proven
Altered sense of taste	Median: NA vs. NA HR: 1.37 [0.39; 4.82]; p = 0.624	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	Mean: -0.65 vs. -1.01 MD: 0.37 [-3.23; 3.96]; p = 0.840	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales		

Table 17: Extent of added benefit at outcome level: olaparib vs. placebo (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib vs. placebo** **median time to event (months) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Global health status	Median: 34.3 vs. NA months HR: 0.66 [0.35; 1.24]; p = 0.199	Lesser benefit/added benefit not proven
Physical functioning Age < 65 years	Median: NA vs. NA HR: 0.76 [0.31; 1.91]; p = 0.551	Lesser benefit/added benefit not proven
≥ 65 years	Median: NA vs. NA HR: 5.65 [1.11; 102.84]; HR: 0.18 [0.01; 0.901][c]; p = 0.034 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: “minor”
Role functioning	Median: 19.4 vs. NA months HR: 1.16 [0.64; 2.09]; p = 0.631	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NA vs. NA HR: 0.97 [0.49; 1.89]; p = 0.921	Lesser benefit/added benefit not proven
Emotional functioning	Median: 16.6 vs. 8.3 months HR: 0.66 [0.35; 1.26]; p = 0.204	Lesser benefit/added benefit not proven
Social functioning	Median: 26.9 vs. NA months HR: 1.52 [0.75; 3.06]; p = 0.241	Lesser benefit/added benefit not proven
EORTC QLQ-PAN26		
Satisfaction with medical care	Median: NA vs. NA HR: 1.43 [0.72; 2.84]; p = 0.303	Lesser benefit/added benefit not proven
Sexuality	Median: NA vs. NA HR: 1.21 [0.53; 2.73]; p = 0.654	Lesser benefit/added benefit not proven
Body image	Median: NA vs. NA HR: 1.17 [0.54; 2.55]; p = 0.687	Lesser benefit/added benefit not proven
Worries about the future	Median: NA vs. NA HR: 1.42 [0.54; 3.76]; p = 0.477	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: olaparib vs. placebo (multipage table)

Outcome category **outcome** **effect modifier** **Subgroup**	**Olaparib vs. placebo** **median time to event (months) or mean change** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Restrictions in the planning of activities	Median: 26.9 vs. NA months HR: 1.78 [0.81; 3.93]; p = 0.153	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 38.7 vs. NA months HR: 1.24 [0.58; 2.65]; p = 0.582	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 11.9 vs. 19.4 months HR: 1.38 [0.77; 2.48]; p = 0.280	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 2.29 [0.41; 12.64]; p = 0.342	Greater/lesser harm not proven
Myelodysplastic syndrome (AE)	No usable data	Greater/lesser harm not proven
Acute myeloid leukaemia (AE)	No usable data	Greater/lesser harm not proven
Pneumonitis (AE)	No usable data	Greater/lesser harm not proven
Decreased appetite (AE)	Median: NA vs. NA HR: 2.93 [1.36; 6.32]; HR: 0.34 [0.16; 0.74][c]; p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the CI_u.
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of olaparib in comparison with watchful waiting

Positive effects	Negative effects
–	Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting (EORTC QLQ-C30): indication of lesser benefit – extent: "considerable"
–	Health-related quality of life ▪ physical functioning (EORTC QLQ-C30) ▫ age (≥ 65 years) hint of lesser benefit – extent: "minor"
–	Non-serious/non-severe side effects ▪ decreased appetite: hint of greater harm – extent: "considerable"
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30	

In the overall consideration, there were only negative effects of olaparib versus watchful waiting, each with the probability "hint" and up to the extent "considerable".

In summary, there is a hint of lesser benefit of olaparib in comparison with the ACT watchful waiting for the maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after at least 16 weeks of platinum-containing treatment as part of first-line chemotherapy.

Table 19 summarizes the result of the assessment of the added benefit of olaparib in comparison with the ACT.

Table 19: Olaparib – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Maintenance treatment of adult patients with gBRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and whose disease has not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	Watchful waiting[b]	Hint of lesser benefit[c]
a. Presentation of the respective ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that the first-line chemotherapy has been completed or that a continuation of the first-line chemotherapy is not indicated at the time point of the therapeutic decision for olaparib. c. Only patients with an ECOG PS of 0 or 1 were included in the POLO study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; gBRCA: human epidermal growth factor receptor		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 13.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. AstraZeneca. Olaparib in gBRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO) [online]. 2020 [Accessed: 08.12.2020]. URL: https://ClinicalTrials.gov/show/NCT02184195.

4. AstraZeneca. A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy [online]. [Accessed: 08.12.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001589-85.

5. Golan T, Hammel P, Reni M et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019; 381(4): 317-327. https://dx.doi.org/10.1056/NEJMoa1903387.

6. Hammel P, Kindler HL, Reni M et al. Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib. Ann Oncol 2019; 30(12): 1959-1968. https://dx.doi.org/10.1093/annonc/mdz406.

7. European Medicines Agency. Assessment Report Lynparza (olaparib); Procedure No.: EMEA/H/C/003726/II/0033 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.ema.europa.eu/en/documents/variation-report/lynparza-h-c-003726-ii-0033-epar-assessment-report-variation_en.pdf.

8. Myriad Oncology. BRACAnalysisCDx [online]. [Accessed: 17.02.2021]. URL: https://myriad-oncology.com/bracanalysiscdx/.

9. AstraZeneca. Lynparza 100 mg/- 150 mg Filmtabletten [online]. 2020 [Accessed: 20.01.2021]. URL: https://www.fachinfo.de/.

10. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. S3-Leitlinie zum exokrinen Pankreaskarzinom. Langversion 1.0, AWMF-Registernummer: 032/010OL [online]. 2013 [Accessed: 23.09.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-010OLl_S3_Exokrines_Pankreaskarzinom_21112013-abgelaufen.pdf.

11. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Leitlinie Pankreaskarzinom (ICD-10 C25). Stand: Oktober [online]. 2018 [Accessed: 23.09.2020]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/pankreaskarzinom/@@guideline/html/index.html.

12. Ducreux M, Cuhna AS, Caramella C et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 Suppl 5: v56-68. https://dx.doi.org/10.1093/annonc/mdv295.

13. Sohal DPS, Kennedy EB, Cinar P et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. J Clin Oncol 2020: JCO2001364. https://dx.doi.org/10.1200/JCO.20.01364.

14. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364(19): 1817-1825. https://dx.doi.org/10.1056/NEJMoa1011923.

15. Robert Koch-Institut. Krebs in Deutschland für 2015/2016 [online]. 2019 [Accessed: 23.09.2020]. URL: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2019/krebs_in_deutschland_2019.pdf;jsessionid=53D2F8F7B8143F239C214EB45D074A04.1_cid290?__blob=publicationFile.

16. Zentrum für Krebsregisterdaten. Datenbankabfrage - Bauchspeicheldrüse (C25) [online]. 2020 [Accessed: 23.09.2020]. URL: https://www.krebsdaten.de/Krebs/DE/Datenbankabfrage/datenbankabfrage_stufe1_node.html.

17. Holter S, Borgida A, Dodd A et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol 2015; 33(28): 3124-3129. https://dx.doi.org/10.1200/JCO.2014.59.7401.

18. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 13.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_DWA-Entwurf-fuer-Version-6-0_V1-0.pdf.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 01.03.2021]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a20-115.html.