For public–
contains AIC and CIC information reducted

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations

Technology appraisal committee A [4th July 2023]

Chair: Radha Todd

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External assessment group (EAG): Liverpool Reviews & Implementation Group (LRiG)

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Company: Pfizer

Key abbreviations

aBC	advanced breast cancer
AI	aromatase inhibitor
AT/T	anthracycline chemotherapy and/or taxane
BRCA	breast cancer gene
eBD	early breast cancer
ET	endocrine therapy
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
ICER	incremental cost effectiveness ratio
ITT	intention to treat
OS	overall survival
QALY	quality-adjusted life year
PARP	poly ADP-ribose polymerase
PCT	physician's choice of treatment
PD	progressed disease
PDL1	programmed cell death ligand 1
PFS	progression-free survival
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PPS	post progression state
RBC	red blood cells
RDI	relative dose intensity
RPSFTM	rank preserving structural failure time model
TE	technical engagement
tala	talazoparib
TNBC	triple negative breast cancer
TTD	time to treatment discontinuation

Key clinical effectiveness issues

All key issues that are unresolved

Issue	Resolved?	Impact	Questions
Population and subgroups	No – for discussion	Unknown	Are subgroups of interest? If so, what subgroups are relevant?
Comparators	No – for discussion	Unknown	What are the appropriate comparators?
Interpreting EMBRACA OS results	No – for discussion	Unknown	What is the committee's view on talazoparib's treatment effect on OS?
Transfusion rates in EMBRACA	No – for discussion	Large	Is a 38.1 % transfusion rate acceptable to patients and representative of what would happen in the NHS?
Clinical benefits of talazoparib	No – for discussion	Unknown	How do clinicians and patients value these benefits?

Other clinical effectiveness issues

Issues considered resolved by the technical team

Issue	Resolved?	Impact	Technical team's initial view
Talazoparib positioning	Partly – for confirmation	Unknown	Company's positioning is appropriate.
Comparators - PCT	Partly – for confirmation	Unknown	PCT is a relevant comparator.
Prior treatments in EMBRACA	Partly – for confirmation	Unknown	Prior treatments in EMBRACA do not substantially affect generalisability.

Background: advanced breast cancer (aBC)

This appraisal covers HER2-negative locally advanced or metastatic BC with BRCA

Epidemiology

- 47,000 new breast cancer cases in England every year (2016-2018)
- 85% diagnosed with early breast cancer (eBC)
- 15% with de novo aBC (of whom ~2/3 have locally advanced BC and 1/3 metastatic BC)

Classification

- 70% HER2-negative/HR-positive BC, 15% TNBC (oestrogen and progesterone negative [HR-negative], HER2-negative BC) and 15% HER2-positive (outside of this appraisal)

Prognosis

- Metastatic BC worse than locally advanced BC
- TNBC worse than HER2-negative/HR-positive BC
- Clinical expert: cancer that is inoperable nor can be cured at this stage

BRCA mutation: 5% of HER2-negative/HR-positive and 10% of TNBC

Company: 900 HER2-negative aBC with BRCA diagnoses in England every year

Background: BRCA testing

Within 4 weeks of diagnosis if eligible and up to 12 weeks for results

Key national genomic testing eligibility criteria:

- Breast cancer (<40 years), OR
- Triple negative breast cancer (< 60 years), OR
- Breast cancer and strong family history of cancers OR
- High-risk HER2-negative breast cancer eligible for adjuvant olaparib (TA886)

Clinical expert:

- BRCA HER2-negative/HR-positive BC underdiagnosed as most women develop BC post-menopause (>40 years) and may not be eligible for BRCA testing.

Talazoparib (Talzenna, Pfizer)

Marketing authorisation received in 2019	Monotherapy for adults with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer: • previously treated with anthracycline and/or a taxane in neo/adjuvant, locally advanced or metastatic setting unless not suitable, and • HR-positive breast cancer should have been treated with a prior endocrine-based therapy unless not suitable.
Mechanism of action:	Talazoparib is a PARP inhibitor. PARPs are enzymes that repair damaged DNA. Talazoparib works by preventing cancer cells from repairing, allowing them to die.
Administration:	oral, 1mg per day (dose reductions of 0.25mg, 0.5 mg or 0.75 mg)
Price:	• £4,965 for 30 pack of 1mg capsules • £1,655 for 30 pack of 0.25mg capsules • patient access scheme (PAS) is applicable

Decision problem

	Final scope	Company	EAG comments
Population	Adults with HER2-negative locally advanced or metastatic breast cancer with germline BRCA 1/2-mutations that has previously been treated with an anthracycline and/or a taxane in the neo/adjuvant, locally advanced or metastatic setting or for whom these treatments would not be suitable.		Subgroups by both HR-status and line of therapy should be considered
Intervention	Talazoparib		-
Compa-rators	• Vinorelbine • Capecitabine • Eribulin (after at least 2 chemotherapy regimens)	• PCT (vinorelbine, capecitabine, eribulin) assuming same efficacy • Post TE a scenario with platinum was added	Platinum should also be considered as used in the NHS
Outcomes	OS, PFS, RR, AE, HRQoL		-

Current treatment pathway and proposed positioning

HER2-negative/HR-positive breast cancer with BRCA

Talazoparib only given after:

- anthracycline and/or a taxane therapy (AT/T) unless not suitable, and
- HR-positive BC should have been treated with a prior endocrine therapy (ET) unless not suitable.

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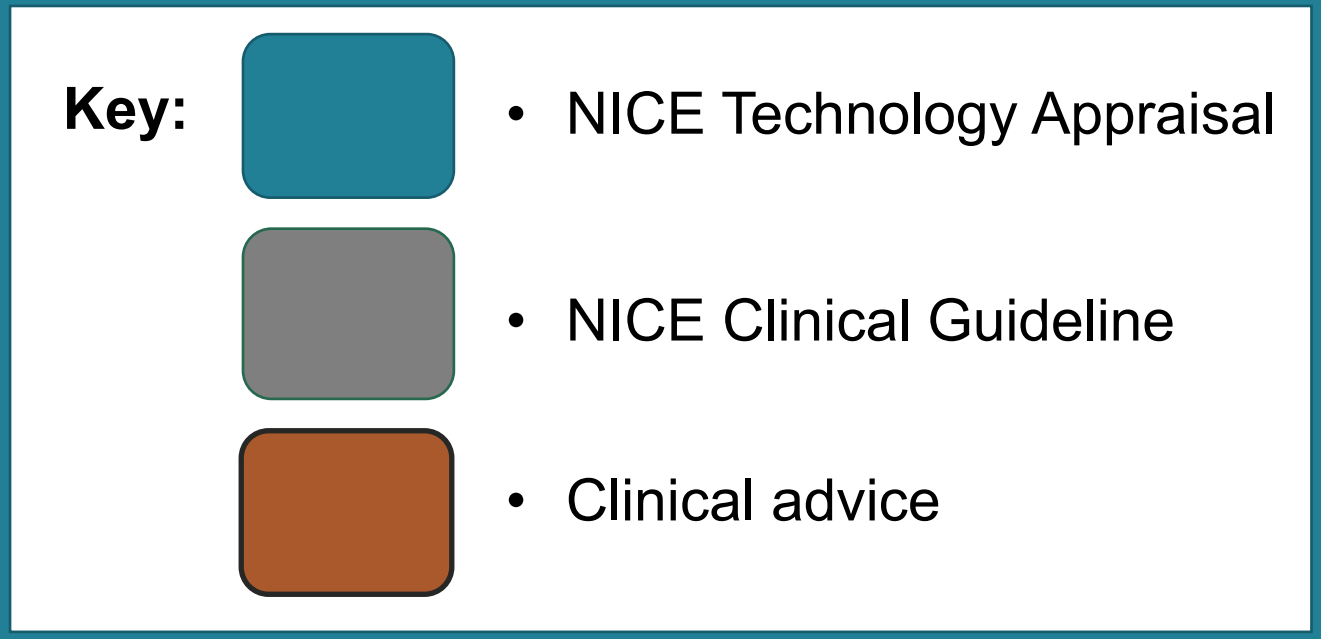

HER2-negative/HR-positive with BRCA - *previously treated aBC*

Company: talazoparib most likely used 2nd- line if AT/T in neoadjuvant setting

Current pathway – simplified

1st

CDK4/6 + AI (TA495, TA496, TA563) or fulvestrant if relapse on or within 1 year AI for eBC (TA836, TA687, TA725)

2nd

- Alpelisib + fulvestrant for PIK3CA (TA816)
- Everolimus + exemestane (TA421)
- Anthracyclines, taxane, capecitabine, vinorelbine if not used yet (CG81)
- Platinum if not used yet (TE advice)

3rd

- Eribulin after 2+ chemo (TA423)
- Chemotherapy - capecitabine or vinorelbine (whichever was not use yet; CG81)

Clinical advice: **up to 50% had** anthracycline chemotherapy and/or taxane (AT/T) and platinum in neo/adjuvant setting, talazoparib would be used after 1st line CDK4/6 inhibitors:

2nd → Talazoparib BRCA

Clinical advice: if no prior AT/T (**50%+**), tala would be used after 2nd line anthracycline or taxane:

3rd → Talazoparib BRCA

HER2-negative/HR-positive with BRCA - *de novo aBC*

Company: talazoparib most likely used 3rd line

Current pathway – simplified

1st

CDK4/6 + AI (palbociclib, ribociclib, abemaciclib; TA495, TA496, TA563)

2nd

- Alpelisib + fulve-strant for PIK3CA (TA816)
- Everolimus + exemesta-ne (TA421)
- Anthracyc-lines or docetaxel (CG81)
- Platinum (TE advice)

3rd

capecitabine or vinorelbine (CG81)

Clinical advice: de-novo metastatic cancer (~5% BC) or inoperable locally advanced (<5% BC):

- Talazoparib would be used after 1st line CDK4/6 inhibitors, and
- anthracyclines or docetaxel 2nd line for aBC:

3rd → Talazoparib BRCA

NICE **Key:** CDK4/6, cyclin-dependent kinases 4 and 6; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

HER2-negative/HR-positive BRCA locally advanced or metastatic BC: talazoparib positioning and comparators

Chemotherapy is the key comparator, but everolimus + exemestane and alpelisib + fulvestrant may be relevant comparators for previously treated BC

- **Would PIK3CA BC be treated with talazoparib before PIK3CA-targeted treatment?**

Is the company's proposed talazoparib positioning appropriate, specifically:

For previously treated BC:

- **2nd line**: after 1st line CDK4/6 if AT/T given in the neo/adjuvant setting (~45% of people)
- **3rd line**: after 1st line CDK4/6 and 2nd line anthracyclines or docetaxel (~50% of people)

For de novo BC:

- **3rd line**: after 1st line CDK4/6 and 2nd line anthracyclines or docetaxel (~5% of people)

What are the relevant comparators, specifically:

- Are everolimus + exemestane and alpelisib + fulvestrant relevant comparators for talazoparib in people who had AT/T in neo/adjuvant setting?
- What chemotherapy is comparator for previously treated and de novo BC?

Current treatment pathway and proposed positioning

TNBC with BRCA

Talazoparib only given after:

- anthracycline and/or a taxane therapy (AT/T) unless not suitable, and
- HR-positive BC should have been treated with a prior endocrine therapy (ET) unless not suitable.

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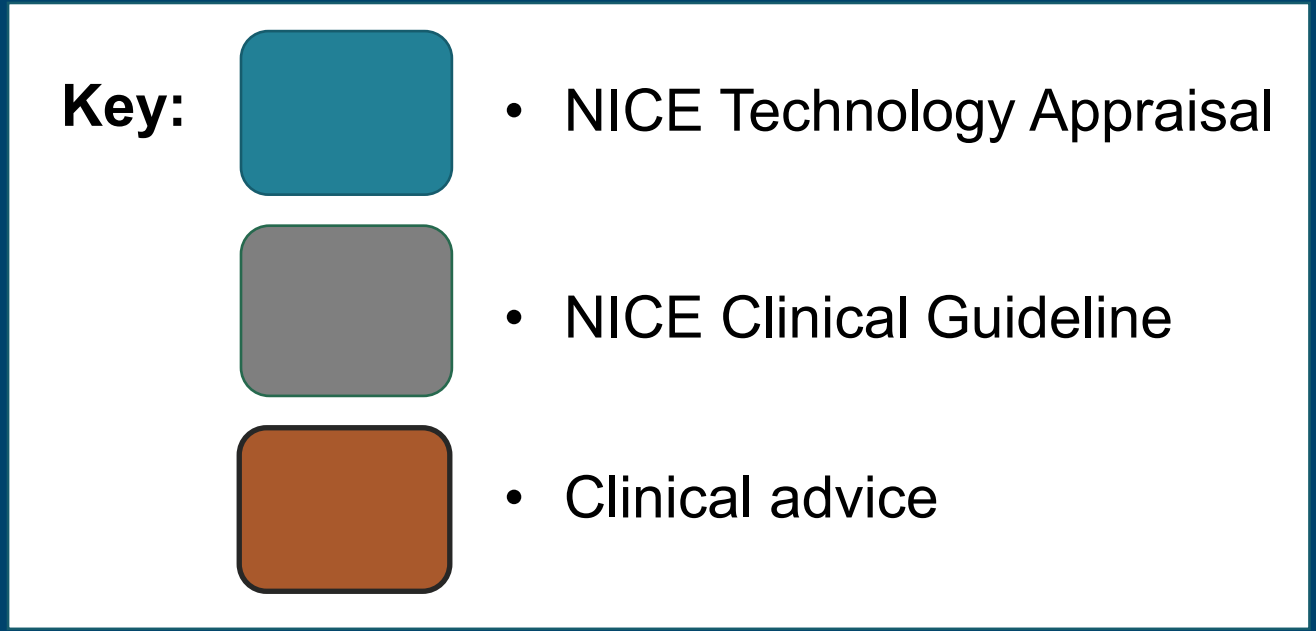

TNBC with BRCA: previously treated aBC

Company: talazoparib most likely used 1st line if AT/T in neoadjuvant setting

Current

1st	Atezolizumab + nab-paclitaxel or pembrolizumab + (nab)paclitaxel: PD-L1 no prior metastatic chemotherapy (TA639, TA801)	Anthracyclines, taxane, capecitabine, vinorelbine if not used yet (CG81)	Platinum if not used yet (TE advice)
2nd	Sacituzumab govitecan: after 2+ systemic therapies, including 1+ for aBC (TA819)	Eribulin - after 2+ prior chemothera-pies (TA423) Likely used before vinorelbine (TE advice)	Capecitabine, vinorelbine if not used yet (whichever was not used yet; NG81)

Clinical advice: **most** have AT/T and platinum in neo/adjuvant setting: tala would be used 1st line:

1st → Talazoparib BRCA

Clinical advice: if no prior AT/T (**very few**), tala would be used after 1st line anthracycline or taxane:

2nd → Talazoparib BRCA

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TNBC with BRCA: de novo aBC

Company: talazoparib most likely used 2nd line

Current

1st	Atezolizumab +nab-paclitaxel or pembrolizumab +(nab) paclitaxel: PD-L1 ≥10 no prior metastatic chemotherapy (TA639, TA801)	Anthracyclines or docetaxel (taxane) (CG81)	Platinum (TE advice)
2nd	capecitabine or vinorelbine (NG81)		
3rd	Sacituzumab govitecan (TA819)	Eribulin (TA423)	Chemotherapy - capecitabine or vinorelbine (NG81)

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Clinical advice: de-novo metastatic cancer (~5% BC) or inoperable locally advanced (<5% BC): talazoparib would be used

- after 1st line immunotherapy + taxane if PDL1-positive, or
- anthracyclines or docetaxel if PDL1-status negative or not known:

2nd ← Talazoparib BRCA

TNBC BRCA inoperable locally advanced or metastatic BC: talazoparib positioning and comparators

Chemotherapy is the key comparator for advanced TNBC, but atezolizumab or pembrolizumab + taxane may be relevant comparators for previously treated BC

- **Would PDL1 BC be treated with talazoparib before PDL1-targeted treatment?**

Is the company's proposed talazoparib positioning appropriate, specifically:

For previously treated TNBC:

- **1st line**: if AT/T given in the neo/adjuvant setting (most people)
- **2nd line**: after 1st line anthracyclines or docetaxel (a few people)

For de novo TNBC:

- **2nd line**: after 1st line anthracyclines or docetaxel (~5% of people)

What are the relevant comparators, specifically:

- Is atezolizumab or pembrolizumab + taxane a relevant comparator for talazoparib in people who had AT/T in the neo/adjuvant setting?
- What chemotherapy is comparator for previously treated and de novo BC?

Patient and clinical perspectives 1/2

Burden of disease

Submissions from a patient, Breast cancer Now, Met Up UK, NCRI-ACP-RCP-RCR, and a clinical expert

- There is no cure for secondary breast cancer, so the aim of treatment is to extend the length of life, while providing a good quality of life.
- Patients are looking for kinder treatments.
- The administration method – one tablet daily – will be welcomed by patients.
- Fewer hospital appointments.

‘I was diagnosed with secondary breast cancer de novo, with spread to the liver and bones. I was 37 at the time. The diagnosis was completely out of the blue and originally I was being treated for back pain. The impact has been devastating for my husband and two girls who are aged 7 and 9 as it poses a constant worry’…

…’mentally, I find that the very fact that I have a life limiting condition with very limited treatment options has had a severe detrimental effect on my mental health and mental wellbeing. … The knowledge that i will possibly not be around to see my children reach life events, such as marriage, children etc breaks my heart’..

Key: NCRI-ACP-RCP-RCR, National Cancer Research Institute – Association of Cancer Physicians - The Royal College of Physicians - The Royal College of Radiologists.

Patient and clinical perspectives 2/2

Unmet needs for HER2-negative advanced BC with BRCA in the NHS

- New treatments that target BRCA needed.
- Many with BRCA mutations have TNBC, with particularly limited treatment options associated with poor prognosis and quality of life.
- Talazoparib benefits seen in both triple negative and HER2 negative/HR-positive cancers
- Barriers to accessing genetic testing, some patients with BRCA mutations not identified.
- Clinical experts: evidence shows that talazoparib associated with clinically important improvements.

…'We live scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Even with the best available drug therapy, for most patients decades of life will be lost. Many of us mourn the loss of jobs and the future loss of families including children or even children that were planned but now will never be born'…

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: EMBRACA

Clinical trial design, outcomes and results

Design	Open label, phase III multicentre randomised trial (N=431)
Key in/ exclusion criteria	**Locally advanced not amenable to curative radiation or surgical cure (6%) and/or metastatic (94%) BC appropriate for single cytotoxic chemotherapy** • HER2-negative/HR-positive (56%) or TNBC (44%) • with germline BRCA1/2-mutations • prior taxane and/or anthracycline, unless contraindicated: 76.8% anthracycline & taxane, 6.3% anthracycline, and 14.2% taxane • max 3 prior cytotoxic treatments for aBC • platinum: excluded if < 6 months (amendment from 12 months) of stable disease after platinum for eBC, or if disease progressed on platinum for aBC
Arms	Talazoparib vs gemcitabine, eribulin, capecitabine, vinorelbine (PCT)
Follow-up (median)	PFS: 11.2 months (Data cut September 2017) OS: 44.9 months talazoparib; 36.8 months PCT (Data cut September 2019)
1° outcome	Progression-free survival (PFS) by blinded independent clinical review
Locations	US, Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK [n=[redacted]], Israel, Russia, Ukraine), Brazil, South Korea, Australia, and Taiwan

EMBRACA - Baseline characteristics		EMBRACA (ITT population)	
		Talazoparib (N=287)	PCT (n=144)
Age	Median (range), years	45.0 (27.0 - 84.0)	50.0 (24.0 - 88.0)
	Mean (STD), years	47.5 (11.61)	49.4 (12.12)
ECOG performance status, n (%)	0	153 (53.3)	84 (58.3)
	1	127 (44.3)	57 (39.6)
	2	6 (2.1)	2 (1.4)
	Missing	1 (0.3)	1 (0.7)
Hormone receptor status, n (%)	Triple-negative	130 (45.3)	60 (41.7)
	HR-positive	157 (54.7)	84 (58.3)
BRCA status, n (%)	BRCA1-positive	133 (46.3)	63 (43.8)
	BRCA2-positive	154 (53.7)	81 (56.2)
BC stage, n (%)	Locally advanced	15 (5.2)	9 (6.2)
	Metastatic	271 (94.4)	135 (93.8)
CNS mets history, n (%)	Yes	43 (15.0)	20 (13.9)
Previous cytotoxic regimens for aBC, n (%)	0	111 (38.7)	54 (37.5)
	1	107 (37.3)	54 (37.5)
	2	57 (19.9)	28 (19.4)
	3	12 (4.2)	8 (5.6)

EMBRACA trial results

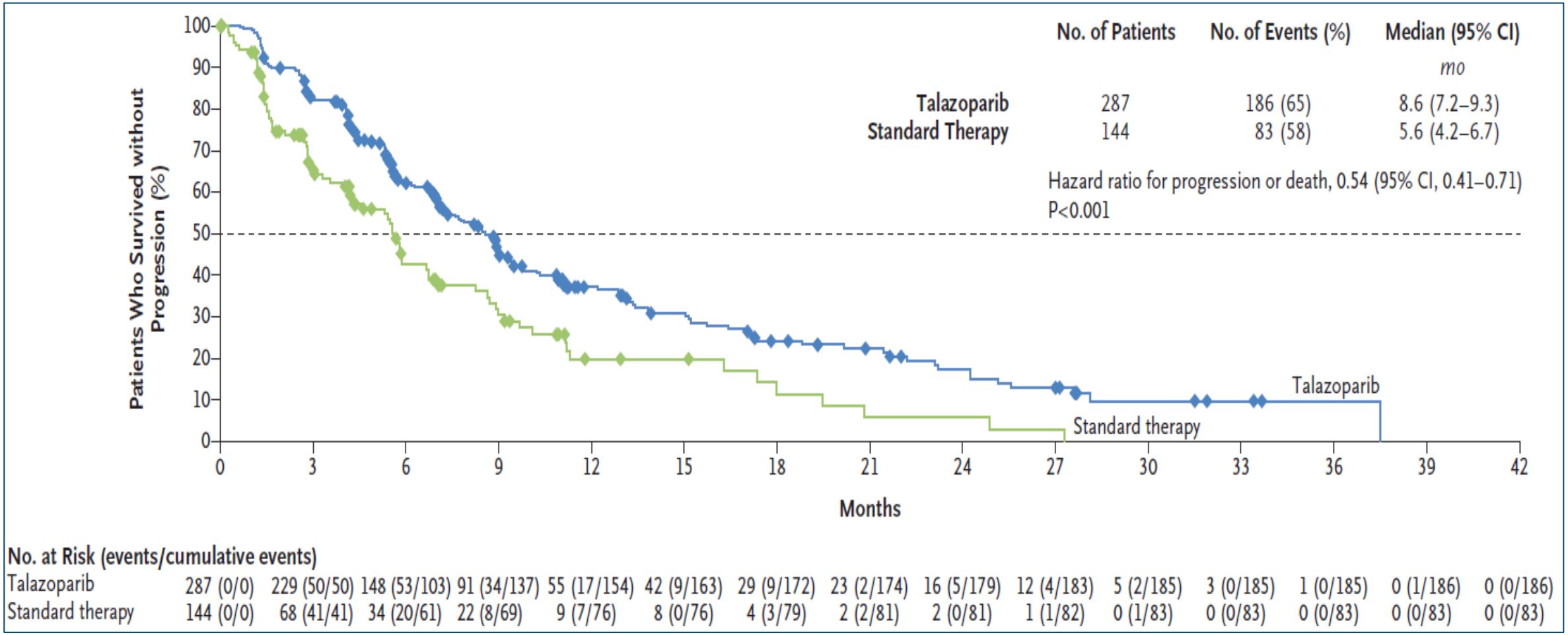
- PFS:
  ITT and subgroups

Trial results: PFS (primary endpoint), ITT population

Talazoparib improves PFS compared with PCT in ITT population

- **PFS HR = 0.54 (95% CI: 0.41-0.71)**

Follow-up time: median 11.2 months



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Source: figure 7, CS; Data cut: September 2017

PFS, by HR status

PFS	All patients		HER2-/HR+ BC subgroup		TNBC subgroup	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	287	144	157	84	130	60
Median, months (95% CI)	8.6 (7.2-9.3)	5.6 (4.2-6.7)	9.4 (8.8-13.0)	6.7 (5.6-8.7)	5.8 (5.3-7.7)	2.9 (1.7-4.6)
HR (95% CI)	**0.54 (0.41 to 0.71)**		**0.47 (0.32 to 0.71)**		**0.60 (0.41 to 0.87)**	

(Source: Table 9, EAG report)

PFS, by prior regimens of cytotoxic therapy for aBC

PFS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	111	54	107	54	69	36
Median, months (95% CI)	9.8 (8.5-13.3)	8.7 (5.5-18.0)	8.1 (5.7-9.2)	4.6 (3.3-8.2)	5.8 (4.4-8.9)	4.2 (1.5-5.7)
HR (95% CI)	**0.57 (0.34 to 0.95)**		**0.51 (0.33 to 0.80)**		**0.56 (0.34 to 0.95)**	

(Source: Table 10, EAG report)

PFS, by both HR status and prior regimens of cytotoxic therapy for aBC: HER2-negative/HR-positive group

PFS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
N	59	28	57	33	41	23
Median, months (95% CI)	12.2 (NR)	8.9 (NR)	9.0 (NR)	5.9 (NR)	7.6 (NR)	5.6 (NR)
HR (95% CI)	**0.41 (0.17 to 0.97)**		**0.43 (0.22 to 0.81)**		0.60 (0.30 to 1.20)	

(Source: Table 11, EAG report)

PFS, by both HR status and prior regimens of cytotoxic therapy for aBC: TNBC

PFS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
N	52	26	50	21	28	13
Median, months (95% CI)	7.3 (NR)	5.5 (NR)	5.4 (NR)	3.5 (NR)	4.3 (NR)	1.5 (NR)
HR (95% CI)	0.67 (0.65 to 1.27)		0.58 (0.29 to 1.12)		0.46 (0.21 to 1.03)	

(Source: Table 11, EAG report)

EMBRACA trial results

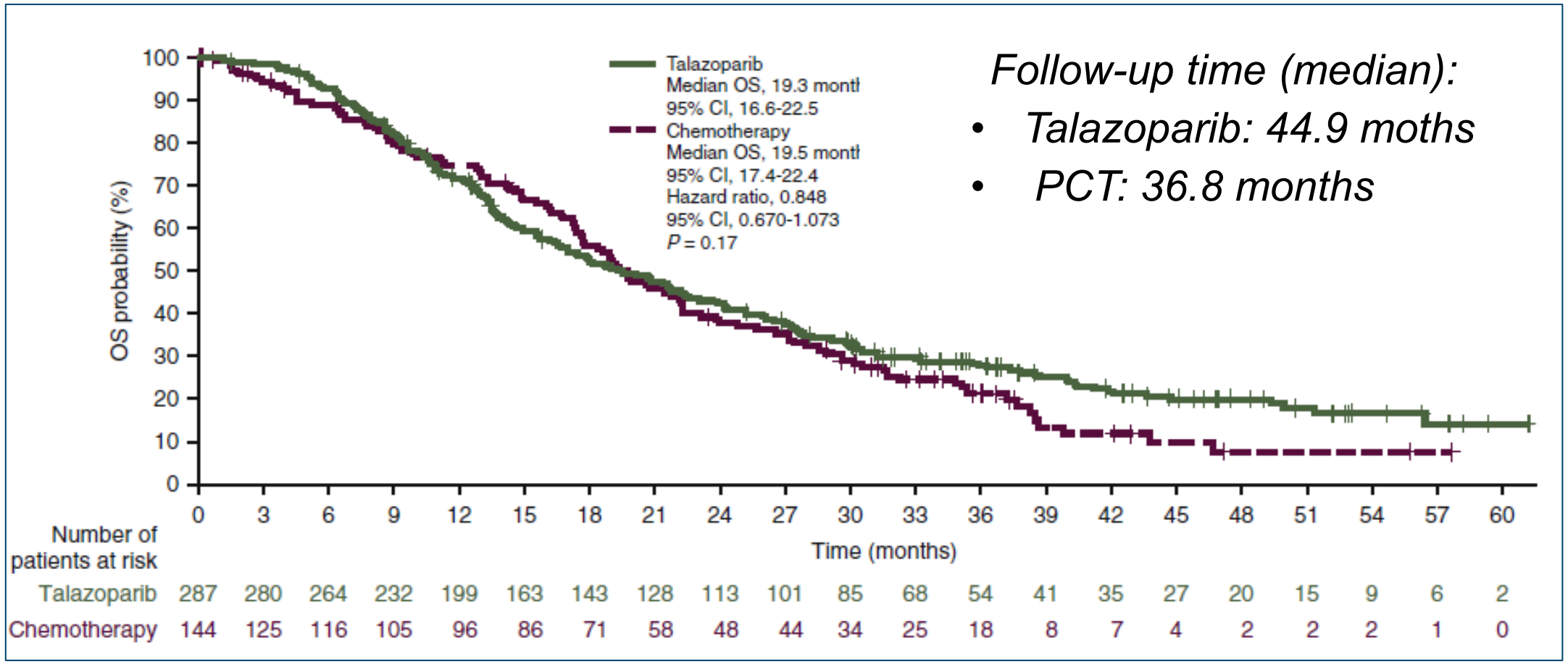
- OS:

  ITT and subgroups

Trial results: OS (secondary endpoint), ITT population

No statistically significant difference between 2 arms; median OS longer in PCT, survival curves crossed twice

- Most patients had subsequent treatments: unadjusted **HR = 0.85 (95% CI: 0.67-1.07)**
- RPSFTM results (adjusting for subsequent PARP inhibitors): **HR = 0.82 (95% CI: 0.62-1.05)**



Follow-up time (median):

- *Talazoparib: 44.9 moths*
- *PCT: 36.8 months*

Source: figure 9, CS; Data cut September 2019; **Key**: RPSFTM, rank preserving structural failure time model.

OS, by HR status

OS	All patients		HER2-/HR+ BC subgroup		TNBC subgroup	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	287	144	157	84	130	60
Median, months (95% CI)	19.3 (16.6-22.5)	19.5 (17.4-22.4)	23.1 (19.3-27.3)	22.4 (17.4-27.5)	13.4 (10.9-16.3)	18.6 (11.3-20.7)
HR (95% CI)	0.85 (0.67 to 1.07)		0.83 (0.60 to 1.14)		0.90 (0.63 to 1.28)	

(Source: Table 9, EAG report)

OS, by prior regimens of cytotoxic therapy for aBC

OS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	111	54	107	54	69	36
Median, months (95% CI)	27.8 22.7-31.4	29.1 20.7-37.4	16.6 14.2-21.7	17.4 12.8-19.2	13.6 11.4-16.3	17.4 13.1-24.0
HR (95% CI)	0.89 (0.58 to 1.36)		0.70 (0.48 to 1.01)		1.10 (0.68 to 1.76)	

(Source: Table 10, EAG report)

OS, by both HR status and prior regimens of cytotoxic therapy for aBC: HER2-negative/HR-positive BC patients

OS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	59	28	57	33	41	23
Median, months	NR	NR	NR	NR	NR	NR
HR (95% CI)	0.87 (0.47 to 1.60)		0.62 (0.37 to 1.04)		1.32 (0.72 to 2.45)	

(Source: Table 11, EAG report)

OS, by both HR status and prior regimens of cytotoxic therapy for aBC: TNBC patients

OS	0 regimens		1 regimen		≥2 regimens	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	52	26	50	21	28	13
Median, months	NR	NR	NR	NR	NR	NR
HR (95% CI)	0.97 (0.53 to 1.77)		0.84 (0.48 to 1.45)		0.78 (0.38 to 1.63)	

(Source: Table 11, EAG report)

Adverse events (AEs)

Similar rate AEs but more Grade 3 or 4 AEs related to study drug with talazoparib

EMBRACA: Summary of adverse events:

Adverse events Source: table 18 CS	Talazoparib (N=286)	PCT (N=126)
Any	98.6%	97.6%
Grade 3 or 4	70.3%	64.3%
Related to study drug	89.5%	88.9%
Leading to death	2.1%	3.2%
Serious	36.0%	31.0%
Grade 3 or 4 related to study drug	58.4%	49.2%
Leading to study dose modification	68.9%	60.3%

Treatment-related AEs experienced (≥20%)

- PCT: [redacted]
- Talazoparib: [redacted]

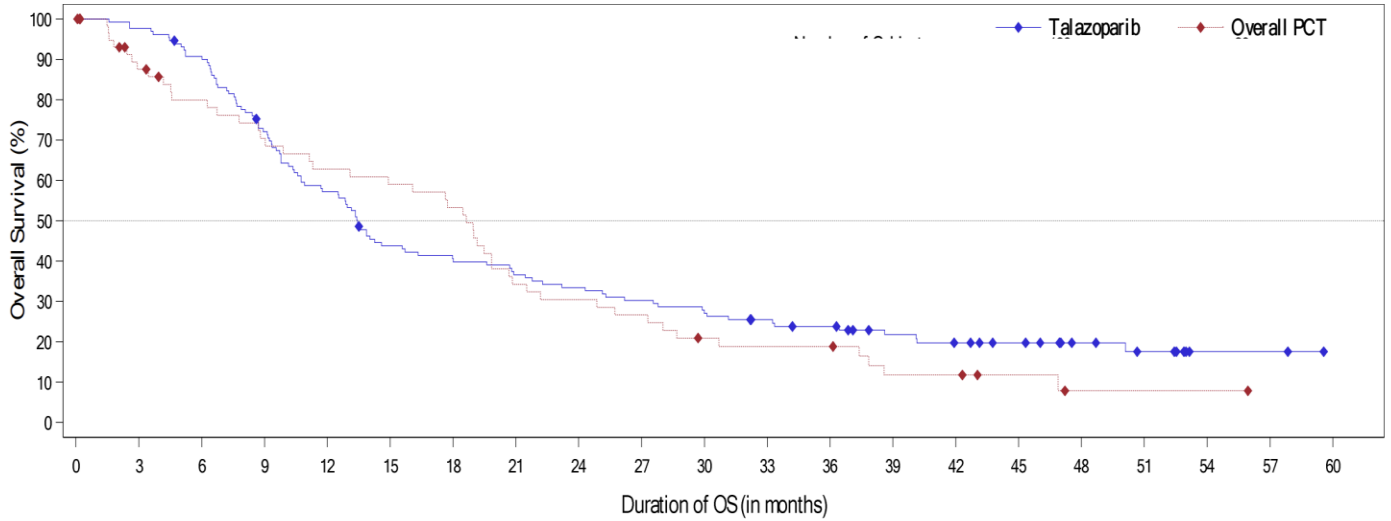
Key issue: Interpreting OS results of EMBRACA 1/2

EAG: OS results challenging to interpret, particularly in TNBC group

Median OS and HR differences in ITT population and by HR status (talazoparib vs PCT):

- **ITT population: 19.3 vs 19.5 months (HR=0.85)**
- HR+/HER2- BC subgroup: 23.1 versus 22.4 months (HR=0.83)
- **TNBC subgroup: 13.8 vs 18.6 months (HR=0.90)**

KM curves for OS in TNBC subgroup



Talazoparib: Evt/Cum.	0/0	3/3	9/12	24/36	19/55	17/72	4/76	5/81	4/85	4/89	4/93	2/95	2/97	2/99	2/101	0/101	0/101	1/102	0/102	0/102	0/102
Patients at Risk	130	127	117	92	73	55	51	46	42	38	34	30	27	21	18	15	10	7	2	2	0
Overall PCT: Evt/Cum.	0/0	7/7	4/11	5/16	4/20	2/22	3/25	10/35	2/37	2/39	3/42	1/43	0/43	3/46	0/46	0/46	1/47	0/47	0/47	0/47	0/47
Patients at Risk	60	48	42	37	33	31	28	18	16	14	10	9	9	5	5	3	1	1	1	0	0

Company

- difference in median OS may be driven by subsequent treatments received in PCT.
- statistically significant PFS and QoL results favouring talazoparib over PCT.
- patients and clinicians considered PFS clinically meaningful outcome.

NICE

Source: Figure 3, company response to TE

Key issue: Interpreting OS results of EMBRACA 2/2

EAG: talazoparib's treatment effect on OS uncertain

Clinical experts comments

- Subgroup results not relevant as subgroup confidence intervals do not exclude the ITT group point estimate of effect for the endpoints of interest.
- Trial demonstrated significant improvements in QoL and delay in onset of clinically meaningful deterioration.
- ITT did not show OS benefit. Results in subgroups consistent with ITT.
- Subsequent treatment seems to be an important and clinically relevant confounder.

EAG comments

- Missing subgroup KM curves by both HR status & line of treatment.
- Size and direction of the OS treatment effect of talazoparib versus PCT for the ITT population is uncertain.

What is the committee's view on talazoparib's treatment effect on OS? Does the committee consider that talazoparib's treatment effect on OS may differ by hormone receptor status, and previous lines of treatment?

Key issue: Population and subgroups 1/2

EAG and company differ on relevance of subgroups

Background

- EMBRACA included patients with HR-positive/HER2-negative BC and TNBC.
- Clinical advice to EAG, supported by trial results, suggested talazoparib efficacy may differ by HR status and line of treatment.

Company

- Scope of submission covers ITT population as assessed in EMBRACA.
- EMBRACA trial designed with adequate power to detect 90% and 80% effect sizes for PFS and OS in ITT population.
- Any analyses across subgroups would not be powered to detect significant differences, and therefore not appropriate.
- Subgroups by prior cytotoxic treatment is only a proxy for line of treatment as data not available.

Key issue: Population and subgroups 2/2

Recent appraisal of Olaparib in HER2-negative/HR-positive BRCA eBC (TA886)

- Committee considered clinical and cost-effectiveness results of key trial (N=1,836) by subgroups (not powered to show statistically significant differences):
  - TNBC (n=1,509), and HER2-negative/HR-positive BC (n=325);
- Olaparib was recommended for whole ITT population.

EAG comments

- Median PFS and OS results suggest that HER2-negative/HR-positive subgroup (SG) have better prognosis that TNBC SG. Similarly, SGs with fewer prior cytotoxic regimens for aBC have better prognosis than SGs with more prior regimens.
- Missing KM curves and medians for SGs by both HR status & line of treatment.
- SGs by HR status & line of treatment are clinically important, although the small numbers of patients and events contributing to subgroup results, and the absence of reported medians, mean that it is difficult to draw any conclusions.

What is the committee's view of the population, ITT versus subgroups?
What subgroups are relevant for decision-making?

Key issue: Red blood cell (RBC) transfusions

The rate of transfusion in EMBRACA is high

Background

- The rate of transfusion in EMBRACA was 38.1% in the talazoparib arm:
  - Talazoparib: 109 patients (38.1%) had RBC transfusions; the median per patient was [redacted] had platelet transfusion.
  - PCT: [redacted] had RBC transfusions; the median per patient was [redacted]. [redacted] had platelet transfusion.
- Talazoparib SPC (summary of product characteristics) states that it should be stopped if haemoglobin (Hb) falls below 8g/dL and is not to be not resumed (at a lower dose) until Hb increases to 9g/dL. Complete blood count is monitored monthly.
- Currently, in UK practice only a few patients with metastatic breast cancer have transfusions.

What is the committee's view of the EMBRACA transfusion rate?
Is this rate acceptable to patients?
Are the results representative of what would happen in the NHS?

Other issues – for discussion

The technical team consider these issues to be resolved

Comparators - PCT

- Scope defined comparators as eribulin, capecitabine and vinorelbine.
- PCT (n=126): 9.5% gemcitabine, 43.7% capecitabine, 39.7% eribulin, 7.1 % vinorelbine.
- Company used PCT, but removed gemcitabine as not used in NHS.
- Clinical advice that company's PCT without gemcitabine reflects NHS.

Technical team's initial view: PCT is a relevant comparator as it is used in the NHS

EMBRACA previous treatments

- Few patients in EMBRACA (n=431) had treatments currently available to the NHS (CDK4/6 inhibitors, immunotherapy and platinum).
- No evidence that prior treatments would influence talazoparib effectiveness.

Technical team's initial view: EMBRACA results are generalisable to the NHS

What is the committee's view on PCT without gemcitabine as a comparator?
What is the committee's view on the prior treatments used in EMBRACA trial?

Clinical benefits of talazoparib

Clinicians and patients experience

- Statistically significant PFS benefit (median 3 months)
- No OS benefit
- Statistically significant QoL benefit (median time to clinically meaningful deterioration in global health status was longer in talazoparib [24.3 months] than PCT [6.3 months])
- Potential variation in benefit between subgroups
- High rate of RBC transfusion (38.1%)
- Once-a-day tablet

What are the overall clinical benefits of talazoparib?
How do clinicians and patients value these benefits?

Equality considerations

Company:

- BRCA mutations more common in certain ethnicities and population groups.
- We wish to avoid inequity in access to talazoparib by subgrouping ITT population, given the unmet need and clinical benefit in PFS and QoL demonstrated in EMBRACA.

Clinical expert:

- Germline BRCA1/2 mutation more prevalent in young women.
- They are often young mothers, current regimens for HER2-positive breast cancer often intravenous and associated with significant time and financial impact.
- Talazoparib is oral therapy associated with fewer hospital attendances, so would be especially welcomed.

Technical team

- TNBC is more common in some ethnicities and patient groups.

Key clinical effectiveness issues

All key issues that are unresolved

Issue	Resolved?	Impact	Questions
Population and subgroups	No – for discussion	Unknown	Are subgroups of interest? If so, what subgroups are relevant?
Comparators	No – for discussion	Unknown	What are the appropriate comparators?
Interpreting EMBRACA OS results	No – for discussion	Unknown	What is the committee's view on talazoparib's treatment effect on OS?
Transfusion rates in EMBRACA	No – for discussion	Large	Is a 38.1 % transfusion rate acceptable to patients and representative of what would happen in the NHS?
Clinical benefits of talazoparib	No – for discussion	Unknown	How do clinicians and patients value these benefits?

Other clinical effectiveness issues

Issues considered resolved by the technical team

Issue	Resolved?	Impact	Technical team's initial view
Talazoparib positioning	Partly – for confirmation	Unknown	Company's positioning is appropriate.
Comparators - PCT	Partly – for confirmation	Unknown	PCT is a relevant comparator.
Prior treatments in EMBRACA	Partly – for confirmation	Unknown	Prior treatments in EMBRACA do not substantially affect generalisability.

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key cost- effectiveness issues

Cost-effectiveness issues with large or unknown impact on ICER

Issue	Resolved?	Impact	Questions
Using EMBRACA ITT data in model	No – for discussion	Unknown	What population including subgroups, should be used in the model?
BRCA testing	No – for discussion	Unknown	Does the cost of BRCA testing need to be included for some patients?
Modelling time to treatment discontinuation (TTD)	No – for discussion	Large	Is company's extrapolation or KM curves directly from EMBRACA more appropriate?
RBC transfusion rates	No – for discussion	Large	Is EMBRACA rate of 38.1 % or Mahtani 2022 rate of 8.3% more appropriate?
Utilities	No – for discussion	Large	Talazoparib or per arm utility for PFS?
Relative dose intensity (RDI)	No – for discussion	Large	Is it appropriate to include company's RDI multipliers in the model?

Other cost - effectiveness issues

Cost-effectiveness issues with mostly small impact on ICER

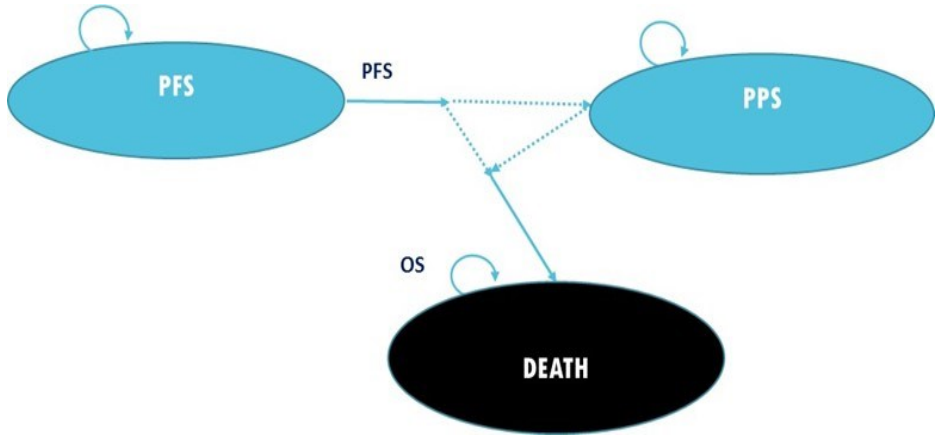
Issue	Resolved?	Impact	Technical team's initial view
QALY weighting for severity	Partly – for confirmation	Large	The severity modifier of 1.2 for QALY weighting is appropriate.
Health state resource use	Partly – for confirmation	Small	EAG's approach of not differing resource use in PFS state by response preferred.
Modelling OS in PCT arm	Partly – for confirmation	Small	EAG's approach of the Weibull curve preferred.
Subsequent treatments	Partly – for confirmation	Small	EAG's micro-costing approach preferred.
Cost of neutropenia	Partly – for confirmation	Small	EAG's cost of a 14-day adverse effects episode preferred.
Utilities - PD	Partly – for confirmation	Small	EAG's utility of 0.650 for PD preferred.

Company's model overview

A cohort partitioned-survival model

Model structure

- 3 states, progression-free (PFS), post-progression survival (PPS) and death
- Costs and QALYs assigned to each health state and QALYs varied depending on type of treatment received



- Results presented for ITT population only
- **Assumptions with the greatest ICER effect**:
  - time to treatment discontinuation (TTD)
  - red blood cell transfusion rate
  - PFS health state utility values
  - relative dose intensity (RDI) adjustments
- Severity weighting of 1.2 applied to incremental QALYs

How company incorporated evidence into model

Population	• EMBRACA
Intervention efficacy	• PFS: HR = 0.54 (95% CI: 0.41-0.71) • OS: RPSFTM HR 0.82 (95% CI 0.62-1.05) adjusted for subsequent PARPi
Comparator efficacy	• PCT (43.7% capecitabine, 39.7% eribulin, 7.1 % vinorelbine) in key trial with gemcitabine removed as not used in the NHS – exploratory scenario assuming platinum use in 15% TNBC (90:10 carboplatin and cisplatin) and same efficacy as PCT, but no evidence supporting company's assumptions included.
Extrapolating survival	• Talazoparib: Log-normal curve • PCT arm: modelled by applying RPSFTM HR of 0.82 to tala
TTD	• parametric survival curves
Utilities	• PFS: Talazoparib [redacted] and PCT [redacted] (EMBRACA) • PD: 0.626 (midpoint Huang 2020 & Lambert-Obry 2018)
Resource use	• cost for PFS state differs by response type

Key issue: EMBRACA ITT (intention to treat population) data

EAG: considered cost-effectiveness results for subgroups needed

Background

- Company presented economic results only for the whole trial population (ITT).
- EAG considers that subgroups by hormone status and line of treatment relevant.

Company

- EMBRACA not powered to detect statistically significant differences by subgroup.
- Inequity in access of talazoparib if subgrouping ITT population.
- No changes made post TE.

EAG comments

- If analyses suggest a new treatment cost-effective for a specific subgroup (or not) then it should be recommended (or not) for that subgroup.
- Cost-effectiveness analyses by relevant subgroups needed.

Is the committee able to make sufficient recommendations based on ITT population only, or does want to make the company to supply subgroups results?

Key issue: BRCA testing

Testing may not be available for all patients potentially eligible for talazoparib

- Company assumes all patients receive routine BRCA testing and cost is not included.

Recent appraisal of Olaparib in HER2-negative/HR-positive BRCA eBC (TA886)

- Committee discussed whether BRCA testing costs should be included for HER2-negative/HR-positive patients, and for TNBC patients aged over 60.
- Cost of BRCA testing was not included because the committee considered that early BC at high risk of recurrence meet the current BRCA testing criteria.
- After TA886 was published, criteria were updated to include all eligible for olaparib.

NICE manual section 4.8

- If a diagnostic test to identify a biomarker is not routinely used in the NHS but is introduced to support the treatment decision for the specific technology, the associated costs should be included (plus sensitivity analysis without the cost of the test).

NICE

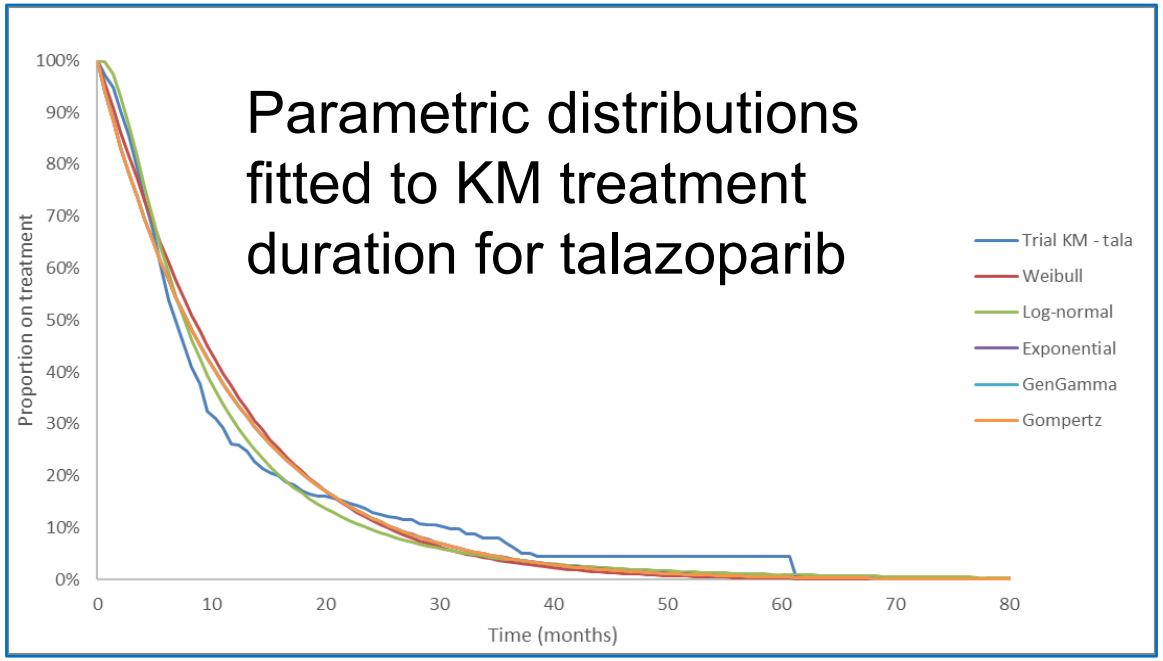
Does the cost of BRCA testing need to be included for some patients?

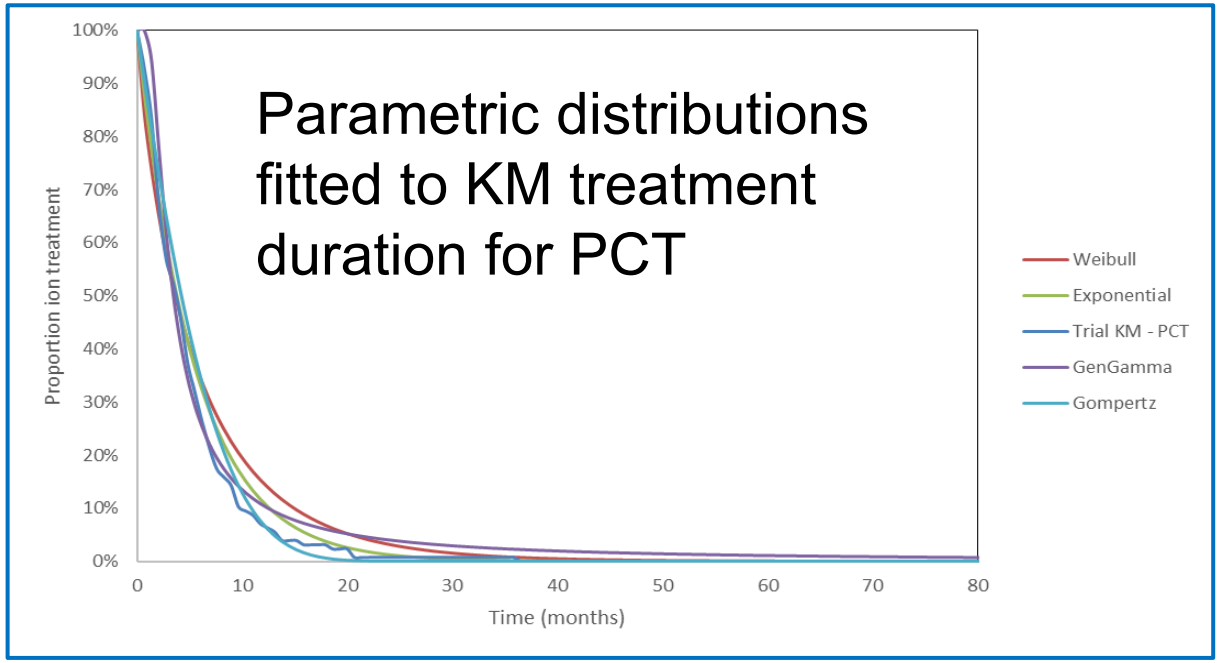
Key issue: Time to treatment discontinuation (TTD) 1/2

Company fitted survival curves to TTD for talazoparib post-TE

Background

- Company originally used median TTD from trial to estimate treatments costs.
- EAG then used KM data from the trial as at the end of 5 years no patients were still on PCT, and only 4.4% on talazoparib may still be receiving treatment.
- Post TE, company fitted parametric survival curves for TTD because KM data not complete and to align with PFS data.





Source: Figures 1 and 2 in company's TE response

Key issue: Time to treatment discontinuation (TTD) 2/2

EAG: using KM curves directly from the trial a better approach

Company

- Based on AIC/BIC values, generalised gamma distribution is a good fit to both arms. However, based on visual inspection, it may be more appropriate to use lognormal distribution for PCT arm.

EAG comments

- KM data may underestimate the cost of talazoparib (and ICERs), but all talazoparib TTD curves appear to be very poor visual fit to KM data.
- EMBRACA trial complete for PCT arm.
- More appropriate to use talazoparib's TTD KM data directly in model.

Is the TTD KM curve for talazoparib directly from the trial or its extrapolated curve more appropriate for decision making?

Key issue: Red blood cells (RBC) transfusion rates

EAG uses EMBRACA rate of 38.1 % and company Mahtani 2022 rate of 8.3%

Company

- EMBRACA rates do not reflect NHS practice.
- Correlation between transfusion rates, dose modifications and efficacy unknown.
- Post TE scenario: PCT's transfusion rate of 6% and median PFS for talazoparib are comparable with US real-world talazoparib data. So, it assumed talazoparib has same (lower) utility as PCT (0.687) and transfusion rate of 8.3%. This increased ICER slightly, providing upper bound for uncertainty around more realistic transfusion rates.

EAG comments:

- EMBRACA rates preferred as efficacy, TTD & QoL depend on RBC transfusion rate.
- Similarity of median PFS in EMBRACA and US RW study insufficient to conclude lowering transfusion rates in EMBRACA would not affect outcomes.

Clinical experts comments

- 38.1 % is high and level of 8.3% more reflective of day-to-day clinical practice.
- 38.1% rate should be used.

NICE

What transfusion rate is suitable for decision-making?

Key issue: Utilities for progression free survival (PFS)

Company's utilities differ by treatment while EAG uses same utility for both arms

Company

- Derived from EMBRACA trial EORTC QLQ-30 data for talazoparib and PCT.

Utilities	PFS - EMBRACA based
Talazoparib	[redacted]
PCT	[redacted]

EAG comments

- EMBRACA trial was an open-label trial, potential for bias in response by treatment arm exists; inappropriate to use PFS health state utilities that differ depending on treatment in company's base case.
- PFS health state talazoparib utility value ([redacted]) used in both treatment arms.

For PFS health state, does the committee consider applying the same utility value or varying utility value by treatment received more appropriate?

Key issue: Relative dose intensity multipliers 1/2

EAG: unclear how RDI multiplier was calculated as no accurate dosing data

EMBRACA – relative dose intensity (RDI), % (Source CS table 17):

	tala (N=286)	Capecitabine (N=55)	Eribulin (N=50)	Vinorelbine (N=9)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]

Background

- Based on EMBRACA, company stated they used RDI multiplier for talazoparib ([redacted]) and PCT (see above in table).
- EAG: this is not in the model, instead cost estimated by proportions of patients receiving specific doses – (table on right).

Proportions of patients receiving different doses of talazoparib in pre-TE model:

Talazoparib	Proportion
1mg	[redacted]
0.75mg	[redacted]
0.5mg	[redacted]
0.25mg	[redacted]

Source: EAG table 29.

Key issue: Relative dose intensity multipliers 2/2

EAG removed all RDI multipliers from its preferred base case

Company

- Post TE: updated model assuming that 100% of patients received 1 mg dose of talazoparib, with RDI of 90.8% as observed in EMBRACA. This increased the pre-TE ICER slightly.

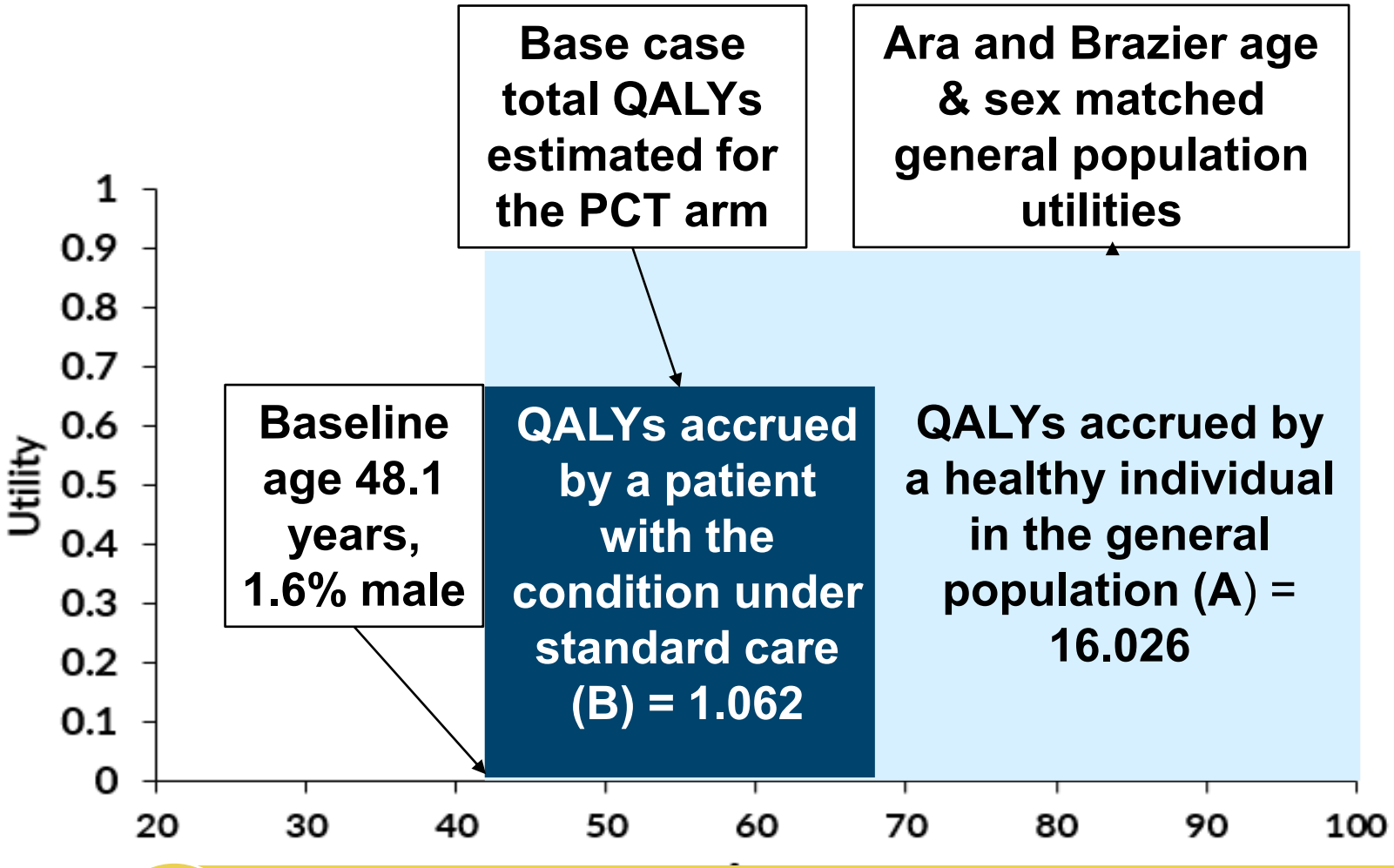
EAG comments

- Price of a 1mg dose is the same as that of 0.75 mg dose (3 x 0.25 mg tablets). The 0.5 mg (2 x 0.25 mg tablets) and 0.25 mg doses are cheaper than the 1 and 0.75 mg doses.
- If the application of RDI multiplier represents a change in dose from 1mg to 0.75mg it will underestimate cost of talazoparib as it introduces savings where no savings exists.
- Until accurate dosing data are available, all RDI multipliers should be excluded.

Does the committee prefer applying or removing relative dose intensity multipliers for the analysis?

QALY weighting for severity

EAG: agreed with a severity modifier of 1.2 for QALY weighting



Absolute shortfall
= 16.026 – 1.062 = 14.964
Proportional shortfall
= (16.026 – 1.062) / 16.026 = 0.934

Corresponding QALY weights:

- **Absolute shortfall** = 1.2
- **Proportional shortfall** = 1.2

The weight of 1.2 was applied

Does the committee consider the severity modifier of 1.2 for QALY weighting appropriate?

Other issues – for confirmation 1/3

The technical team consider these issues to be resolved

Modelling OS in PCT

- Company: applied rank preserving structural failure time model (RPSFTM) HR of 0.82 adjusted for subsequent use of PARP inhibitors to talazoparib log-normal curve.
- EAG: Weibull curve as proportional hazards (PH) assumption does not hold (KM data cross 2x) and separate functions are needed.

Technical team's initial view: EAG's approach is preferred as PH assumption not met

Health state resource use

- Company assumed that resource use in PFS health state differs depending on whether patients have complete/partial response (CR/PR) or stable disease.
- EAG given no evidence to support using differential resource use by response state, explored a scenario in which resource use does not differ by response type.

Technical team's initial view: EAG's approach is preferred as no evidence for the company's approach

What is the committee's view on OS modelling?

What is the committee's view on health state resource use that differs by response type?

Other issues – for confirmation 2/3

The technical team consider these issues to be resolved

Cost of subsequent treatments

- Company used PCT arm cost and applied in PD health state to all patients.
- Model has a micro-costing option that uses EMBRACA's per arm subsequent treatment data, adjusted by removing PARP inhibitors.
- EAG re-weighted the micro-costing approach and applied it in its preferred base case.

Technical team's initial view: EAG's approach is preferred as it utilises trial data.

Neutropenia

- Company modelled cost of treating neutropenia using an NHS outpatient appointment cost and the cost of treatment with an immunostimulant (filgrastim) in PFS health state.
- EAG used the cost of a 14 days course of filgrastim for treating an episode of neutropenia as filgrastim posology is a daily dose for no more than 14 days.

Technical team's initial view: EAG's approach is preferred as it follows clinical advice.

What is the committee's view on the cost of subsequent treatments?
What is the committee's view on the cost of neutropenia?

Other issues – for confirmation 3/3

The technical team consider these issues to be resolved

PD utility

- Company used 0.626 for PD health state, a midpoint between Huang 2020 (0.601) and Lambert-Obry 2018 (0.650).
- EAG used 0.650 from peered reviewed paper Lambert-Obry 2018 only as Huang 2020 is abstract with unclear population information.

Technical team's initial view: EAG's approach is preferred as it uses more reliable source.

What is the committee's view on utility for PD heath state?

Summary of company and EAG base case assumptions		
Assumption	**Company**	**EAG**
Population	EMBRACA – ITT population	ITT, but subgroups analyses needed – not currently available.
TTD	parametric survival curves	EMBRACA trial TTD KM data
Severity	QALY weighting of 1.2	QALY weighting of 1.2
RBC transfusion rates	Mahtani 2022 rate of 8.3%	EMBRACA rate of 38.1%
Utilities PFS	• PFS utilities by treatment	• talazoparib utility for PFS
RDI multipliers	Applied to both arms	Removed: no RDI multipliers
resource use in PFS	differs by response type	does not differ by response type
OS in PCT	RPSFTM HR of 0.82 to talazoparib log-normal curve	Weibull extrapolation
Subsequent treatments and neutropenia costs, and PD utility	• cost of PCT treatment • Filgrastim cost in PFS state • 0.626 for PD health state	• updated micro-costing • 14 days filgrastim cost • 0.650 for PD health state

Cost-effectiveness results: summary results

Talazoparib is not cost effective in the ITT population

- The EAG made minor corrections to the company base case resulting in a minor ICER increase (RDI set to original value in CS model, resource use in PFS health state in line with CS model, some eMIT prices updated).
- When all the confidential prices and the severity modifier are applied, both the company's and EAG's preferred ICERs for talazoparib versus PCT in HER2-negative locally advanced or metastatic breast cancer (ITT population) are higher than £30,000 per QALY gained.
  - Company's exploratory scenario assuming platinum use in 15% TNBC (90:10 carboplatin and cisplatin) and same efficacy as PCT resulted in a small increase in ICER.
- No subgroup results were provided.

Key cost- effectiveness issues

Cost-effectiveness issues with large or unknown impact on ICER

Issue	Resolved?	Impact	Questions
Using EMBRACA ITT data in model	No – for discussion	Unknown	What population including subgroups, should be used in the model?
BRCA testing	No – for discussion	Unknown	Does the cost of BRCA testing need to be included for some patients?
Modelling time to treatment discontinuation (TTD)	No – for discussion	Large	Is company's extrapolation or KM curves directly from EMBRACA more appropriate?
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Cost of neutropenia	Partly – for confirmation	Small	EAG's cost of a 14-day adverse effects episode preferred.
Utilities - PD	Partly – for confirmation	Small	EAG's utility of 0.650 for PD preferred.

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Thank you.