For public –
AIC and CIC information redacted

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

Technology appraisal committee A [5th September 2023]

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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
eBC	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

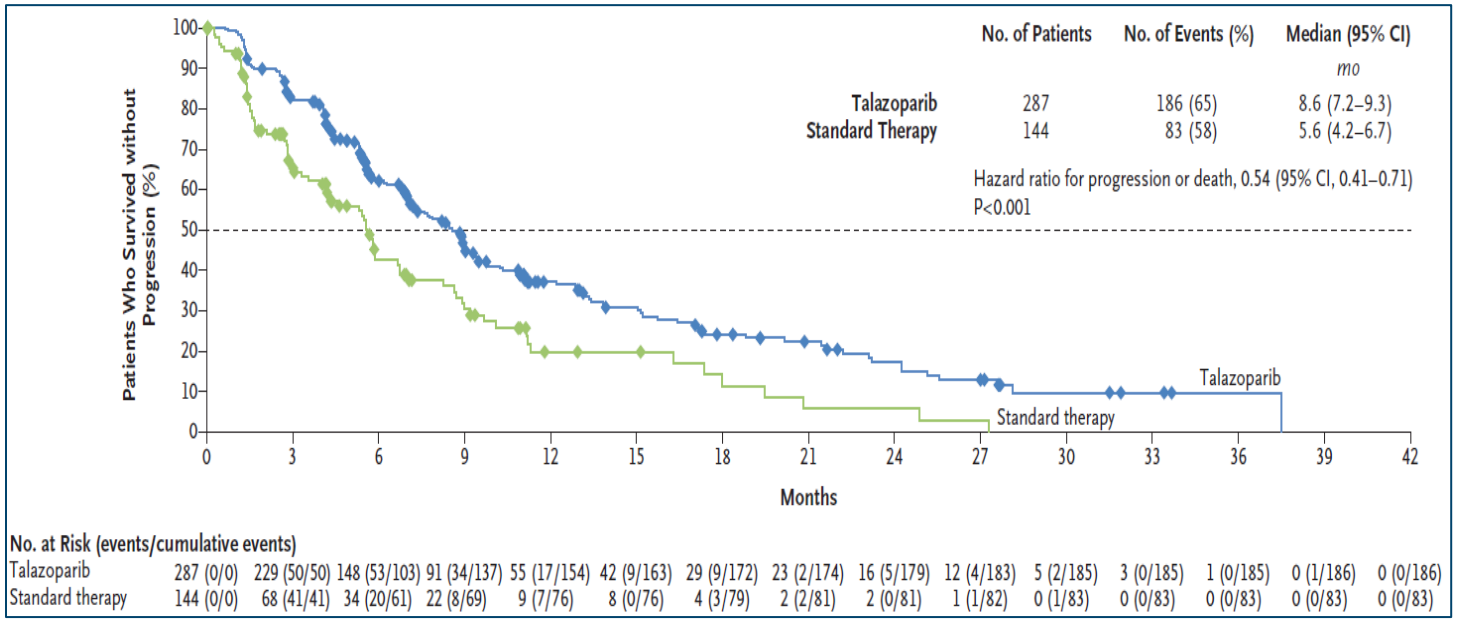
Talazoparib not recommended for HER2-negative BRCA aBC

- High disease burden for people with HER2-negative advanced breast cancer with germline BRCA mutations and high unmet need
- Population in EMBRACA, phase 3, open-label RCT of tala vs physician's choice chemo (N=431) may be representative of those seen in the NHS but heterogeneity
- Talazoparib associated with improved PFS; PFS important for people with the condition
- Evidence from trial did not show talazoparib improved OS; OS results in EMBRACA's pre-defined subgroups by HR-status difficult to interpret

ACM1 key committee's conclusions

- Both results for overall population and subgroups by hormone receptor status needed to inform decision making
- Stated preferred assumptions and requested analyses
- Severity modifier of 1.2 appropriate
- Talazoparib was not cost-effective in the ITT population

Trial results: PFS (primary endpoint), ITT population



ACM1: talazoparib improves PFS compared with PCT; PFS important for people with the condition

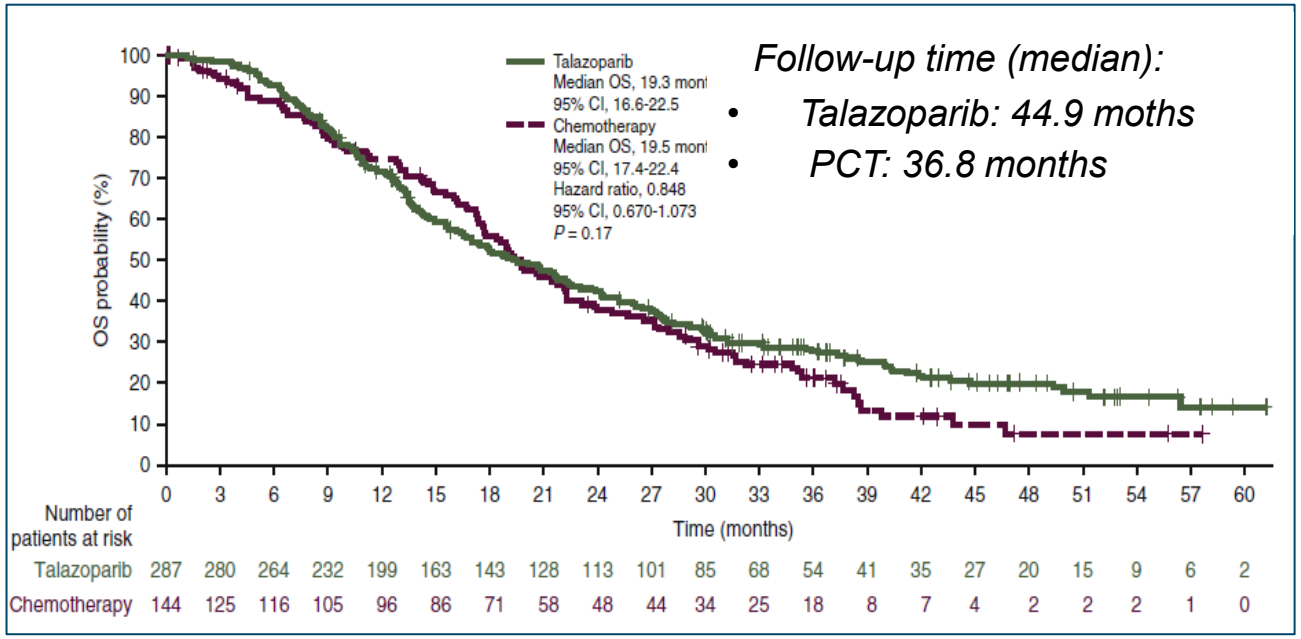
Follow-up time: median 11.2 months

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

Subgroups	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

Trial results: OS (secondary endpoint), ITT population



ACM1: evidence from EMBRACA did not show talazoparib improved OS; OS results in subgroups difficult to interpret

- survival curves crossed twice
- **HR = 0.85 (95% CI: 0.67-1.07)**
- **RPSFTM HR** adjusted for subsequent PARP inhibitors **= 0.82 (95% CI: 0.62-1.05)**

Source: figure 9, CS; Data cut September 2019

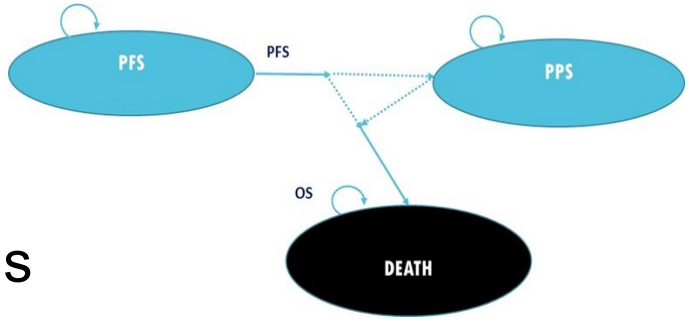
Subgroups	All patients		HER2-/HR+ BC subgroup		TNBC subgroup	
	Tala	PCT	Tala	PCT	Tala	PCT
Population, N	287	144	157	84	130	60
Median, months (95% CI)	19.3 (16.6-22.5)	19.5 (17.4-22.4)	23.1 (19.3-27.3)	22.4 (17.4-27.5)	13.4 (10.9-16.3)	18.6 (11.3-20.7)
HR (95% CI)	0.85 (0.67 to 1.07)		0.83 (0.60 to 1.14)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

Source: Table 9 EAG report; **Key**: RPSFTM, rank preserving structural failure time model.

Economic evidence

Talazoparib was not cost effective

A cohort partitioned-survival model:



Preferred key assumptions

- TTD: KM curves to estimate TTD preferred. More flexible methods may result in a better fit.
- RDI: detailed analysis on RDI multipliers in the model. In the absence of the analysis, removing the modifier is preferred.
- RBC transfusion rate: a value between EMBRACA and Mahtani study. Additional information on triggers of blood transfusion and analyses exploring relationship between dosing, dose reduction, RBC transfusion rate and treatment effect of tala requested.
- PFS: same value preferred but noted there may be other factors affecting utility when having talazoparib or PCT.
- OS: evidence did not show talazoparib improved OS; committee preferred modelling separate curves for OS but requested additional analysis assuming no OS benefit.

Overview of consultation responses

- **Breast Cancer Now** – commented on transfusions, unmet need and additional benefits of talazoparib
- **Met Up UK** – commented on transfusions, unmet need and additional benefits of talazoparib
- **NHS England and NHSE Genomics Unit** – considered that BRCA testing should be included
- **Clinical experts** – responded to queries on utilities and transfusions, and BRCA testing
- **Web comments** (1 submission) – supported recommendation
- **Company** – responded to committee considerations and presented new analyses with updated PAS

Consultation responses: issues for discussion

Unresolved issues: for discussion	Impact
PFS utilities	Large
OS modelling	Large
RBC transfusion rates	Large
BRCA testing	Large
Additional uncaptured benefits	Unknown
Population: ITT vs HR subgroups	Large

Issues for confirmation: technical team view approaches sufficient	
RDI	Company excluded RDI multipliers from model, no further analysis
TTD	Company used KM curves from EMBRACA, but did not explore more flexible methods
Clinical benefit in subgroups	Company provided KM curves for OS for subgroups, but no additional evidence on prognosis by hormone receptor status

Resolved issues: preferred assumptions applied
Resource use
PD utility
Neutropoenia
Subsequent treatments

Summary slide link

Key issues: OS modelling 1/2

ACM1: evidence did not show talazoparib improved OS; committee preferred modelling separate curves for OS but requested additional analysis assuming no OS benefit

Company

- Final OS HR was 0.848 (95% CI: 0.670, 1.073; p = 0.1693). This is 15% reduction in risk of death.
- 32.6% patients in PCT and only 4.5% patients in tala had subsequent PARP inhibitors which may influence OS. RPSFTM HR adjusted for PARP inhibitors was 0.82 (95% CI: 0.62, 1.05).
- Survival probabilities at 2-, 3- and 4-year favoured talazoparib vs PCT
- Numerical difference in OS was accepted in TA784 (ovarian cancer)
- Consider it not appropriate to disregard OS data based on the uncertainty – appropriate to model separate curves using unadjusted OS data
  - OS data are sampled probabilistically in model to reflect uncertainty
  - Provided a scenario assuming no OS benefit (tala curve used for both arms)

Summary slide link

Key issues: OS modelling 2/2

EAG: uncertainty in OS modelling remains

EAG

- Improvement in OS not statistically significant even after adjustment for subsequent PARP inhibitor use.
- Using separate parametric curves implicitly models OS benefit with talazoparib.
- Probabilistic ICER doesn't capture uncertainty in whether tala provides OS gain.
- Approach to OS in PSA is problematic because there is wide variation in survival estimates (10-year survival in PSA varied between [redacted], vs [redacted] in base case). This implies PSA is confounded and results should not be used to inform decision-making.
- Scenarios assuming no OS benefit result in large increase of ICERs in all analyses.

What is the appropriate approach to modelling OS? Is fitting separate curves or assuming no OS benefit more appropriate for decision making?

Key issues: PFS utilities

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Summary slide link

ACM1: preferred same PFS utility value for both arms (used talazoparib value) but noted there may be other factors affecting utility when having talazoparib or PCT

Company

Utilities	EMBRACA
Talazoparib	[redacted]
PCT	[redacted]

- Different values for talazoparib & PCT are reasonable
- Despite some limitations uses utilities from EMBRACA
- Real-world evidence showed 0.08 difference values between PARP inhibitors and chemotherapy (Mahtani 2022) – higher than difference of [redacted] in EMBRACA
- Some NICE appraisals in BC used different utility in PFS (e.g. TA423 and TA704)
  - Scenario based on TA423: 0.701 for PCT (difference of [redacted])
  - Scenario based on TA704: 0.720 for PCT (difference of [redacted])
- No analyses exploring additional factors on health-related quality of life (e.g. disutilities)

EAG

- EMBRACA is open-label trial so prone to bias in self-reported outcomes, company has not addressed this - treatment-specific utility values derived from it should not be used

Summary slide link

Key issues: PFS utilities 2/2

ACM1: preferred same PFS utility value for both arms (used tala value) but noted there may be other factors affecting utility when having talazoparib or PCT

Clinical experts

- "The alternative chemotherapy regimens usually require many more hospital visits for blood tests prior to often weekly or 2/3 weekly IV chemo sessions. Patient time away from home and family and travel expense is a major issue and is in my experience much more impacted by the chemotherapy alternatives than oral PARPi therapy."
- "Having chemo is burdensome for patients and units in terms of attendances for blood testing, nurse review, line care (weekly flushes if peripherally inserted catheter). Most of these happen 24-48 hrs prior to the day of treatment. The value of the QoL benefit with talazoparib versus standard of care chemo should not be underestimated."

Is applying the same utility value or varying utility value by treatment more appropriate? Which utility values does the committee prefer?

Summary slide link

Key issues: RBC transfusions 1/2

ACM1: rate of RBC transfusion likely a value between EMBRACA and Mahtani 2022; requested additional analyses exploring dosing, transfusion rate and treatment effect

Company

- Rate of 23.1%; the midpoint of 38.1% (EMBRACA) and 8.3% (Mahtani 2022) as per DG
- Provided scenario with post-amendment EMBRACA rate of 32.4%
- Evidence insufficient to explore dosing, transfusion rate and treatment effect relationship

Breast Cancer Now and Met Up UK

- EMBRACA's transfusion rate is too high to reflect NHS
- Even midpoint gives too much weight to protocol that is not reflective of NHS

EAG

- Agrees rates will be lower in NHS, but prefers post-amendment EMBRACA rate of 32.4% because transfusion rates could directly impact outcomes, including EQ-5D, PFS and OS due to the explicit link between Hb levels and dose reduction or time on treatment

Summary slide link

Key issues: RBC transfusions 2/2

Clinical experts: anaemia managed rapidly by dose reduction in practice and rarely leads to blood cell transfusion

Clinical experts

- "Data for palliative chemo will have come from an era where less restrictive transfusion approaches was the norm … and we do not see reduced efficacy of palliative vinorelbine/Taxol etc with lower threshold."
- "Talazoparib transfusion protocol was set at an inappropriately high threshold and we have no reason to think using this drug with transfusion thresholds and dose modification approaches will have detrimental efficacy impact."
- "Talazoparib does cause some anaemia but this is managed rapidly by dose reduction and rarely leads to blood transfusion in real clinical practice."

Which RBC transfusion rate is the most appropriate for the model?

Summary slide link

Key issues: BRCA testing 1/2

ACM1: cost of BRCA testing not needed in model

NHS England and NHSE Genomics England

- Cost should be included for some people with HR-positive/HER2-negative BC:

Scenario A: Tests for de novo metastatic BC only as everyone with eBC already tested: 1,400 people out of 7,500 people need testing

Scenario B: Tests for de novo metastatic BC and some people whose disease progressed from eBC (excluding people with high-risk disease, currently tested per olaparib TA886 criteria): 3,900 people out of 7,500 people need testing.

- Current NHS practice is probably closer to scenario B than scenario A (both scenarios assumed 15% of people already tested as part of familial BRCA testing).

EAG

- £525 per test and 10% incidence: testing cost is £5,250 per BRCA positive patient
- scenario A: 19% of ITT population will require a BRCA test
- scenario B: 52% of ITT population will require a BRCA test

Key issues: BRCA testing 2/2

Summary slide link

Clinical experts

- Most patients who need BRCA test already meet the testing criteria approved by NHSE; some have been missed due to medical education but that is changing fast.
- Scenario A is closer to reality than Scenario B but is still an overestimate of the number of tests that will need to be performed.
- Please also consider the other criteria for testing for HR+/HER2- BC such as strong family history, age <40 (irrespective of family history), as well as olaparib eligibility.
- Some of the assumptions used in the NHSE scenarios, such as estimated relapse rates and the current lack of access to testing, are too high.
- Assuming all with prior eBC have been tested is incorrect, but scenario B overestimates the need for additional tests.

Company

- Argues that BRCA testing is already routinely used and not being introduced as a new test
- Genomic testing is UK wide government initiative as stated in ‘Genome UK: the future of healthcare’
- TA886 considered a similar issue; committee concluded BRCA testing costs should not be included

NICE

What approach to modelling BRCA testing does the committee consider appropriate for decision making?

Key issues: Populations and subgroups 1/2

Summary slide link

ACM1: analyses for subgroups by HR status as well as ITT population needed for decision making

Company

- Provided subgroup analysis by HR status, but EMBRACA not powered for subgroups
- EMBRACA enrolled molecularly selected population; BRCA1/2 mutations account for about 4-6% of all BC cases in women and around 11-12% of cases in men.
- 'Clinical experts explained that there was no biological mechanism that would predict that HR status would affect the treatment effect of talazoparib in people with aBC' (DG 3.11)
- High unmet need in TNBC raises concerns of equity. TNBC can be more aggressive and harder to treat, resulting in poorer outcomes, with a lack of targeted treatment options.
- TNBC is more common in younger women and in black or Hispanic ethnic backgrounds.
- Notes potential 1.7 severity weighing for TNBC subgroup, as close to cut-off value:

Absolute shortfall (AS): 17.95 -1.02 = 16.93

Proportional shortfall (PS): (17.95-1.02)/17.95 = 0.943

Weight	AS	PS
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

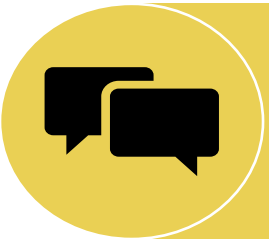
Summary slide link

Key issues: Populations and subgroups 2/2

ACM1: analyses for subgroups by HR status as well as ITT population needed for decision making

EAG

- EMBRACA was powered enough to detect differences in OS in the ITT population but not in subgroups.
- If nonsignificant OS gain is modelled in ITT regardless of this power, nonsignificant subgroup OS results should also be modelled.
- OS extrapolations in subgroups overly reliant on tails of EMBRACA trial; EAG explored projections compared with trial data.
    - OS projections are uncertain and favour talazoparib, particularly in TNBC subgroup; all ICERs should be considered optimistic.



Is the ITT population or subgroups by HR status appropriate for decision-making?
If considering subgroups, is the 1.7 severity modifier for TNBC appropriate?

Summary slide link

Key issues: Additional benefits of talazoparib

Company: talazoparib is innovative oral treatment

Company

- Lack of capacity within oncology departments (Association of Cancer Physicians 2023)
- Oral treatment with PFS improvement can minimise inpatient attendance and resource use
- [redacted] people eligible for talazoparib. This will be lower since TA886 recommended olaparib for eBC. Budget impact and associated absolute decision risk for this appraisal are low.

Breast Cancer Now and Met Up UK

- "Depending on intravenous chemotherapy regimen, patients can spend 2 days every week or every 3 weeks at hospital having bloods checked or taking treatment…hospital visits, with associated routine long waits are debilitating, time and energy draining, and take your soul; extremely difficult for patients who know their lives are already shortened by cancer."
- "As talazoparib is taken as a daily tablet, it can potentially mean fewer hospital visits are required compared to intravenous chemotherapy which is valued by patients."

Are there additional benefits of talazoparib that are not captured in modelling?

Summary slide link

Equality considerations

Company:

- BRCA mutations more common in certain ethnicities and population groups.
- TNBC is more common in younger women and in black or Hispanic ethnic backgrounds.
- 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:

- BRCA mutations 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.

Met up UK – response to DG:

- BRCA mutations more common in young women, Ashkenazi Jewish people and although BC is rare in males, it is more common in males with BRCA gene than other males.

Cost-effectiveness results: ACM2 summary results

EAG corrected errors in the company's revised base case, neutropenia and subsequent treatment cost, and some treatment costs. This resulted in a small increase in ICERs.

- All ICERs are reported in PART2 slides because they include confidential comparator discounts

- Analyses shown in part 2 include:
  - Company's base case
  - Committee's preferred analysis at ACM1 (company base case + equal PFS utilities)
  - Alternative PFS utilities and RBC transfusion rates
  - No OS benefit
  - BRCA testing costs
  - Subgroups

Summary

Key issues for discussion

- What are the committee's preferred assumptions?
  - OS modelling – slides 9 & 10
  - PFS utilities – slides 11 &12
  - RBC transfusion rates – slides 13 &14
  - BRCA testing – slides 15 &16
- What population, ITT or subgroups by HR-status, are appropriate for decision-making? [slides 17 & 18]
- Has talazoparib any additional benefits that are not included in the model? [slides 19]
- Are there any potential equality issues? [slide 20]

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Thank you.