For public handouts, no confidential information

Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy - STA

1st Appraisal Committee meeting

Clinical Effectiveness

Lead team: Jeremy Braybrooke, Ellen Rule, Pam Rees

ERG: BMJ TAG

NICE technical team: Irina Voicechovskaja, Zoe Charles

16 January 2018

Key issues: clinical effectiveness

- What are the committee's conclusions on the NOVA clinical trial that compared niraparib with placebo:
  - quality, risk of bias and generalisability?
- What are the committee's conclusions on the results of the trial for:
  - patients with a hereditary germline BRCA mutation (gBRCA cohort)?
  - patients without a hereditary germline BRCA mutation (non-gBRCA cohort)?
  - patients in the non-gBRCA cohort with homologous recombination deficiency-positive tumours (HRD-positive subgroup) given the experimental nature of the test used to assess HRD status?
- Can any conclusions be drawn about overall survival given the immaturity of the data?
- What is the importance of 'PFS2'?
- For the comparison of niraparib and olaparib is it appropriate to assume clinical equivalence of the two drugs?

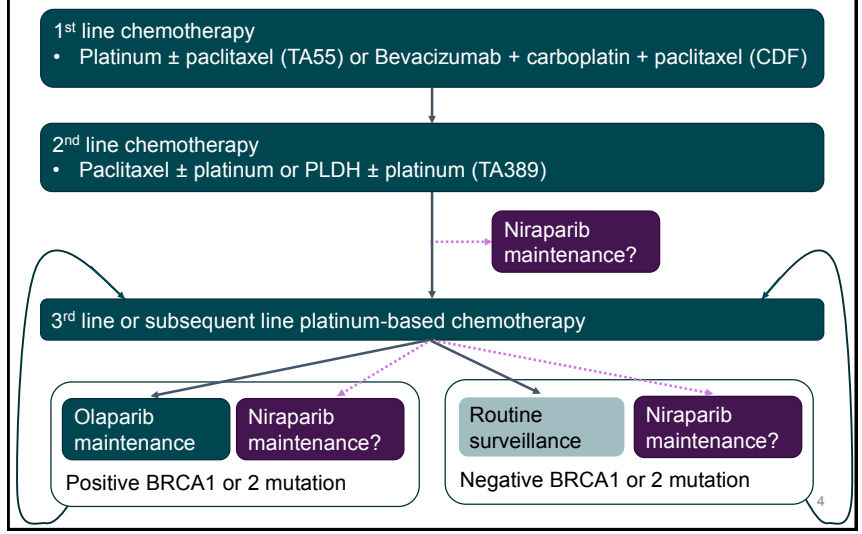
2

Ovarian cancer: disease background

- 6,198 diagnoses in England in 2015; incidence increases with age
- Main symptoms: persistent bloating, loss of appetite, pelvic or abdominal pain, increased urinary urgency/frequency
- Early stages can be asymptomatic or mimic symptoms of other diseases (leading to late diagnosis)
  - most people have advanced disease at diagnosis (58% have stage III or IV)
- 90% of ovarian cancers arise from epithelial cells; 70% of these are high-grade serous tumours
  - high-grade serous ovarian cancers defined histologically based on microscopic appearance and immunohistochemical findings
  - highly sensitive to chemotherapy but associated with a worse prognosis compared with other histologic subtypes of epithelial ovarian cancer
  - includes fallopian tube and primary peritoneum tumours
- ~15% of people with epithelial ovarian cancer have mutations in breast cancer susceptibility gene (BRCA) 1 or BRCA2
  - present in 0.2% of general population

3

Management of advanced platinum-sensitive ovarian cancer



4

Diagnostic testing in current practice

Breast cancer susceptibility gene mutation (BRCAmut)	• Blood testing for germline BRCA mutations (gBRCA) part of routine practice (some variability throughout the country)
	• Somatic testing not routine, but becoming more common
	• Everyone considered for niraparib would be tested because:
	  • NICE guideline for familial breast cancer (CG164) recommends testing people with ≥10% probability of having these mutations
	  • incidence of BRCA is >10% in people with high-grade serous ovarian tumours, the population in this appraisal

Homologous recombination DNA repair deficiency (HRD)	• HRD assessment could identify patients whose tumours are more likely to respond to niraparib treatment (in xenograft models, HRD negative tumours did not respond) • Experimental, not validated in clinical setting • Not currently routinely funded or available within the NHS

5

Clinician perspectives

- OS:PFS relationship 2:1: difficult to estimate the magnitude of the overall survival benefit with niraparib as affected by many factors but there is a clinically significant improvement
- Increase in median progression-free survival/time to first subsequent therapy of at least 4-6 months would be a clinically significant treatment response
- Germline testing: accepted part of standard management - many large centres offer testing at diagnosis; others at first relapse
- Somatic testing: not routinely available, limited use via commercial company
- HRD test: 2 tests available but both failed to discriminate between patients who would/would not benefit from therapy - considered experimental
- No data to support the use of niraparib as a first line maintenance treatment

6

Impact on patients and carers

- Ovarian cancer is often diagnosed unexpectedly
- *"Very difficult and frightening condition to live with." "Isolating"*
- UK survival rates for ovarian cancer are amongst the worst in the western world
- Ovarian cancer is frequently managed as a chronic condition rather than curative
- Women with advanced disease are more likely to face a future of recurrent ovarian cancer
- Current treatment is very debilitating, requiring extensive surgery and gruelling repeated chemotherapy
- *"Huge unmet need …from diagnosis to death!" "…treatment options are limited."*

7

Patients' view

- Niraparib is an oral medication taken at home
- It would *"significantly increase choice and diversity of drugs available to women with high-grade serious ovarian cancer and increase UK survival rates."*
- Increased choice and continued input from oncology teams offers significant psychological as well as health benefits
- *"If niraparib were approved for second line treatment, then women who progressed on it would still have several more options left for other types of chemotherapy drugs."*
- By prolonging remission and delaying the need for further chemotherapy to treat subsequent relapse, women will have a longer period of time without chemotherapy and an opportunity to live life relatively normally
- *"The interval between chemotherapy… is likely for many to outweigh the possible side effects associated with niraparib"*

8

Decision problem

Population	People who have recurrent, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy
Intervention	Niraparib
Comparators	• Routine surveillance • Olaparib (only for people with BRCA1 or BRCA2 mutations who have responded to the third or subsequent course of platinum-based chemotherapy)
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • PFS2 (i.e. PFS on next line of therapy) • Time to next line of therapy • AEs of treatment • HRQoL

The company note that the EMA recognise PFS2 as an important endpoint in ensuring that maintenance treatments do not impact the response to subsequent treatments, because this can negatively affect the potential OS benefit.

9

The technologies

	Niraparib	Olaparib
Marketing authorisation	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ***BRCA*-mutated (germline and/or somatic)** high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy
Mechanism of action	PARP inhibitor	
Administration & dosage	300 mg once daily (3 x 100 mg capsules) with or without food	400 mg twice daily (16 x 50 mg capsules) without food
Duration of treatment	Until disease progression	Until disease progression
Cost	Confidential patient access scheme approved (simple discount)	£3,550 per pack (28 days' treatments), free after 15 months (patient access scheme)
Pivotal trial	NOVA	Study 19

10

Phase III study: NOVA

Study design	Phase III randomised double blind placebo controlled trial including 10 UK centres
Population (n=553)	• Adults with platinum-sensitive, recurrent, high-grade, serous ovarian, fallopian tube, or primary peritoneal cancer • Previously received ≥2 platinum-based regimens • Responsive (partial or complete) to last platinum regimen
2 cohorts	With (n=203)/without (n=350) hereditary germline BRCA mutation, the latter including a HRD-positive subgroup
Technologies (crossover not permitted)	Niraparib 300 mg (n=372), Placebo (n=181)
	Continuous 28-day cycles (no breaks) until progression, unacceptable AEs, death, withdrawal/loss to follow-up
Primary endpoint	Progression-free survival (RECIST v1.1 blinded central review)
Key secondary endpoints	• Time to first and time to second subsequent therapy • Chemotherapy-free interval • Progression-free survival 2 • Overall survival • Quality of life (EQ-5D-5L)
Median follow up	16.9 months

BRCA, breast cancer susceptibility gene; RECIST, Response Evaluation Criteria in Solid Tumors

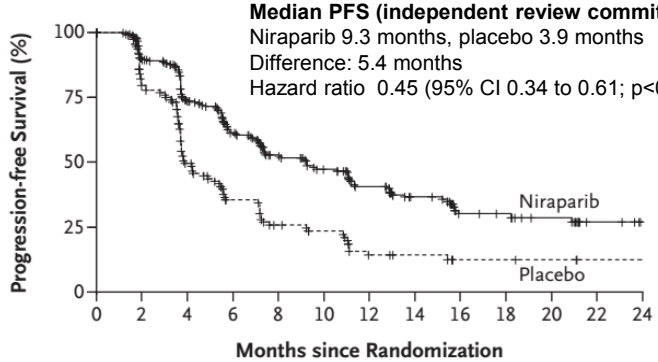
NOVA summary of baseline characteristics

Characteristic	Non-gBRCA		gBRCA 2L		gBRCA 3L+	
	Niraparib (n=234)	Placebo (n=116)	Niraparib (n=79)	Placebo (n=37)	Niraparib (n=58)	Placebo (n=28)
Median age, years (range)	63 (33, 84)	61 (34, 82)	56.6 (37, 83)	57.3 (38, 71)	57.1 (36, 76)	57.1 (41, 73)
Primary tumour site %						
Ovary	82.1	82.8	91.1	86.5	84.5	75.0
Peritoneum	10.3	6.9	3.8	2.7	6.9	17.9
Fallopian	7.7	9.5	5.1	10.8	8.6	7.1
Histologic subtype, %						
Serous	88.6	90.8	90.8	91.9	85.7	89.3
Endometrioid	6.1	4.6	2.6	8.1	10.7	0
Cancer stage at time of diagnosis %						
I or II	9.4	4.3	16.5	18.9	17.2	10.7
III	73.9	74.1	72.2	64.9	63.8	78.6
IV	16.2	20.7	11.4	16.2	19.0	10.7
Mean time since diagnosis, years	3.33	3.59	3.30	2.75	5.90	5.98

Source: table 10 company submission and table 5 of clarification response

NOVA primary endpoint: PFS non-gBRCA 2L+ cohort (ITT population)

Median PFS (independent review committee)
Niraparib 9.3 months, placebo 3.9 months
Difference: 5.4 months
Hazard ratio 0.45 (95% CI 0.34 to 0.61; p<0.001)



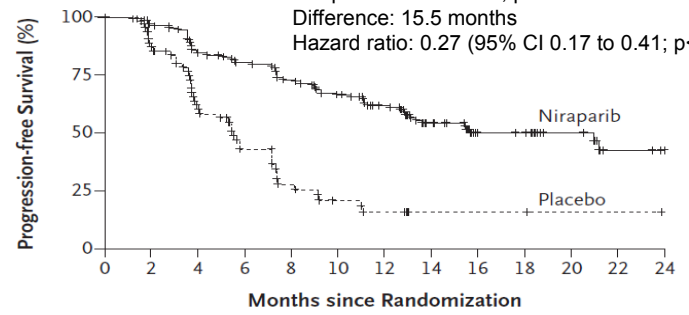
No. at Risk													
Niraparib	234	188	145	113	88	75	57	41	23	21	16	7	3
Placebo	116	88	52	33	23	19	10	8	4	4	3	1	1

Source: figure 6 company submission

13

NOVA primary endpoint: PFS gBRCA 2L+ cohort (ITT population)

Median PFS
Niraparib 21.0 months, placebo 5.5 months
Difference: 15.5 months
Hazard ratio: 0.27 (95% CI 0.17 to 0.41; p<0.001)



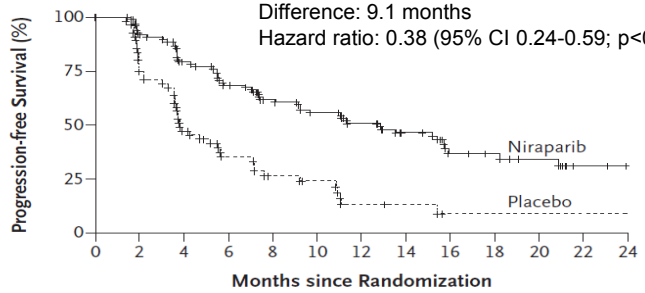
No. at Risk													
Niraparib	138	125	107	98	89	79	63	44	28	26	16	3	1
Placebo	65	52	34	21	12	8	6	2	2	2	1	1	0

Source: figure 4 company submission

14

NOVA primary endpoint: PFS non-gBRCA 2L+ cohort, HRD-positive subgroup

Median PFS
Niraparib 12.9 months, placebo 3.8 months
Difference: 9.1 months
Hazard ratio: 0.38 (95% CI 0.24-0.59; p<0.001)



No. at Risk

Niraparib	106	90	75	64	52	46	40	29	16	14	11	4	2
Placebo	56	41	26	16	11	9	4	3	1	1	1	1	1

Source: figure 5 company submission

15

Summary of results for PFS

Cohort/subgroup	Niraparib	Placebo	HR, (95% CI)
gBRCA cohort			
Number	138	65	
Median PFS, months (95% CI)	21.0	5.5	0.27 (0.17-0.41)
Difference, months	15.5		p<0.001
Non-gBRCA cohort			
Number	234	116	
Median PFS, months (95% CI)	9.3	3.9	0.45 (0.34-0.61)
Difference, months	5.4		p<0.001
HRD-positive subgroup of the non-gBRCA cohort			
Number	106	56	
Median PFS, months (95% CI)	12.9	3.8	0.38 (0.24-0.59)
Difference, months	9.1		p<0.001

Source: table 13 company submission

16

CONFIDENTIAL

Overall survival in the NOVA trial (Data cut 30th May 2016)

- Survival results are immature – fewer than 20% of patients in the intention-to-treat population had died at the latest analysis
  - 35 (19%) of all 181 patients randomised to placebo had died
  - 60 (16%) of all 372 patients randomised to niraparib had died

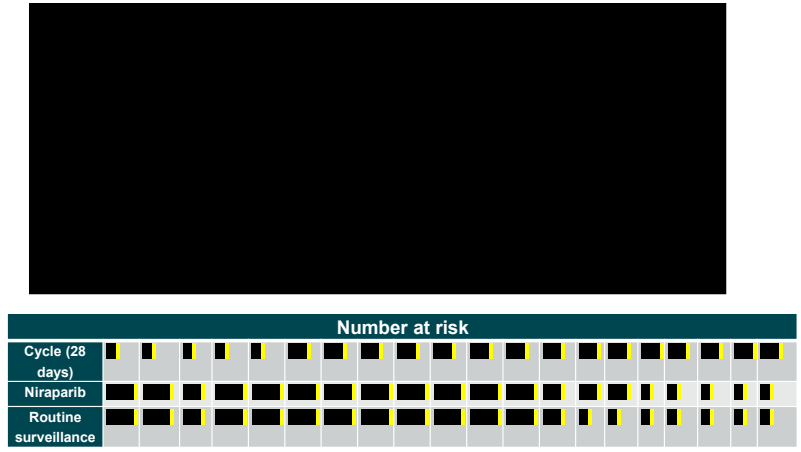
	non-gBRCA 2L+	gBRCA 2L+
Median overall survival	not reached	not reached
Hazard ratio (niraparib versus routine surveillance)	[redacted]	[redacted]
95% confidence interval	[redacted]	[redacted]

Source: page 8 clinical study report

17

CONFIDENTIAL

Overall survival in the NOVA trial: non-gBRCA 2L+ cohort (ITT population)



Source: figure 1 of the company submission appendix L

18

CONFIDENTIAL

Overall survival in the NOVA trial: gBRCA 2L subgroup (ITT population)

[redacted]

Number at risk																							
Cycle (28 days)																							
Niraparib																							
Routine surveillance																							

Source: figures 2 and 3 company submission appendix L

Progression-free survival 2 (PFS2)* and time to subsequent treatment

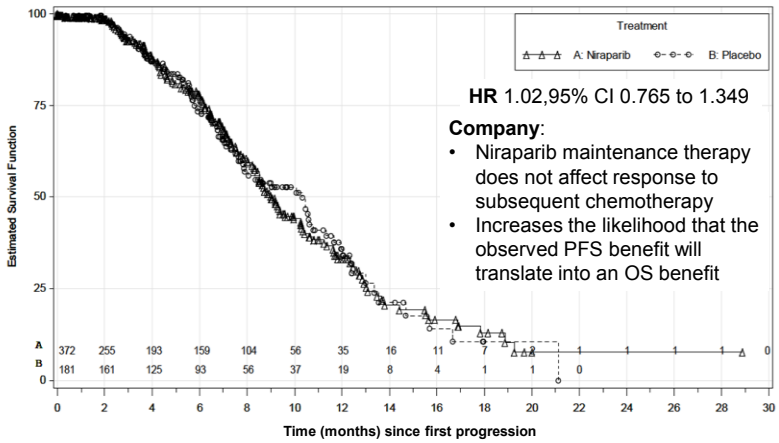
Endpoint	gBRCA (ITT)		Non-gBRCA (ITT)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
PFS2 (data immature)				
P value	0.006		0.03	
Hazard ratio (95% CI)	0.48 (0.28 to 0.82)		0.69, (0.49 to 0.96)	
Time to first subsequent treatment				
Median, months	21.0	8.4	11.8	7.2
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.31 (0.21 to 0.48)		0.55 (0.41 to 0.72)	
Time to second subsequent treatment (TSST) (data immature)				
P value	[redacted]		[redacted]	
Hazard ratio (95% CI)	[redacted]		[redacted]	

Italics show non-significant differences between treatments for non-gBRCA cohort

***PFS2**: time from randomisation to the date of progression during the next anti-cancer therapy after the study treatment, or until death by any cause*

Exploratory endpoint: PFS2-PFS1*

pooled gBRCAmut and non-gBRCAmut cohorts: niraparib vs placebo



HR 1.02,95% CI 0.765 to 1.349

Company:

- Niraparib maintenance therapy does not affect response to subsequent chemotherapy
- Increases the likelihood that the observed PFS benefit will translate into an OS benefit

*The time between progression after niraparib maintenance therapy/placebo and progression after receiving the next subsequent anti-cancer therapy. Source: figure 9 company submission

CONFIDENTIAL

Chemotherapy-free interval and subsequent platinum based chemotherapy

Endpoint	gBRCA		Non-gBRCA	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Chemotherapy free interval				
Median (months)	22.8	9.4	12.7	8.6
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.26 (0.17 to 0.41)		0.50 (0.37 to 0.67)	
Subsequent platinum based chemotherapy				
Subsequent therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent platinum based therapy n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report Table 17, adapted from company submission page 61, and clarification response A16

Adverse events and quality of life

- **Adverse events (AEs)**
- Most common AEs with niraparib: nausea, thrombocytopenia events, fatigue, anaemia events, constipation, neutropenia events, headache, lost appetite
- Grade ≥3 AEs: 74.1% (niraparib) and 22.9% (placebo)
  - Most common grade ≥3 AEs: thrombocytopenia events, anaemia events, neutropenia events, hypertension, and fatigue
- Few stopped treatment due to AEs: 14.7% (niraparib) and 2.2% (placebo)
  - 66.5% (niraparib) and 14.5% (placebo) of patients had ≥1 treatment interruption due to an AE
  - 68.9% (niraparib) and 5.0% (placebo) required dose reductions due to an AE
- Niraparib's relative dose intensity was 65%.
- **Health-related quality of life (HRQoL)**
- According to both measures (EQ-5D-5L and the Functional Assessment of Cancer Therapy – Ovarian Symptom Index [FOSI]), HRQoL was similar in both groups throughout the study and was maintained at pre-treatment levels

23

CONFIDENTIAL

Company's comparison of niraparib and olaparib

- Naïve comparison of PFS in trials (gBRCA 2L+ population):
  - niraparib improved PFS by a median of 15.5 months in NOVA
  - olaparib improved PFS by a median of 6.9 months in Study 19
  - median PFS was 21.0 months with niraparib and 11.2 with olaparib
- Following clarification, company presented a formal indirect comparison of PFS (gBRCA 2L+ population) using a fractional polynomial network meta-analysis - no statistically significant differences between groups
- Company's model assumed that niraparib and olaparib were equivalent

	Niraparib		Olaparib		Niraparib versus olaparib
Mnth	PFS	HR vs PBO	PFS	HR vs PBO	HR
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

24

ERG critique of clinical evidence

- NOVA trial was well conducted and considered to be at low risk of bias
- Baseline characteristics were well balanced between treatment groups within each of the cohorts
- Trial population was representative of patients who would be eligible for niraparib therapy in clinical practice
- PFS assessment by the Independent Review Committee (IRC) was not done concurrently with that of the trial investigators, which led to some patients being treated with niraparib beyond IRC-determined progression and others stopping early before IRC determined progression – may have an effect on OS
- Interim results for PFS2 and TSST show a substantially smaller difference between niraparib and placebo than for PFS
  - initial observed clinical benefit of niraparib does not seem to be maintained on subsequent treatment
- Concerned about the data presented due to inconsistencies in the Kaplan-Meier curve, which would inform the calculated hazard ratio
  - ERG exploratory analysis using data from the company submission showed that patients who had niraparib seemed to have a shorter PFS on subsequent therapy than patients who had placebo

25

ERG critique of clinical evidence

- Results for non-gBRCA HRD-positive subgroup may not be reliable as the HRD test to define this population has not been clinically validated and remains experimental, as acknowledged by company
- Naïve comparison of olaparib and niraparib:
  - ignores the benefits of randomisation in each trial
  - subject to the same biases as a comparison of independent cohort studies
  - NOVA and Study 19 have different study designs and baseline characteristics
- Indirect comparison of olaparib and niraparib (provided at clarification):
  - adjusted indirect comparison more appropriate than naïve
  - OS not included due to immaturity of data
  - based on fractional polynomials which does not rely on the proportional hazards assumption being met; the company did not explain the rationale for choosing assumptions and not clear what model was used. ERG unable to reproduce analyses
  - ERG used alternative codes and explored additional powers which resulted in better statistical fit than company's chosen fractional polynomials – no statistically significant differences between olaparib and niraparib

26

Key issues: clinical effectiveness

- What are the committee's conclusions on the NOVA clinical trial that compared niraparib with placebo:
  - quality, risk of bias and generalisability?
- What are the committee's conclusions on the results of the trial for:
  - patients with a hereditary germline BRCA mutation (gBRCA cohort)?
  - patients without a hereditary germline BRCA mutation (non-gBRCA cohort)?
  - patients in the non-gBRCA cohort with homologous recombination deficiency-positive tumours (HRD-positive subgroup) given the experimental nature of the test used to assess HRD status?
- Can any conclusions be drawn about overall survival given the immaturity of the data?
- What is the importance of 'PFS2'?
- For the comparison of niraparib and olaparib is it appropriate to assume clinical equivalence of the two drugs?

27