Characterization of long-term responders to olaparib from study D0810C000019

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BACKGROUND

- Olaparib is the most studied PARP inhibitor
- Olaparib maintenance monotherapy significantly prolonged PFS in patients with platinum-sensitive relapsed serous ovarian cancer
  - Patients with a *BRCA* mutation (*BRCA*m) receive greater treatment benefit
  - Non-mutation carriers may also benefit from olaparib therapy

OBJECTIVES

• To clinically, molecularly and genomically characterize the long (>2 years) and short-term (<3 months) responders on olaparib maintenance

• Focus on the pivotal study D0810C000019: Phase II randomised, double blind, study of olaparib in patients with platinum sensitive relapsed serous ovarian cancer following treatment with two or more platinum containing regimens

METHODS

- **Retrospective molecular analysis of prospectively collected specimens and data**
  - Clinical data:
    - Previous lines of chemotherapy, initial stage, platinum free interval
    - Response to platinum chemotherapy according RECIST 1.1 at the time of olaparib maintenance
  - Germline *BRCA1/2* testing by Myriad Genetics
  - Molecular variables from archival tumor samples
    - Myriad Genetics:
      - Homologous Recombination Deficiency (HRD) score (positive ≥42)
      - *BRCA1* methylation
    - Foundation Medicine: FoundationOne® panel (entire coding sequence of 315 cancer-related genes plus select introns from 28 genes)
- **Statistical analysis**

Fisher's exact test to test the association between presence and absence of any factor comparing short-term vs long-term responders

RESULTS

Patients on olaparib maintenance therapy

Treatment duration	Clinical Status				*BRCA* Status		
Patients All (n=136)	**No prior chemo**	**Initial FIGO** (n pts)	**RECIST at baseline** (n)	**Platinum sensitivity status** (n)	***BRCA*m** (n=74)	***BRCA* wt/vus** (n=57)	***BRCA* missing** (n=5)
< 3 months 21 pts (15%)	2.8 [2-5]	1 IIb / 6 IIIi 2 IIIb / 11 IIIc 1 IV	PR: 16 CR: 5	6-12 mths: 9 > 12 mths: 12	10 (14%) 7 *BRCA1*	9 (16%)	2
>2 years 32 pts (24%)	2.9 [2-8]	2 Ic / 1 IIc 26 IIIc / IV 3	PR: 14 CR: 18	6-12 mths: 11 > 12 mths: 21	21 (28%) 9 *BRCA1*	11 (19%) 2 vus	0

CR: complete response; m, mutation; mths: months; No: number; PR: partial response; pts: patients; ud: undetermined; vus, variant unknown significance; wt, wild type

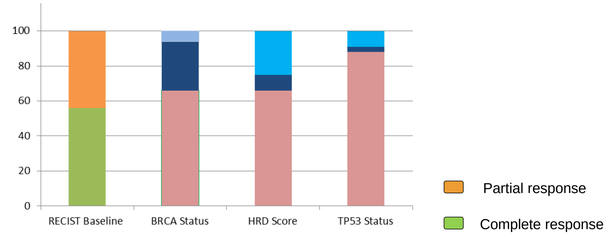
	Short-term responders							Long-term responders						
Short and long term responders	**All pts** (n=21)	**HRD Score positive** (n=9/ 43%)	**HRD Score negative** (n=5/ 24%)	**HRD Score missing** (n=7/ 33%)	**TP53 mutations** (n=12/ 57%)	**TP53 wildtype** (n=4/ 19%)	**TP53 missing** (n=5/ 24%)	**All pts** (n=32)	**HRD Score positive** (n=21/ 66%)	**HRD Score negative** (n=3/ 9%)	**HRD Score Missing** (n=8/ 25%)	**TP53 mutations** (n=28/ 88%)	**TP53 wildtype** (n=1/ 3%)	**TP53 Missing** (n=3/ 9%)
***BRCA*m** (n=31)	10 (48%)	6 (67%)	1 (20%)	3 (43%)	7 (58%)	1 (25%)	2 (40%)	21 (66%)	17 (81%)	2 (67%)	2 (25%)	21 (75%)	0	0
***BRCA*vus** (n=2)	0	–	–	–	–	–	–	2 (6%)	2 (9.5%)	0	0	2 (7%)	0	0
***BRCA*wt** (n=18)	9 (43%)	2 (22%)	3 (60%)	4 (57%)	5 (42%)	3 (75%)	1 (20%)	9 (28%)	2 (9.5%)	1 (13%)	6 (75%)	5 (18%)	1 (100%)	3 (100%)
***BRCA*missing** (n=2)	2 (9%)	1 (11%)	1 (20%)	0	0	0	2 (40%)	0	–	–	–	–	–	–

Patients on placebo maintenance therapy

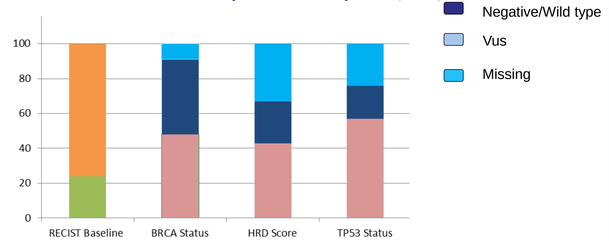
Treatment duration	Clinical Status				*BRCA* Status		
Patients All (n=129)	**No prior chemo**	**Initial FIGO** (n pts)	**RECIST at baseline** (n)	**Platinum sensitivity status** (n)	***BRCA*m** (n=62)	***BRCA* wt/vus** (n=61)	***BRCA* missing** (n=6)
< 3 months 40 pts (31%)	2.8 [2-8]	1 Ic / 2 IIc 1 IIIi / 5 IIIb 21 IIIc / 8 IV	PR: 25 CR: 15	6-12 mths: 22 > 12 mths: 18	19 (31%) 16 *BRCA1*	18 (30%)	3
>2 years 5 pts (4%)	2 [2]	5 IIIc	PR: 1 CR: 4	6-12 mths: 1 > 12 mths: 4	5 (8%) 4 *BRCA1*	0	0

	Short-term responders							Long-term responders						
Short and long term responders	**All pts** (n=40)	**HRD Score positive** (n=18/ 45%)	**HRD Score negative** (n=11/ 27.5%)	**HRD Score missing** (n=11/ 27.5%)	**TP53 mutations** (n=29/ 73%)	**TP53 wildtype** (n=1/ 2%)	**TP53 missing** (n=10/ 25%)	**All pts** (n=5)	**HRD Score positive** (n=4/ 80%)	**HRD Score negative** (n=0)	**HRD Score Missing** (n=1/ 20%)	**TP53 mutations** (n=4/ 80%)	**TP53 wildtype** (n=1/ 20%)	
***BRCA*m** (n=24)	19 (48%)	13 (72%)	1 (9%)	5 (46%)	16 (55%)	0	3 (30%)	5 (100%)	4 (100%)	–	1 (100%)	4 (100%)	1 (100%)	
***BRCA*wt** (n=18)	18 (45%)	5 (28%)	10 (91%)	3 (27%)	13 (45%)	1 (100%)	4 (40%)	0	0	–	0	0	0	
***BRCA* missing** (n=3)	3 (7%)	0	0	3 (27%)	0	0	3 (30%)	0	–	–	–	–	–	

Markers of long-term response to olaparib (n=32)



Markers of short-term response to olaparib (n=21)



Univariate analysis

- Predictive markers of long-term response to olaparib
  - Complete response at the time of olaparib maintenance (p=0.026)
  - HRD status (p=0.026) associated with long term responders
  - Long-term group: trend for the presence of *TP53* mutation (p=0.051)
    - Long term responders: 28/29 pts with *TP53* mutations (97%)
    - Short term responders: 12/16 pts with *TP53* mutations (75%)
      - ➔ Pathology review on-going
- These factors did not discriminate the long versus short term responders in the placebo group

BRCA1 Methylation

All Patients on placebo/olaparib maintenance therapy

- Long-term responders: 27/37 long-term pts had *BRCA1* methylation status available and none were methylated
- Short-term responders: 42/61 short-term pts had *BRCA1*methylation status available and 8 (19%) had *BRCA1* methylation

Genome sequencing – Long-term responders to olaparib

Somatic mutations were found in all the long-term responder patients, with most of them identified with at least 2 mutations

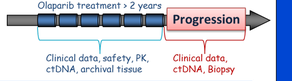
- Most commonly *TP53* and *BRCA* mutations
- Other type of mutations

ARID1A/ PPP2R1A	NF2 / Rb1	BRIP1	VHL	FLT3
PIK3R1	PTEN	CDK12	NOTCH1	CDH1/ ARID1A
ATM	NF1	AXL	MAP3K1/Rb1	CSF1R

- Amplification observed in at least 2 pts: Myc (4 pts), CCNE1 (3 pts), MCL1 (3 pts), FGF (3 pts) and KRAS (2 pts)

CONCLUSION

- A significant numbers of patients with recurrent advanced ovarian cancer have prolonged benefit from olaparib
- Markers of long-term sensitivity to olaparib maintenance
  - ➢ Complete response to platinum-based chemotherapy
  - ➢ mBRCA and HRD
- *TP53* needs further investigations
- Methylation of *BRCA1* seems to not confer same degree of *BRCA* like phenotype
- Prospective evaluation: Olala protocol



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