

# Årsmøde DGCG 5. april 2018



Contents lists available at [ScienceDirect](#)

## Cancer Treatment and Research Communications

journal homepage: [www.elsevier.com/locate/ctarc](http://www.elsevier.com/locate/ctarc)



Veliparib and topotecan for patients with platinum-resistant or partially platinum-sensitive relapse of epithelial ovarian cancer with BRCA negative or unknown BRCA status



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# Introduction – relapse of epithelial ovarian cancer

- Recurrence of epithelial ovarian cancer in the majority of patients within 3 years
- Eventually all patients become platinum-resistant
- Few treatment options with limited efficiency (< 20%)
- E.g **topoisomerase I-inhibitor topotecan**
- Induces temporary ssDNA breaks

# Introduction – PARP inhibitors

- PARPi initially proposed as chemotherapy sensitizers
- PARP enzyme repairs ssDNA breaks
- PARPi interfere with DNA repair and replication by several mechanisms
- Numerous different PARPi approved

# Hypothesis

- Can co-administration of veliparib with topotecan enhance anti-tumor effect in **non-*BRCA1/2* patients** with relapse of epithelial ovarian cancer?

# End points

- MTD (maximum tolerated dose)
- DLT (dose limiting toxicity)
- Identify dose for phase II
- Rate of response to combination treatment (phase II)
  
- *PFS*
- *OS*
- *Safety and toxicity*

# Study design phase I + II

Enrollment

Treatment

End of study

Platinum resistant or partially sensitive recurrent ovarian cancer

*BRCA1/2* germline test: negative (unknown status)

Phase I

MTD:  
Veliparib **30 mg. BID** (day 1-3, 8-10, 15-17)

Topotecan **2 mg/m<sup>2</sup>** (day 2, 9 and 16)  
q 28 days

Phase II

Veliparib + topotecan  
q 28 days

Disease progression by RECIST 1.1 or GCIG CA-125 criteria

Evaluation q three cycles

Characteristics		Value
<b>N = 27</b>		
<b>Age – years</b>	Median Range	56.0 35.8-73.5
<b>Histological tumor type – N (%)</b>	Serous adenocarcinoma <i>HGSC</i> <i>LGSC</i> Not graded/unknown Non-serous <i>Endometrioid</i> <i>Clear cell carcinoma</i>	24 (88.9) 17 (63.0) 1 (3.7) 6 (22.2) 3 (11.1) 1 (3.7) 2 (7.4)
<b>ECOG performance status – N (%)</b>	0 1 2	17 (63.9) 9 (33.3) 1 (3.7)
<b>Number of previous treatment regimens – N (%)</b>	1 2 3 ≥ 4	0 7 (25.9) 6 (22.2) 14 (51.9)
<b>Baseline CA-125 kU/L</b>	Median Range	504 16-21575
<b>Platinum sensitivity – N (%)</b>	Partially sensitive Resistant	2 (7.4) 25 (92.6)
<b>No. of treatment cycles</b>	Median Range	3 1-12

# Study results – response rates

125 RECIST N = 27	GCIG CA- N=27	PR (RE) n	SD n	PD n	NE n	Total n	Disease Control n (%)
CR n		0	0	0	0	0	0
PR (RE) n		0	0	0	0	0	0
SD n		1	5	1	2	9	8
PD n		1	8	4	0	13	0
NE n		0	2	2	1	5	2
Total n		2	15	7	3	27	-
Disease control n (%)		1	7	0	2	-	10 (37.0)

# Study results – toxicity

Adverse event	Grade 1-2 – no.(%)	Grade 3-4 – no. (%)
Fatigue	13 (48.1)	2 (7.4)
Dizziness	7 (25.9)	0
Alopecia	7 (25.9)	0
Stomatitis	2 (7.4)	0
Anorexia	9 (33.3)	1 (3.7)
Nausea	8 (29.6)	2 (7.4)
Vomiting	7 (25.9)	1 (3.7)
Diarrhea	8 (29.6)	0
Constipation	5 (18.5)	1 (3.7)
Neuropathy – sensory	6 (22.2)	0
Seizure	4 (14.8)	0
Skin toxicity	2 (7.4)	0
Edema	8 (29.6)	0
Febrile neutropenia	1 (3.7)	1 (3.7)
Fever without neutropenia	5 (18.5)	0
Infection	3 (11.1)	6 (22.2)
Anaemia	22 (81.5)	0
Neutropenia	6 (22.2)	3 (11.1)
Trombocytopenia	8 (29.6)	0
Hypomagnesaemia	11 (40.7)	0
Hypocalcaemia	3 (11.1)	0
Abdominal pain	15 (55.5)	2 (7.4)
Pain unspecified	7 (25.9)	1 (3.7)
Dyspnea	2 (7.4)	0

# Conclusion

- Veliparib in combination with topotecan for recurrent epithelial ovarian cancer in non-*BRCA1/2* germline mutation carriers was a safe treatment regimen
- Best clinical response to the combination treatment was stable disease

# Perspectives

- PARP inhibitors have shown promising response rates in certain populations of epithelial ovarian cancer (including patients with germline *BRCA1/2* mutations, high-grade serous carcinomas, platinum-sensitive disease)
- A non-*BRCA1/2* homologous recombination deficient population sensitive to PARP inhibition is most likely *not* identified among platinum-resistant epithelial ovarian cancers

# Tak til vejledere og samarbejdspartnere

- Professor, dr. med. Anders Jakobsen, Onkologisk Afdeling, Vejle Sygehus
- Professor, ph.d. Karina Dahl Steffensen, Onkologisk Afdeling, Vejle Sygehus
- Læge Hanne Kanstrup, Onkologisk Afdeling, Vejle Sygehus



