Årsmøde DGCG 5. april 2018

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: 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

Mette Hjortkjær[a,b,c,d,*], Hanne Kanstrup[a], Anders Jakobsen[a,c], Karina Dahl Steffensen[a,c]

[a] Department of Oncology, Vejle Hospital, Kabbeltoft 25, DK-7100 Vejle, Denmark
[b] Department of Gynaecology and Obstetrics, Aalborg University Hospital, Reberbansgade, DK-9000 Aalborg, Denmark
[c] Institute of Regional Health Research, University of Southern Denmark, Winsløwparken 19-3, DK-5000 Odense, Denmark
[d] Department of Gynaecology and Obstetrics, Viborg Hospital, Heibergs Allé 4, 8800 Viborg, Denmark

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

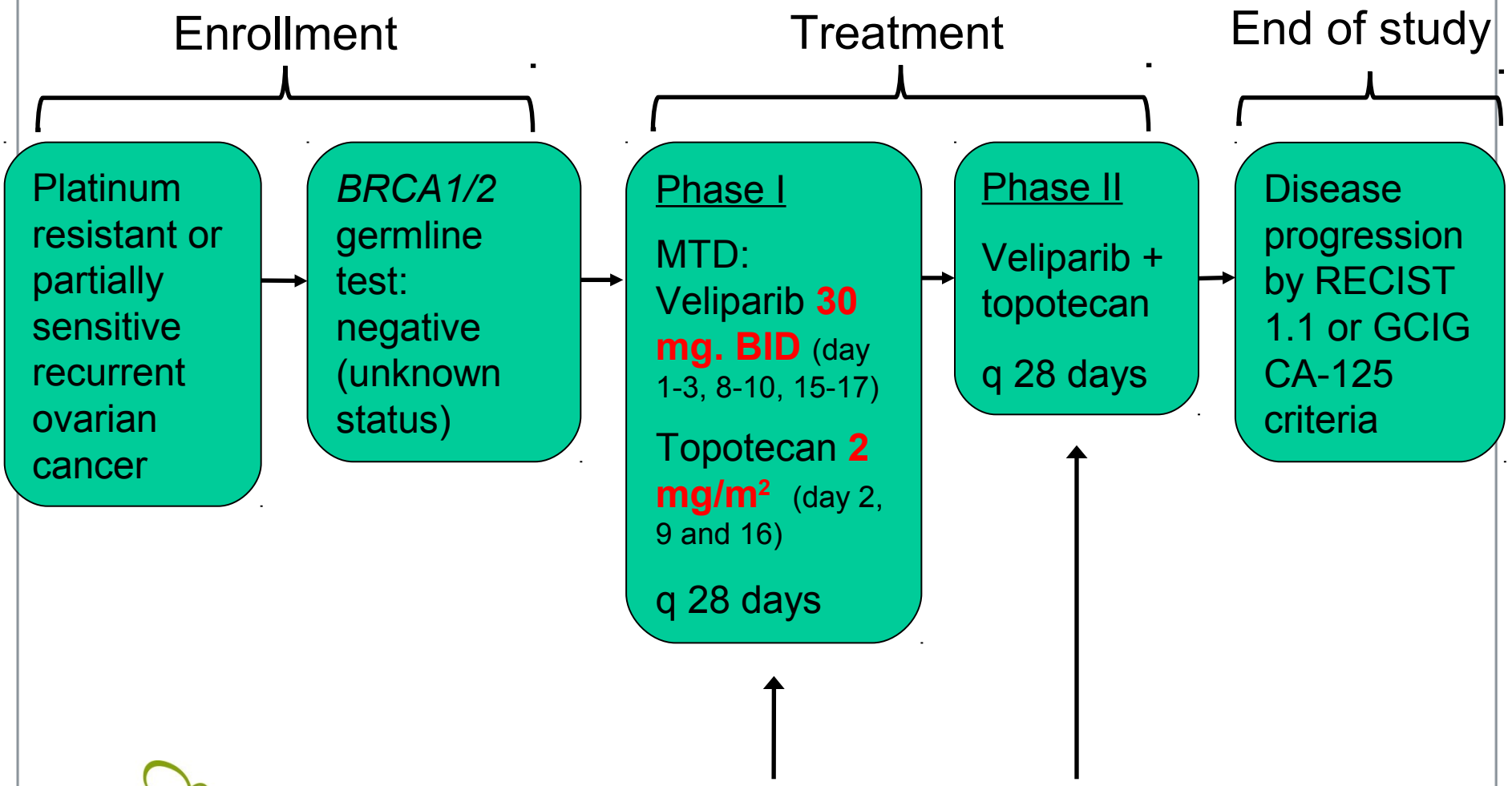
- Can co-administration of veliparib with topotecan enhance anti-tumor effect in **non-*BRCA1/2* patients** with relapse of epithelial ovarian cancer?

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



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

Study results – response rates

GCIG CA-125 N=27 / RECIST 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

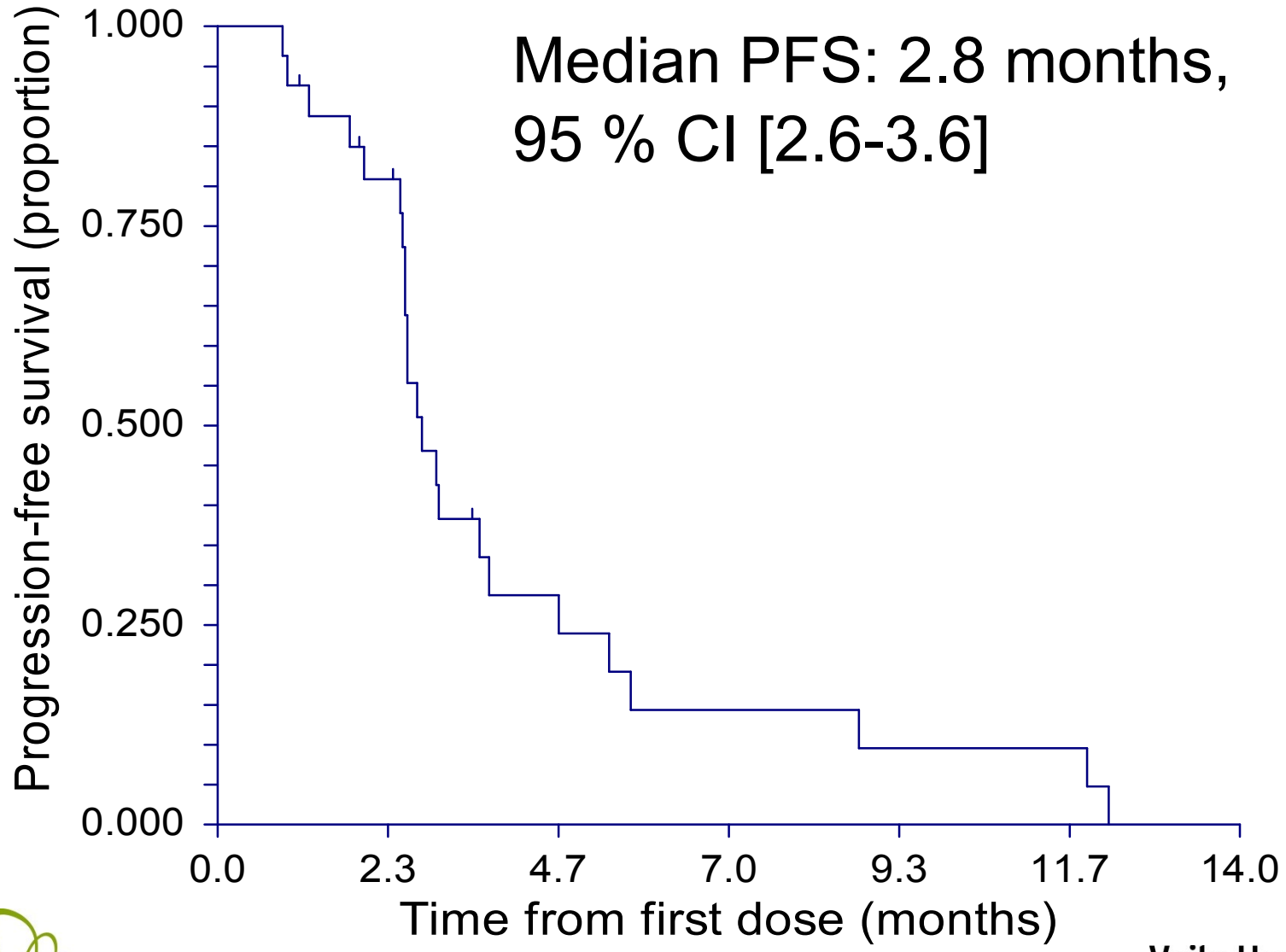
Perspectives

- 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

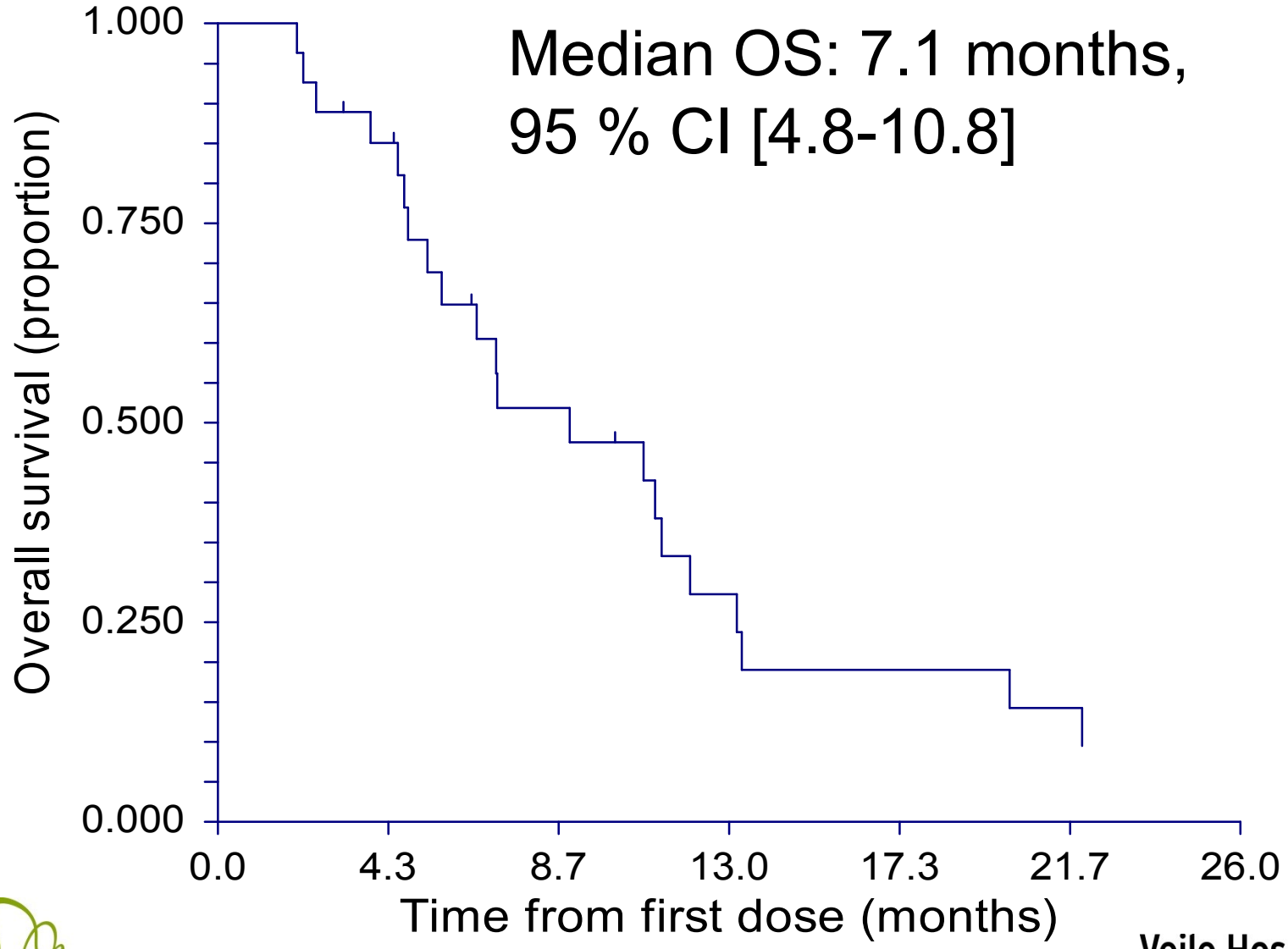
Tak til vejledere og samarbejdspartnere

- 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



Region of Southern Denmark

Vejle Hospital
- part of Lillebaelt Hospital



Region of Southern Denmark

Vejle Hospital
- part of Lillebaelt Hospital