The Israeli Society of Gynecologic Oncology
החברה הישראלית לגינקולוגיה אונקולוגית

Role of PARP Inhibiton and future directions

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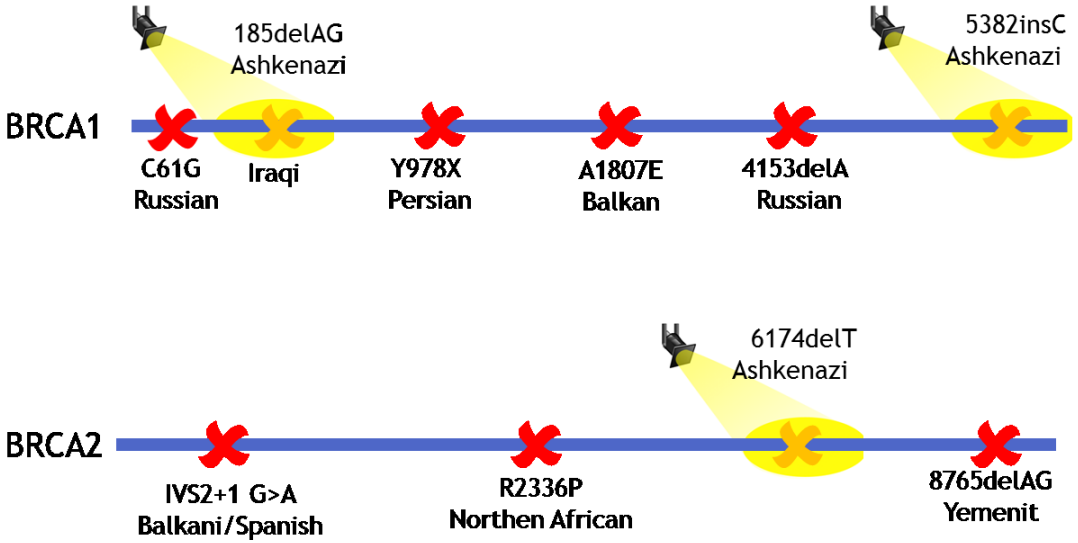
Disclosure

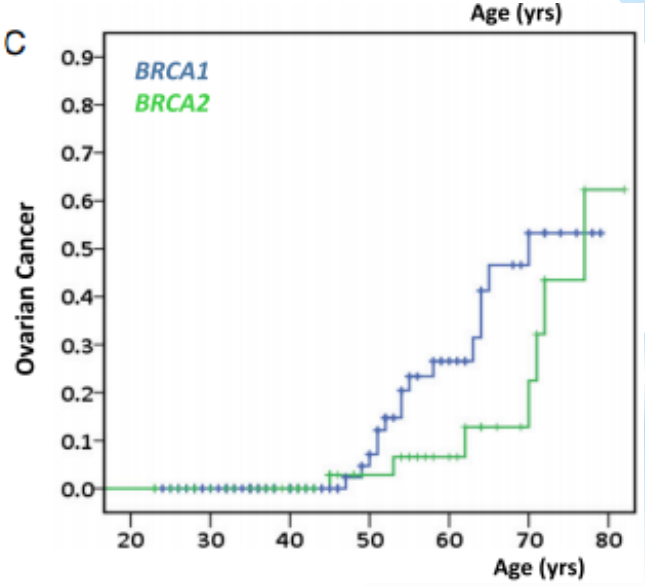
* Travel grant for congress from Astra-Zeneca and Roche

* Remuneration for attending Advisory Boards of Astra-Zeneca

BrCa mutations in Israel

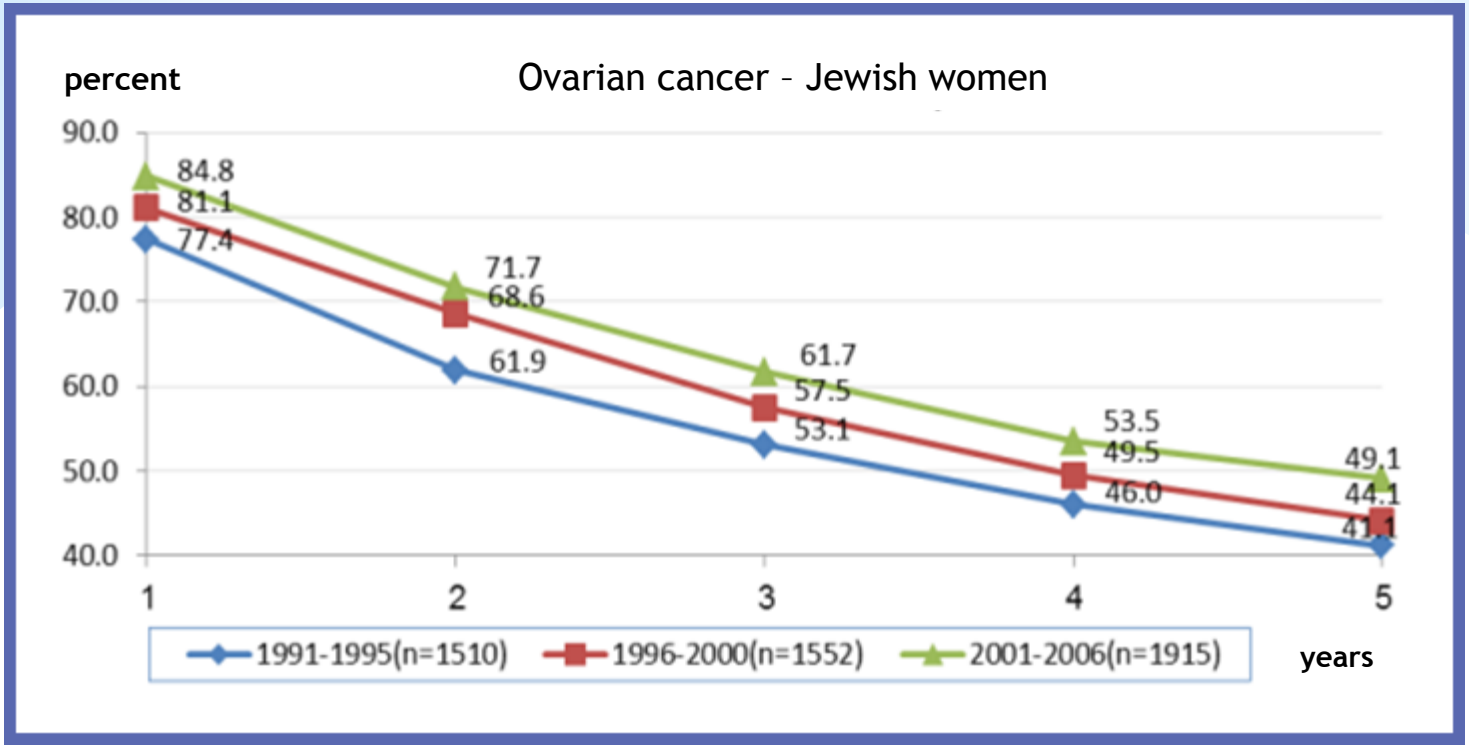
* Exceptional reservoir of mutation carriers:
  - confirmed carriers ~8,000
  - estimated number ~16,000





Gabai-Kapara et al, Proc Natl Acad Sci U S A. 2014 Sep

Survival - ovarian cancer patients in Israel



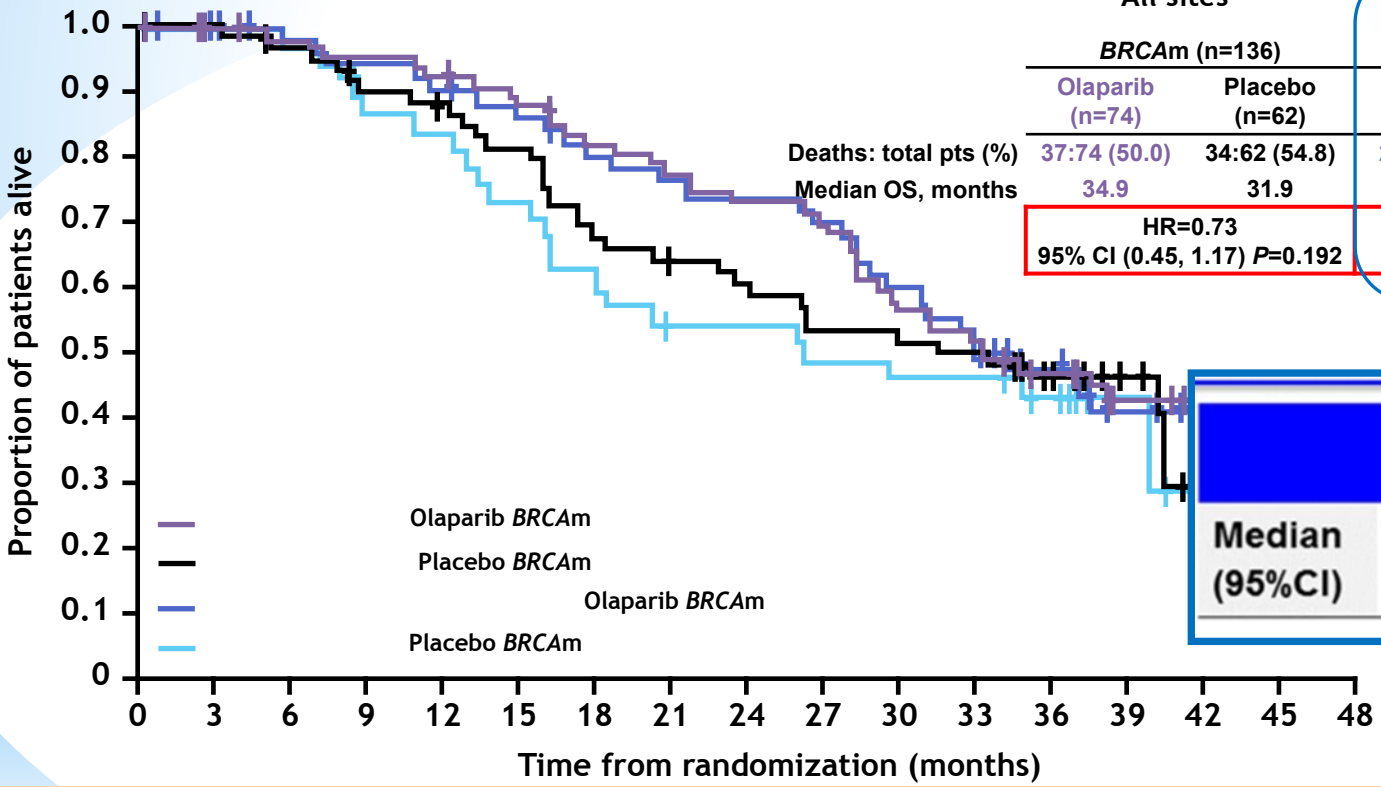
30-40% of Ashkenazi Jewish ovarian cancer patients are BrCa mutation carriers

Survival trends in israel, Israel MOH Cancer registry, 2015
Beller et al, Gyncol Oncol 1997

Israeli participation in PARP inhibitor trials

study	drug	No pts	remarks
012	Olaparib	24 pts	25% of study pts
019	Olaparib	28 pts	20% of Gm carriers
042	Olaparib	136 pts	46% of study pts
ARIEL1	Rucaparib	13 pts	33% of study pts
SOLO2	Olaparib	22 pts	
TESARO NOVA	Niraparib	21 pts	
M13-694	Veliparib	ongoing	
ENGOT-OV26	Niraparib	ongoing	
SOLO3	Olaprib	ongoing	

Exploratory analysis of OS with PARPi sites excluded



	All sites		PARPi excluded	
	*BRCA*m (n=136)		*BRCA*m (n=97)	
	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=40)
Deaths: total pts (%)	37:74 (50.0)	34:62 (54.8)	28:57 (49.1)	22:40 (55.0)
Median OS, months	34.9	31.9	34.9	26.6
	HR=0.73 95% CI (0.45, 1.17) *P*=0.192		HR 0.52 95% CI 0.28–0.97 *P*=0.039	

	Olaparib (N=53)	Placebo (N=43)
Median (95%CI)	11.2 mo (8.3, NC)	4.1 mo (2.9, 5.1)

Olaparib accepted by EMEA for maintenance treatment

For ovarian platinum sensitive patients

Ledermann , NEJM 2012 Matulonis et al , SGO 2015

Olaparib for advanced cancer – study 42

Response status, n (%)	Tumour type					
	Ovarian (n=193)	Breast (n=62)	Pancreas (n=23)	Prostate (n=8)	Other (n=12)	Total (n=298)
Tumour response rate	60 (31.1)	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)	78 (26.2)
CR*	6 (3.1)	0	1 (4.3)	0	0	7 (2.3)
PR*	54 (28)	8 (13)	4 (17)	4 (50)	1 (8.3)	71 (23.8)
SD ≥8 weeks	78 (40)	29 (47)	8 (35)	2 (25)	7 (58)	124 (42)
SD	64 (33)	22 (36)	5 (22)	2 (25)	6 (50)	99 (33)
Unconfirmed PR†	12 (6)	7 (11)	3 (13)	0	1 (8.3)	23 (8)
PD‡	41 (21)	23 (37)	9 (39)	2 (25)	3 (25)	78 (26)
RECIST progression	33 (17)	16 (26)	6 (26)	1 (13)	3 (25)	59 (20)
Early death§	8 (4)	7 (11)	3 (13)	1 (13)	0	19 (6)
Not evaluable	14 (7)	2 (3)	1 (4)	0	1 (8.3)	18 (6)
No follow-up assessments	12 (6)	2 (3)	1 (4)	0	0	15 (5)
SD <8 weeks	2 (1)	0	0	0	1 (8.3)	3 (1)

80% of ovarian cancer patients – 3+ lines of chemotherapy

Kaufman et al , JCO 2015

Olaparib for heavily pre-treated ovarian cancer patients - study 42

- 167 patients with measurable disease
- 80% of patients had 3+ lines of treatment (3-14 lines)

	Platinum sensitive (39)	Platinum resistant (81)	Pltinum refractory (14)	All patients (134)
Response rate	46%	29%	14%	34%
Duration of response	8.2 m	8.0 m	na	8.0 m

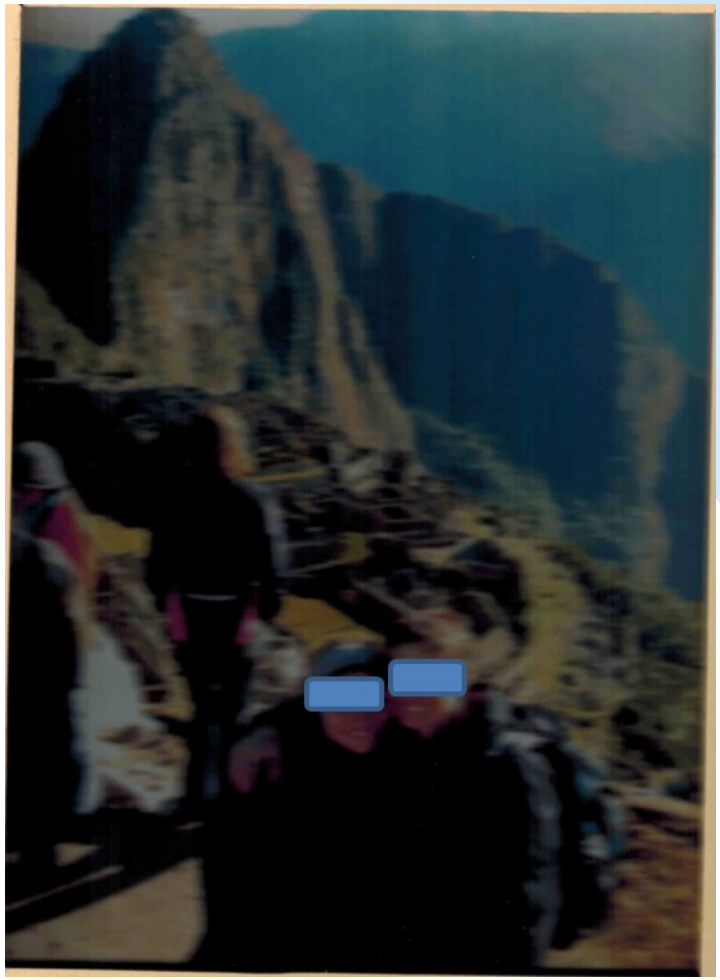
Olaparib accepted by FDA for advanced line treatment

Domchek et al, Gynecol Oncol , in press

Quality Of Life

Year 3 of Olaparib

(Platinum resistant)



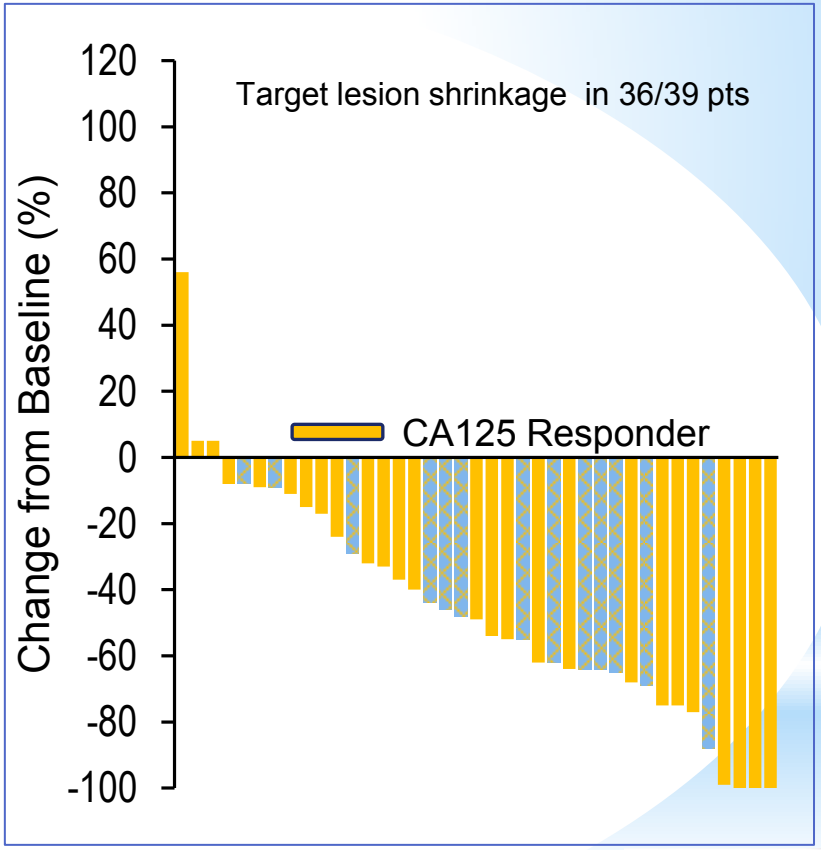
Long term responders
Treatment > 2 Years – 13 pts
Treatment > 3 years – 4 pts
Treatment > 4 years – 2

Domchek et al, Gynecol Oncol , in press

ARIEL1 – phase 1-2 study : Rucaprib for recurrent platinum sensitive patients

* Multi center study
* Platinum sensitive, prior 2-4 lines
* Primary end point – response rate

Overall best response, n (%)	N=39*
RECIST	
CR	3 (8)
PR**	23 (59)
SD	11 (28)
PD	2 (5)
RECIST and/or CA-125	30 (77)
Disease Control Rate, n (%)	
DCR (CR, PR, SD >24 weeks)	34 (87)



Shapira-Frommer et al , ASCO 2015

Conclusions and future directions

* PARP inhibitors show efficacy both in treatment and maintenance of ovarian cancer in BrCa mutated tumors

* About half of the Israeli ovarian cancer patients (germline + somatic mutations) may largely benefit of PARP inhibitors

* Further studies are needed to define the exact role of the PARP inhibitors in the course of disease

* Combination with other drugs may enhance the efficacy of PARP inhibitors (chemotherapy, anti-angiogenic agents, checkpoint inhibitors and others)

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