Targeted Therapies in Gynecological Cancers

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Disclosures

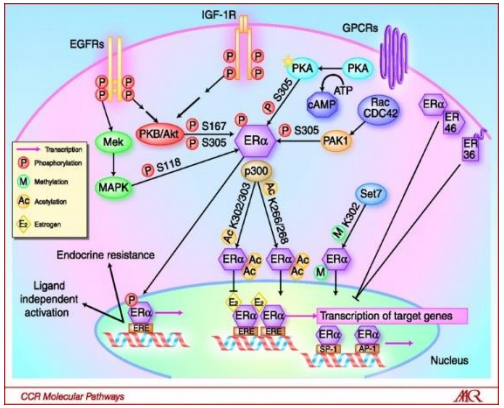
- Advisory Boards- Astra Zeneca, Clovis, Roche, Pfizer
- Honoraria -Astra Zeneca, Pfizer, Roche

Targeted Therapies in Gynecological Cancers

- Broad topic- Brief overview
- Hormonal therapies – prototype of a targeted therapy- long history, but potential still to be realized
- Focus on **angiogenesis inhibitors and PARP inhibitors**
- Horizon scanning- molecular targets- new agents
- Challenges with Trial Design
- Collateral Damage- adverse events and health economics

Hormonal therapies as Targeted Therapy in Gynaecological Cancer

- Hormonal therapy - a molecular targeted treatment strategy
- Inadequately investigated
- Relatively cheap and out of patent
- Suitable for selected patient subsets- not economically attractive to “Pharma”
- Potential yet to be recognised



Ines Barone et al. Clin Cancer Res 2010;16:2702-2708

Hormone Receptor Status in Epithelial Ovarian Cancer

Lancet Oncol 2013; 14: 853–62

	High-grade serous carcinoma (n=1742)	Low-grade serous carcinoma (n=110)	Mucinous carcinoma (n=207)	Endometrioid carcinoma (n=484)	Clear-cell carcinoma (n=390)
PR status					
Data available	1661	101	195	460	363
Negative	1144 (69%)	43 (43%)	163 (84%)	150 (33%)	334 (92%)
Weak	393 (24%)	25 (25%)	15 (8%)	106 (23%)	18 (5%)
Strong	124 (7%)	33 (33%)	17 (9%)	204 (44%)	11 (3%)
ER status					
Data available	1691	104	197	475	381
Negative	326 (19%)	13 (13%)	156 (79%)	111 (23%)	307 (81%)
Weak	347 (21%)	17 (16%)	10 (5%)	78 (16%)	22 (6%)
Strong	1018 (60%)	74 (71%)	31 (16%)	286 (60%)	52 (14%)
ER and PR status					
Data available	1610	95	185	451	354
ER negative/PR negative	254 (16%)	9 (9%)	142 (77%)	83 (18%)	280 (79%)
ER negative/PR positive	52 (3%)	2 (2%)	5 (3%)	20 (4%)	6 (2%)
ER positive/PR negative	857 (53%)	32 (34%)	14 (8%)	64 (14%)	46 (13%)
ER positive/PR positive	447 (28%)	52 (55%)	24 (13%)	284 (63%)	22 (6%)

Implications/ Future Directions

- ER and PR positivity identifies a better prognostic subset in HGSOC and EC
- The magnitude of benefit similar to survival advantage in BRCA population
- ? Also predictive – response to hormonal therapies
- How can we identify the subset who are most likely to respond to hormonal therapies
- Many potential options that could be explored
- Not confined to OC and EC – Endometrial Stromal Sarcoma /Granulosa Cell

Phase 2 studies of Letrazole in EOC

Table 2. Efficacy data in 42 patients

Type of response	Number of patients (%)
CA125	
Response	7 (17)
Less than twice baseline at 6 mo	11 (26)
RECIST	
Partial response	3 (9)
Stable disease at 12 wks	14 (42)
Overall best response	8 (19)
Progression-free survival	
>6 mo	11 (26)
≥2 y	2 (5)

Clin Cancer Res 2007;13(12) June 15, 2007

Confirmatory study – patients with Histoscore> 150- multiple lines of treatment
Higher RR (33%) if high histoscore

AROMATASE INHIBITORS

Initial Phase 2 demonstrated association
Between ER Histoscore and RR

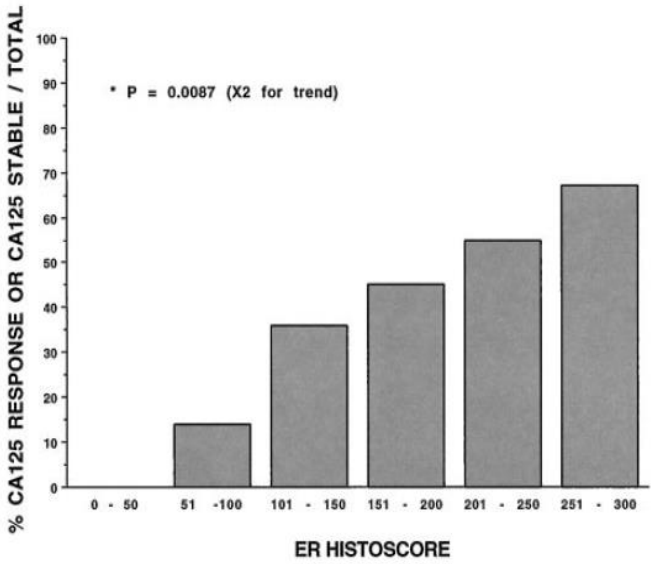


Fig. 4 Association between CA125 response and ER histoscore. A trend between percentage of CA125 stabilization or response and increasing ER was noted ($P = 0.0087$; χ^2 test for trend).

Clinical Cancer Research 2233
Vol. 8, 2233–2239, July 2002

Endometrial Cancer

- Kelly and Baker in 1961 reported the 1st study with a 30% in patients treated with high-dose megestrol acetate and others reported RR of 50% with a number of progestagens
- The response rates in later studies with more rigid criteria for response range from **11% to 25%**
- Phase II studies of aromatase inhibitors in patients with advanced or recurrent endometrial carcinoma. Reported response rates- 9.0-10%, to letrozole ,anastrozole and exemestane – "clinical benefit rates" greater
- **Combination of letrazole and everolimus very active- 40% CBR at 16 weeks –RR 32% durable 9 CR**(Slomovitz et al JCO 2015)

High RR in ER + / PR + endometrioid

***CTNNB1* mutations** high response to everolimus and letrozole in endometrioid endometrial cancers 4/4 patients

Slomovitz et al JCO 2015 VOL. 33 ; 8 930-936

PARAGON

Epithelial Ovarian Cancer
1. Asymptomatic rising CA125
2. Platinum Resistant
3. Low grade Serous

Endometrial Cancer
Recurrent/Metastatic

Endometrial Stromal Sarcoma
Recurrent /Metastatic

Other Gyn Sarcomas
LMS
Adenosarcoma

GCT
recurrent

Screening for Trial Entry
- Measurable disease
- CA125 in EOC Group 1
- Inhibin in GCT
- **ER and / PR positive**
- Consent for Tissue

Primary Aim:
Clinical benefit comprising either response or stable disease.
(Overall response rate as determined by RECIST v1.1 and/*or* CA125 GCIG criteria)

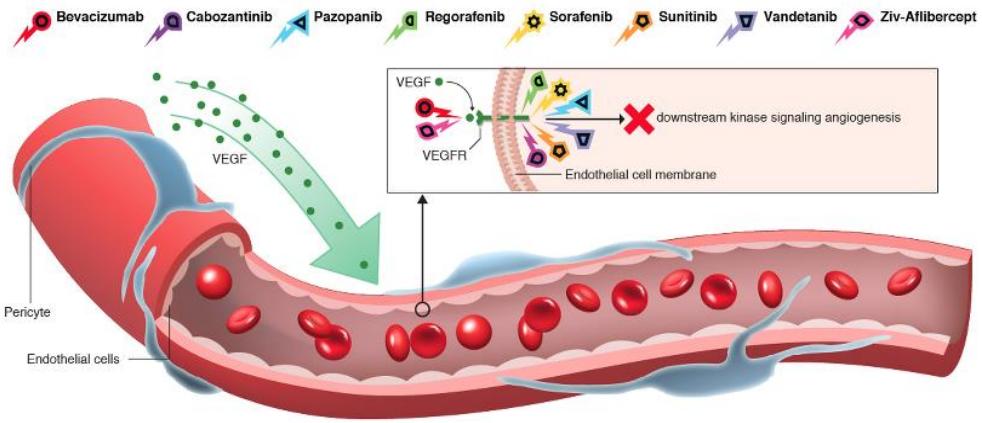
Anastrazole 1 mg daily

300/350 recruited

Targeting Angiogenesis in Gynecological Cancers

Vascular endothelial growth factor [VEGF] pathway, which plays a key role in angiogenesis

- **VEGF inhibitors** Bevacizumab#, Aflibercept
- **Tyrosine kinase inhibitors** e.g pazopanib, nintedanib, cediranib
- **Angipoetin inhibitors-** Trebaninib



bevacizumab is the only licensed anti-VEGF therapy in Gynecological Cancers- ovarian and cervical cancer

Angiopoiesis Foundation

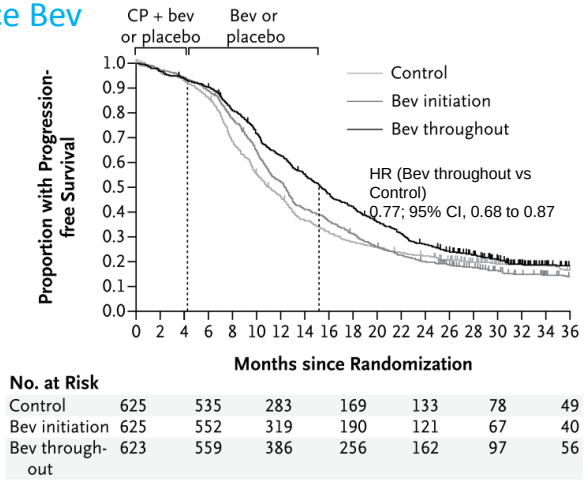
Anti-angiogenic therapy with bevacizumab In First-line treatment of Ovarian Cancer

Two pivotal randomised trials- GOG218 and ICON7

- **Progression-Free survival benefit but no improvement in overall survival**

4 month PFS benefit
With maintenance Bev
14.1 VS 10.3 m

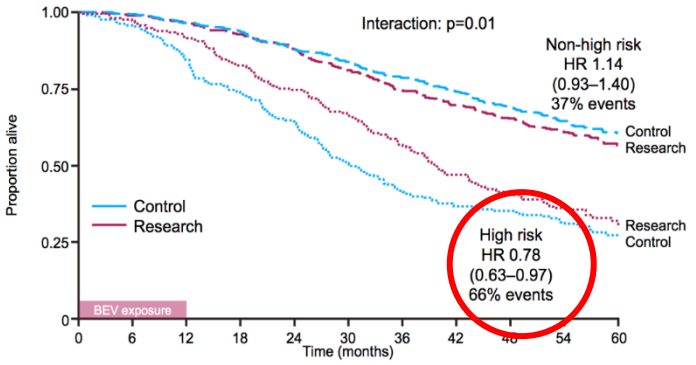
GOG 218
Stage 3/4



No. at Risk							
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

Burger et al N Engl J Med (2011) 365:2473-83

- **Survival benefit in a subset of ICON 7 high risk group (residual disease >1 cm/ Stage IV)**



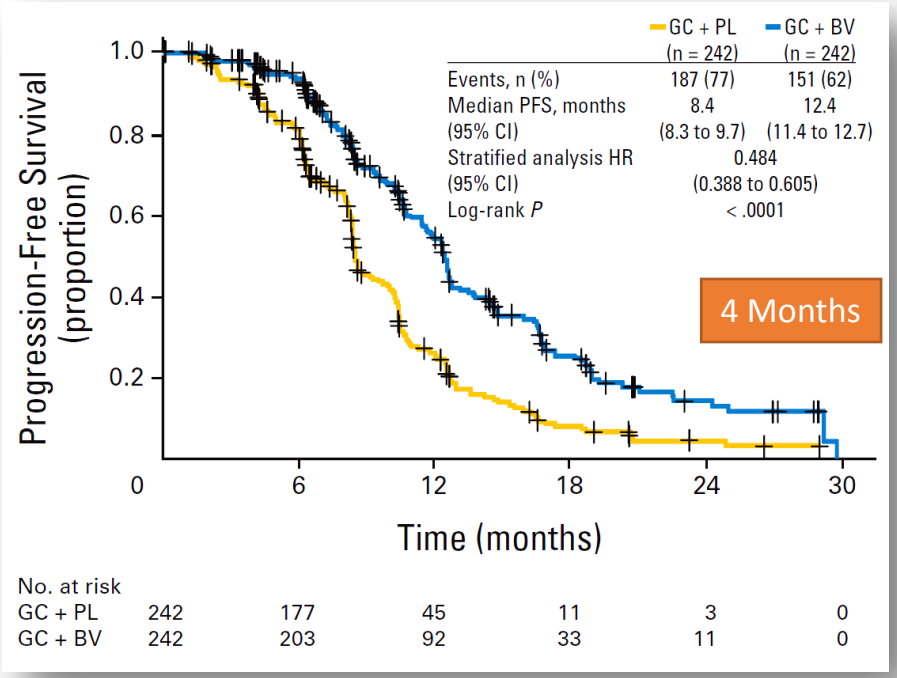
(PFS 20.3 m vs 21.8m in whole population

Oza et al Lancet Oncol 2015

PFS **18.1 months *versus* 14.5 months**; p = 0.002-in High Risk
Increased **median OS (36.6 months *versus* 28.8 months**; p = 0.002)

PBS Approval Australia- High Risk Subset
EMEA Approval – All patients – FDA no approval

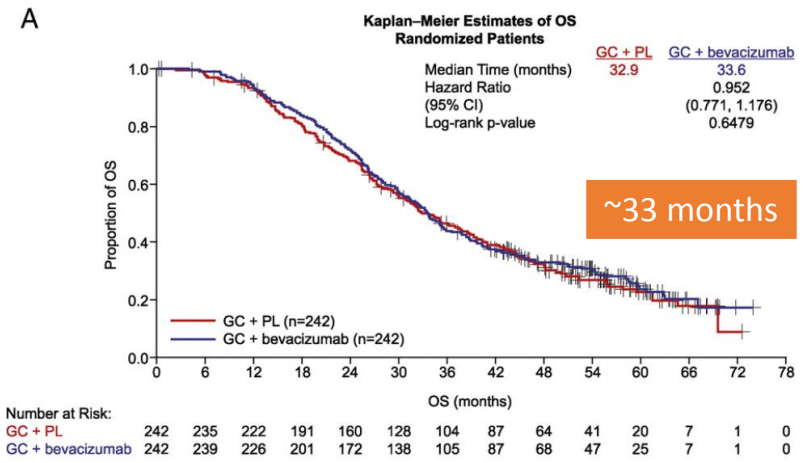
OCEANS- Bevacizumab in Platinum Sensitive Recurrent OC



Response Rate higher with Bev
No Difference in OS
MEDIAN SURVIVAL ~3 years in both arms

- **90% further lines –median 5(1-14)**
- **38% cross over to Bevacizumab**

Final OS data

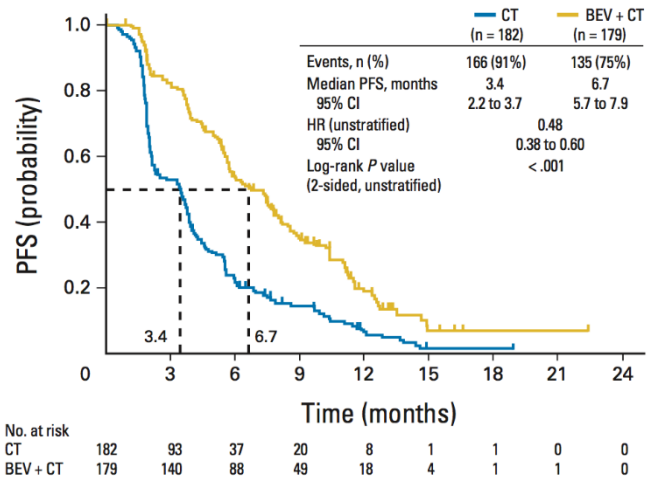


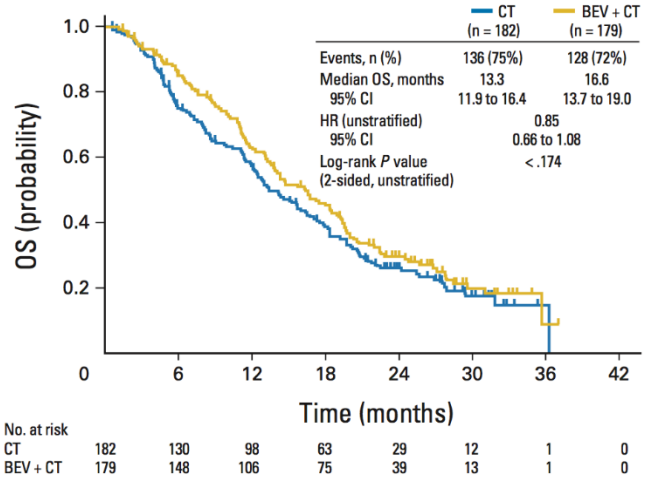
EMEA Approval not FDA

Aghajanian et al JCO 2011

Gynecol Oncol October 2015

AURELIA: bevacizumab in ‘platinum-resistant’ ovarian cancer





Pujade-Lauraine et al J Clin Oncol 2014

EU and FDA Approvals 2014

Anti-angiogenic agents in recurrent ovarian cancer

	Platinum Sensitive			Platinum-resistant (< 6 month PFI) and Partially Platinum-sensitive equally divided	Platinum-Resistant	
	OCEANS (n= 484)	**GOG213 (n=674)**	**ICON6 N= 456)**	**TRINOVA-1***	**AURELIA* (n= 361)**	**MITO11* (n=74)**
	Carboplatin/ gemcitabine ± **bevacizumab**	Carboplatin/ paclitaxel ± **bevacizumab**	Platinum-based ± **cediranib**	Weekly paclitaxel ± **trebananib**	weekly paclitaxel, PLD, topotecan ± **bevacizumab**	Weekly paclitaxel ± **pazopanib**
PFS (med. months)	**8.4 v 12.4**	**10.4 v 13.8**	**8.7 v 11.1**	**7.2 v 5.4**	**3.4 v 6.7**	**3.5 v 6.4**
HR	**0.484 (p<0.0001)**	**0.61 (p<0.0001)**	**0.57 (p=0.00001)**	**0.66 (p < 0.0001)**	**0.48 (p<0.001)**	**0.42 (p=0.0002)**

Similar HR in PSROC and PRROC Striking consistency

Pazopanib and Cediranib: Oral VEGF receptor tyrosine kinase inhibitors
Trebananib (AMG386): Peptibody inhibiting angiopoeitin 2

* Non maintenance therapy

Which agents to select and when in the disease trajectory ?

(OCEANS) Aghajanian et al JCO 2011; (GOG 213) Coleman et al SGO 2015; (ICON6) Ledermann et al ECC (2013);
(TRINOVA-1) Monk et al Lancet Oncol 2014; (AURELIA) Pujade-Lauraine et al JCO 2014;
(MITO11) Pignata et al Lancet Oncol 2015

Courtesy of J Ledermann

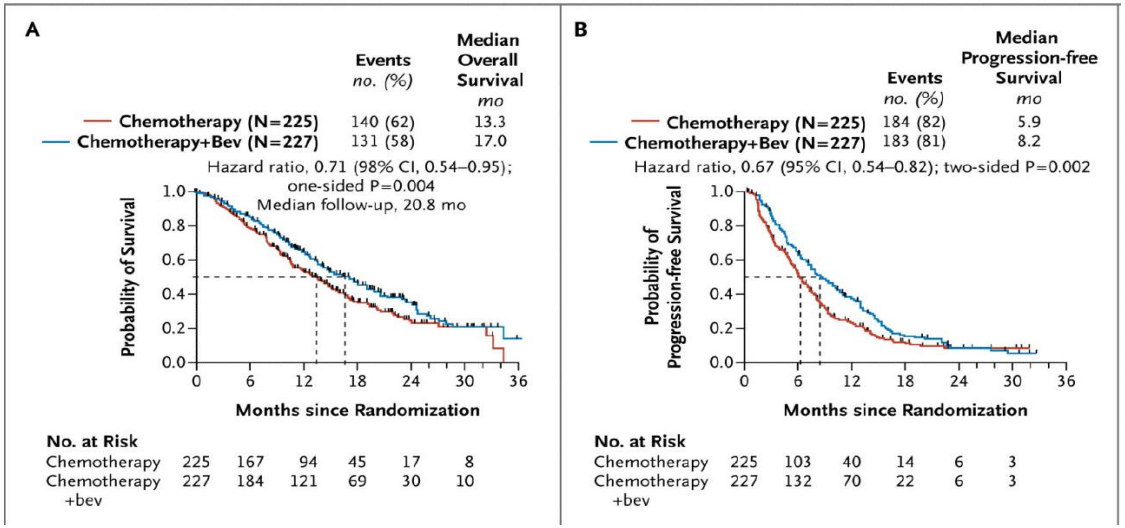
Identifying Subgroups most likely to benefit

- "Volume of disease" associated with benefit of bevacizumab in most tumour types eg breast /colon/lung- **no benefit with adjuvant bevacizumab** (similar with TKI's)
- ICON 7 Stage 4 and Sub-optimal Stage 3 **FIRST LINE STUDY**
- No data relating PFS with *Tumour Volume* in Recurrent Gynecological Cancers
- Are there clinical predictors of response/benefit eg ascites/effusions
- Levels of VEGF and other circulating markers **not predictive** of response to anti-angiogenic therapy
- Gene expression (DIS) Arrays
  - Immune subgroup on molecular profiling have worse outcome with bevacizumab in first-line therapy[1]
  - Benefit related to molecular subtype: 'mesenchymal and proliferative [2]
  - Discriminatory signature including mesothelin, FLT4, AGP and CA-125 [3]

[1] Gourley et al ASCO 2014; [2] Winteroff et al ASCO 3 Collinson Clin Cancer Res 2013

Chemotherapy +/- Bevacizumab in Cervical Cancer GOG 240

(metastatic /persistent /recurrent)



HR 0.7 (CI .54-.95)

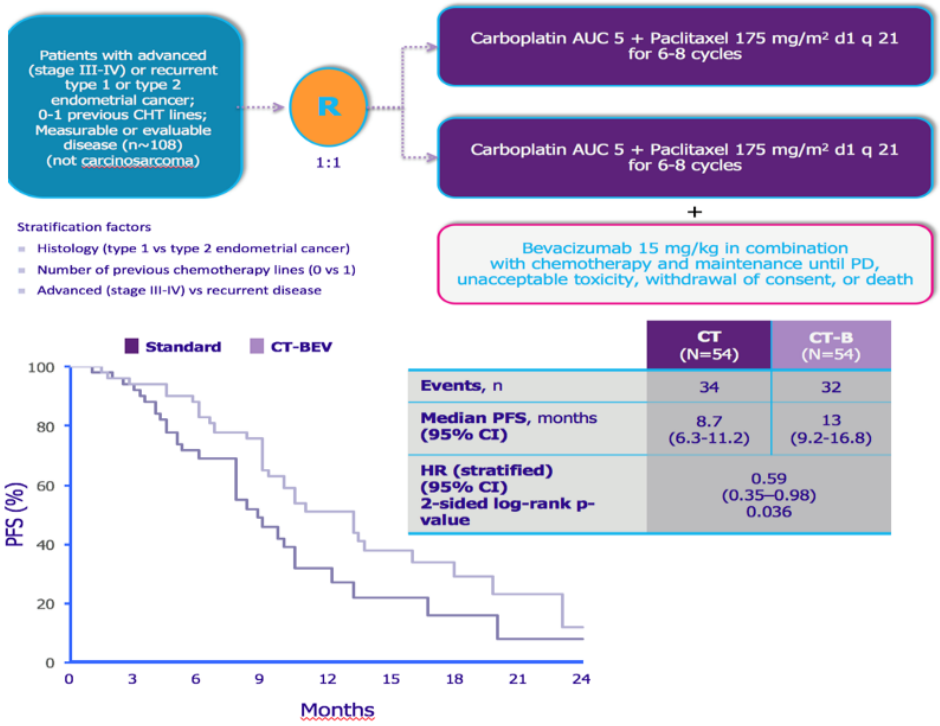
HR 0.67 (0.54-0.82)

Randomized to **chemotherapy +/- Bevacizumab until PROGRESSION** Number of cycles CT+ Bev 7 (range 0-36)
25% of CT + Bev stopped for Adverse Events vs 16 % in Chemo arm- NOTE NO MAINTENANCE BEVACIZUMAB

N Engl J Med. 2014 February 20; 370(8): 734–743.

FDA Approval August 2014

Bevacizumab in Recurrent /Metastatic Endometrial Cancer



	CT (N=54)	CT-B (N=54)
Events, n	34	32
Median PFS, months **(95% CI)**	8.7 (6.3-11.2)	13 (9.2-16.8)
HR (stratified) (95% CI) 2-sided log-rank p-value	0.59 (0.35–0.98) 0.036	

HR 0.59(0.35-0.98)
PFS 13 vs 8.7 months
RR 71 vs 54%

Lorusso et al ASCO 2015

Targeting Angiogenesis in Gynaecological Cancers

Many outstanding questions

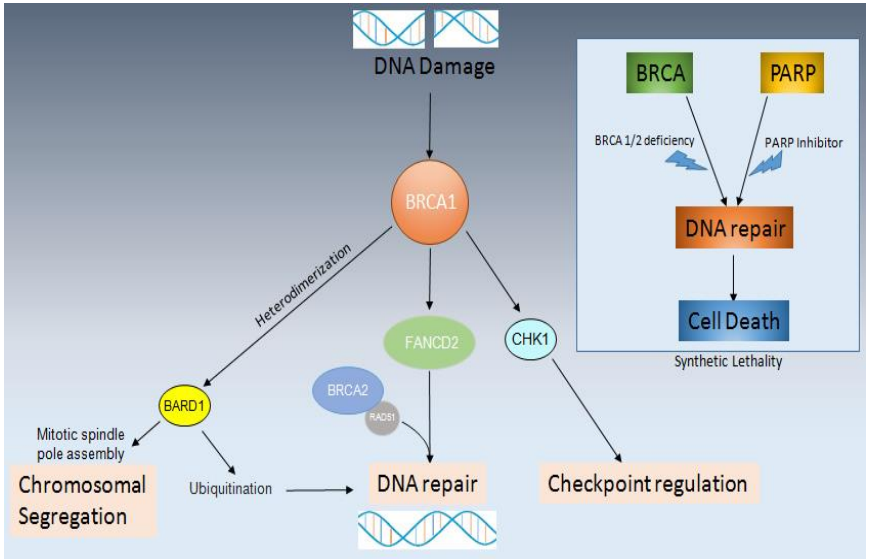
- **Who to treat and when to treat-** 1ST line / 2ND line PSROC /PRROC
- **How long** to continue treatment in 1st line setting
- Optimal **dose**/ schedule
- **Which** angiogenesis inhibitor ?
- No validated **biomarkers** to identify who will benefit/ be harmed
- Mechanisms of **resistance**
- Is there a benefit in **combining** with other agents- e.g PARPi
- Identifying patients at risk of adverse events
- TKI's in Asian population- differential toxicities

PARP INHIBITORS

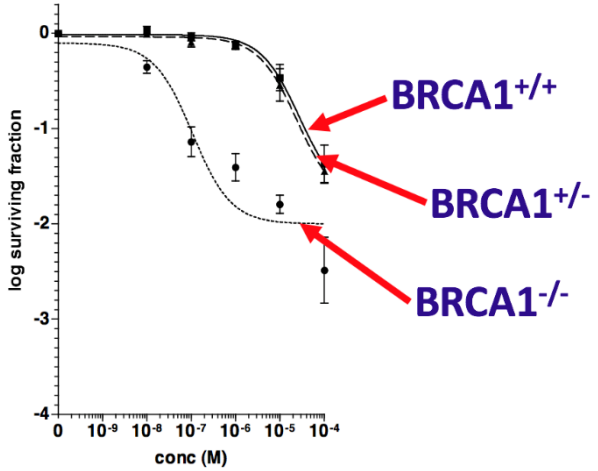
Poly(ADP-ribose) polymerase and DNA REPAIR

Synthetic lethality- increased sensitivity to PARPi in BRCA deficient and HRD cancers

Well validated biomarker to identify patients for treatment



Agarwal et al Discov. Med 2014 ;18;331



***BRCA*-deficient cells up to 1000-fold more sensitive to PARP inhibition**

Farmer et al. Nature 2005; 434:917–21

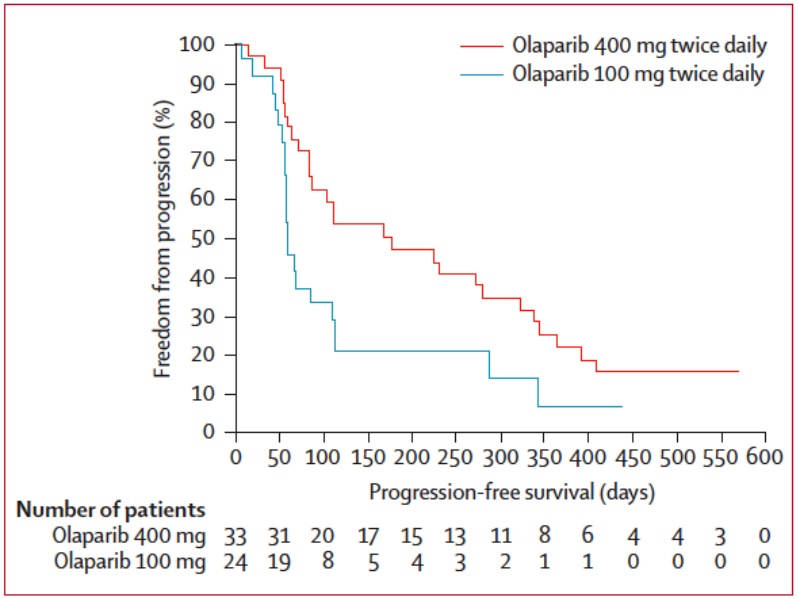
PARP INHIBITORS

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial

Lancet 2010; 376: 245–51

M William Audeh, James Carmichael, Richard T Penson, Michael Friedlander, Bethan Powell, Katherine M Bell-McGuinn, Clare Scott, Jeffrey N Weitzel, Ana Oaknin, Niklas Loman, Karen Lu, Rita K Schmutzler, Ursula Matulonis, Mark Wickens, Andrew Tutt

RECIST Response 33% vs 13%



Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation

Bella Kaufman, Ronnie Shapira-Frommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, and Susan M. Domchek

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

Response	Ovarian (n = 193) No.	%
Tumor response rate	60	31.1
95% CI	24.6 to 38.1	
CR*	6	3
PR*	54	28
Stable disease ≥ 8 weeks	78	40
95% CI	33.4 to 47.7	
Stable disease	64	33
Unconfirmed PR	12	6
PD†	41	21
95% CI	15.7 to 27.7	
RECIST progression	33	17
Early death‡	8	4
Not evaluable	14	7
No follow-up assessments	12	6
Stable disease < 8 weeks	2	1

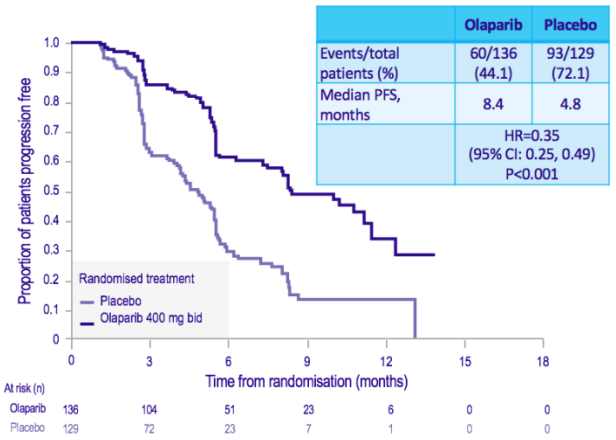
31% Response Rates

- **Median number of prior regimens 4.3(1-14)**
- **All platinum resistant / not considered suitable for further platinum**

On December 19, 2014, the U. S. Food and Drug Administration approved olaparib capsules as monotherapy for the treatment of patients with deleterious or suspected deleterious germline *BRCA* mutated (g*BRCA*m) who have been treated with three or more prior lines of chemotherapy

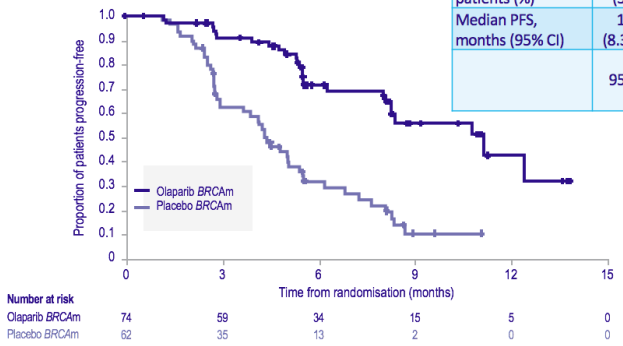
RANDOMISED TRIAL OF MAINTENANCE OLAPARIB IN PLATINUM-SENSITIVE HIGH-GRADE SEROUS RELAPSED OVARIAN CANCER – 'STUDY 19'

Whole population with HGSOC



	Olaparib	Placebo
Events/total patients (%)	60/136 (44.1)	93/129 (72.1)
Median PFS, months	8.4	4.8
	HR=0.35 (95% CI: 0.25, 0.49) P<0.001	

Subpopulation with a BRCA mutation



	BRCAm (n=136)	
	Olaparib	Placebo
Events/total patients (%)	26/74 (35%)	46/62 (74%)
Median PFS, months (95% CI)	11.2 (8.3, NC)	4.3 (3.0, 5.4)
	HR=0.18 95% CI: 0.10, 0.31; P<0.0001	

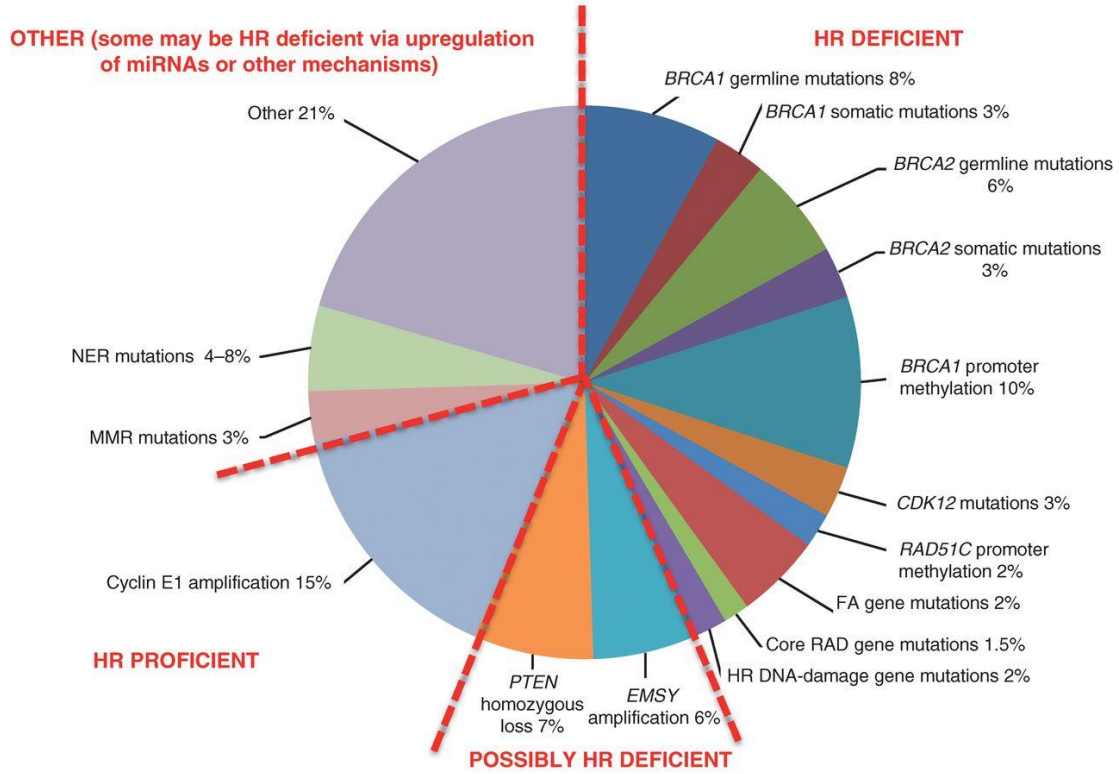
NC, not calculable.

Ledermann J et al. N Engl J Med 2012

Ledermann J et al. Lancet Oncol 2014

Olaparib approved in the EU as treatment for advanced BCRA-mutated ovarian cancer December 2014

Approximately 50% of high-grade serous EOCs have alterations in HR repair genes.



BRCA germline 15%
BRCA somatic 6%

Panagiotis A. Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

AACR American Association for Cancer Research
CANCER DISCOVERY

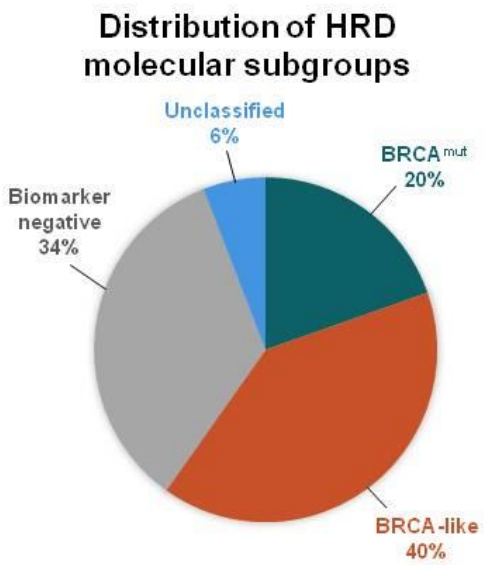
HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling using NGS

Hypothesis - **patients with high genomic LOH will respond to Rucaparib**

ARIEL2 patient characteristics

Parameter	Total (N=204)
Median age, years (range)	65 (31–86)
ECOG PS grade	
0 / 1 / Pending (%)	67 / 30 / 3
Diagnosis	
Epithelial ovarian cancer (%)	80
Primary peritoneal / fallopian tube cancer (%)	12 / 7 (1 unknown)
Histology	
Serous / endometrioid / mixed (%)	96 / 2 / 2
No. of prior treatment regimens	
Median no. of regimens (range)	1 (1–6)
1 (%)	57
≥2 (%)	43
Median no. of platinum-based regimens (range)	1 (1–5)
1 (%)	60
≥2 (%)	40

*Enrollment of known gBRCA patients was capped.
Data cut 01APR2015.



PRESENTED AT: ASCO Annual '15 Meeting

With permission

ORR 81% in GERMLINE BRCA AND 88% IN SOMATIC HIGH LOH

Presented By Iain McNeish at 2015 ASCO Annual Meeting

Modified from original

PARP inhibitors in clinical development#

PARP Inhibitor	Company	Licensed /Trial in progress
Olaparib (AZD2281)	AstraZeneca	**Licensed in EU for maintenance BRCAm;** **≥ 3rd line treatment (FDA) in BRCAm**. Phase III trials with tablet formulation - 1st line and recurrence (SOLO-1; SOLO-2)
Rucaparib (AG-014699; CO-338)	Clovis Oncology	Ongoing phase II studies and III studies in BRCAm, BRCAwt (ARIEL2; ARIEL3). **Breakthrough designation FDA**
Veliparib (ABT-888)	Abbvie	1st line phase III with chemotherapy - commenced
Niraparib (MK4827)	Tesaro	Ongoing phase III (NOVA) maintenance in BRCAm and BRCAwt; plans for 1st line
Talazoparib (BMN-673)	BioMarin (Medivation)	Ovarian cancer strategy – not clear

 # not including trials of a PARP inhibitor in combination with an anti-angiogenic agent e.g PAOLA /ICON 9 etc

Courtesy J Ledermann

Genomic Characteristics and Possible Targets

CANCER	HISTOLOGIC SUB-TYPE	MUTATIONS	COPY NO. ALTERATIONS
OVARIAN	HGSOC	**TP53** ,**BRCA**,CDK12	CCNE(1A),MYC(A),PIK 3CA(A) KRAS (A), PTEN(D),RB1(D)
	LOW GRADE	KRAS, BRAF	9P(L) CDKN2A(D)
	CLEAR CELL	PIK3CA,ARID1A,PTEN	MET(A) ERB2(A)
	MUCINOUS	KRAS	ERBB2(A)
	SMALL CELL	SMARCA4	
	SEX CORD	FOXL2 (GRANULOSA) DICER(sertoli-leydig)	

A= amplification
D=deletion

Modified from Lui et al
Gyn Onc 2015 accepted –in press

Genomic Characteristics and Possible Targets

SITE	HISTOLOGICAL SUBTYPE	MUTATIONS	COPY NUMBER ALTERATIONS
ENDOMETRIAL	HGS	TP53,PIK3CA,	CCNE1(A) ERBB2(A)
	Endometrioid	PTEN,PIK3CA,KRAS, FGFR2,POLE,MMR	
	Clear Cell	PIK3CA,ARID1A	ERBB2(A) MET
CERVICAL	Adenocarcinoma	PIK3CA,KRAS,ELF3	
	Squamous	PIK3CA,MAPK1, TP53	MYC(A),ERBB2(A) BIRCC3(A),LRP1B)D)

Modified from Lui et al
Gyn Onc 2015 accepted –in press

Targeting critical pathways- simply said but not simply done

7 mile bridge run-Bluewater.com

Skyscan photoshelter.com

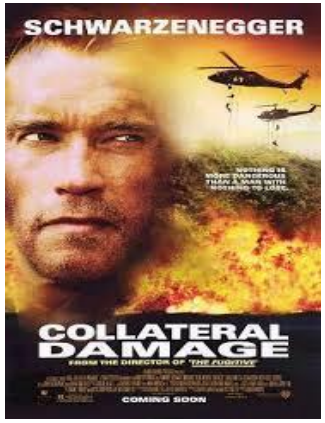
Challenges with signal seeking trials

- Few examples of “driver mutations”/ critical pathways
- TP53 mutations most common – early phase trials
- Multiple somatic mutations in gyn. Tumours
- Potential targets in relatively small subsets e.g BRAF,KRAS,PIK3CA, PTEN etc
- Umbrella trials- histology dependent-many biomarkers –many agents
- Basket- histology agnostic- many biomarkers –many agents e.g NCI MATCH

NCI MATCH- mutation frequency Gyn . Cancers

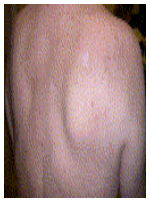
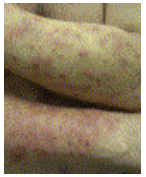
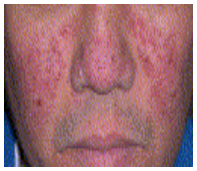
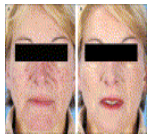
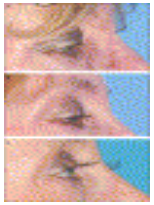
DRUG	MOLECULAR TARGET	OVARIAN	ENDOMETRIAL	CERVICAL
		Mutation frequencies		
AZD9291	EGFR m	2.2%	3.2%	3.8%
DABRAFENIB	BRAF V600	0.6%	0	2.6%
TRASTUZUMAB EMTANSINE	HER 2 amp	Endometrioid 2.1% HGSOC 3% CLEAR CELL 4% MUCINOUS 25%	UPSC 25%	2.3%
DEFACTINIB	NF2 loss	0.3%	2.4%	5.1%
SUNITINIB	C KIT m	2.2%	6.9%	0%
AFATINIB	EGFR m	2.2%	3.2%	3.8%
TRAMETINIB	BRAF non V600	?	?	?

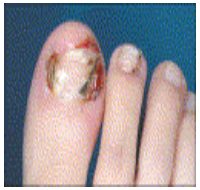
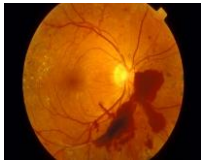
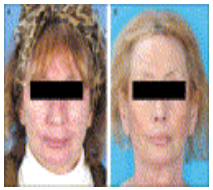
Modified from Moore and Manel
Gyn Onc 2015 accepted –in press

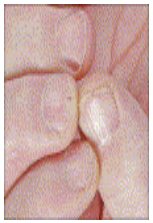
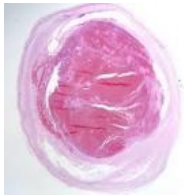
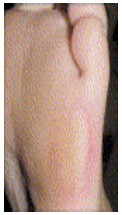
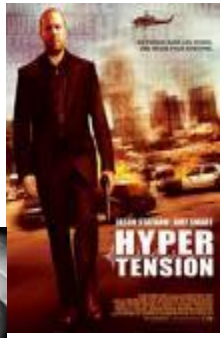


Toxicities with targeted therapies – a partial list !

NO FREE LUNCH!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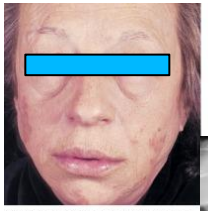
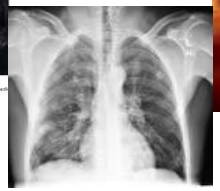
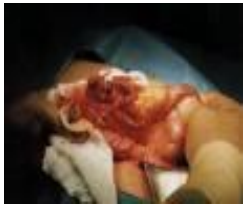
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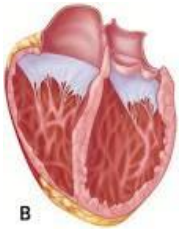


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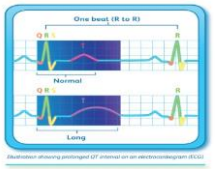

C Robert et al Lancet Oncol. 2005 Jul;6(7):491-500
N Heidary et alJ Am Acad Dermatol. 2008 Apr;58(4):545-70
Google Images.

Counting the Costs of Targeted Therapies

- Addition of bevacizumab to paclitaxel and carboplatin in GOG 218 resulted in an incremental cost-effectiveness ratio**(ICER) of $479,712** per progression-free life-year saved
- In ICON 7 HIGH RISK subgroup - estimated 8-month improvement in OS results in an ICER of **$167,771** per life-year saved
- 3.7 month OS advantage with Chemo+Bev in GOG 240 - ICER of **$155,000** per quality-adjusted life year (QALY).

J Clin Oncol 2011;29:1247–1251. Med Care. 2008 Apr;46(4):349-56 Oncologist. 2014 May; 19(5): 523–527

Gynecol Oncol 2015 Jan;136(1):43-7.

Conclusions

- “Embarrassment of Riches” – many new agents in trial and in development
- Brings both challenges and opportunities
- Clinical trial design – endpoints – recruitment- approvals
- International collaboration essential
- Translational research critically important- biomarkers and companion diagnostics
- Patient reported outcomes also increasingly important
- Learning how manage new toxicities
- Cost Effectiveness and Affordability- cannot be ignored