Targeted Agents – Future Prospects, Including Combination Strategies, in Ovarian Cancer

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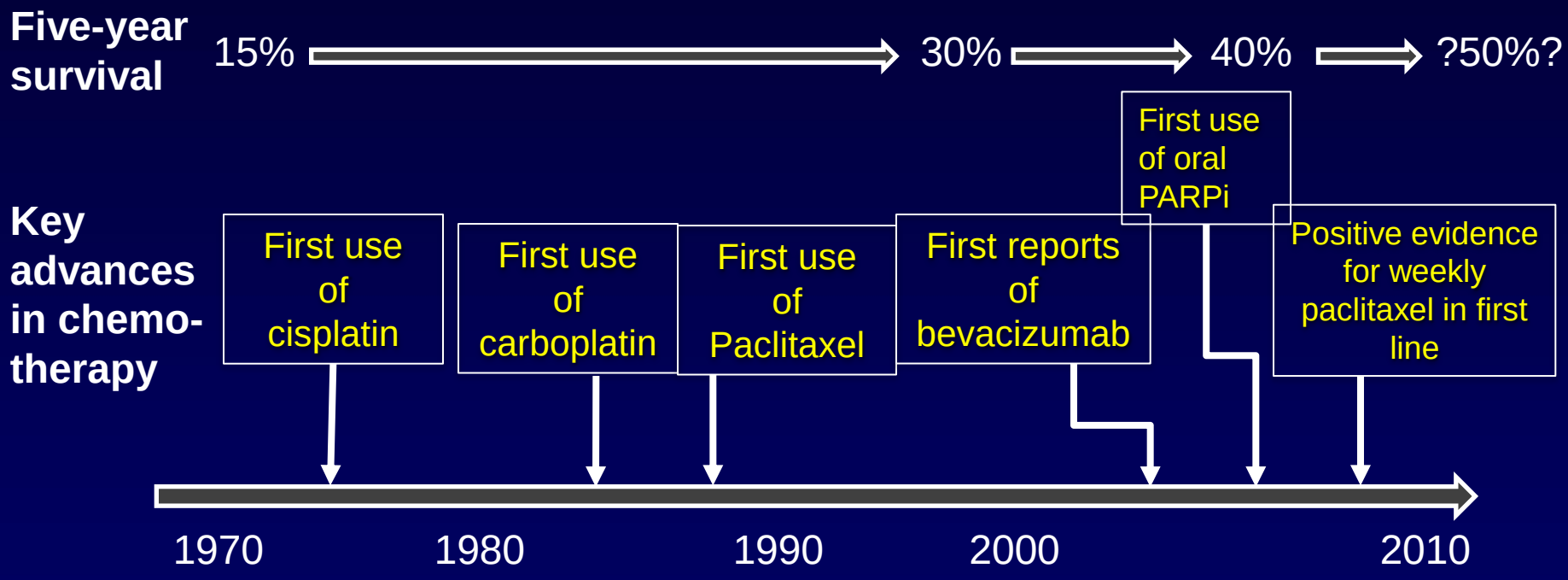
Progress in the Management of Ovarian Cancer: Evolution Over 40 Years

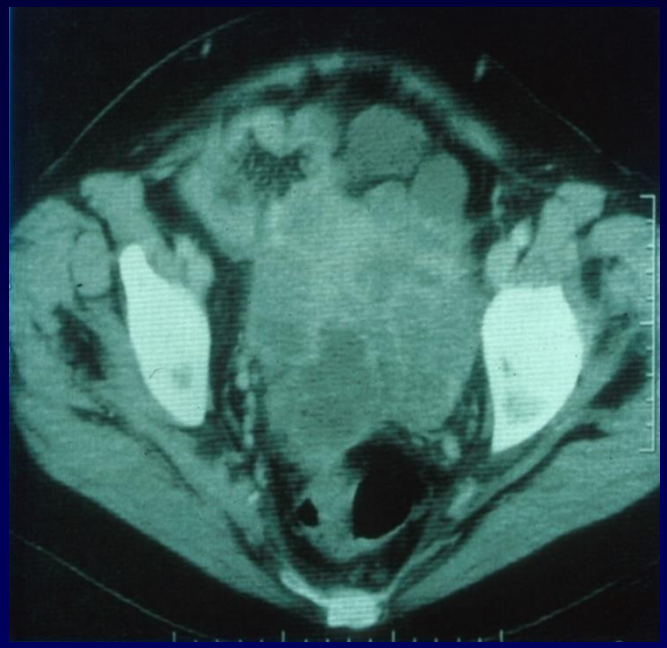


- Standard of care (first line): paclitaxel/carboplatin
  - Median progression-free survival / overall survival is approximately 12-20 m/3-5 years.

Q. How can we do better?

A. Rational molecular targeted therapy

Rational Targets in Ovarian Cancer – Agents Now in the Clinic



Inhibitors of:

- **VEGF and other angiogenic factors**
- **PARP**
- **P13K/AKT**
- **MEK**

2015 update on:

- **Single-agent data**
- **Combination strategies**

Single Agents

Antiangiogenic Agents

- Bevacizumab
- VEGFR /TKIs
  - cediranib
  - pazopanib
  - nintedanib
- Ang1/Ang2
  - trebananib
- Antivascular
  - fosbretabulin

PARP Inhibitors

- Olaparib
- Niraparib
- Rucaparib

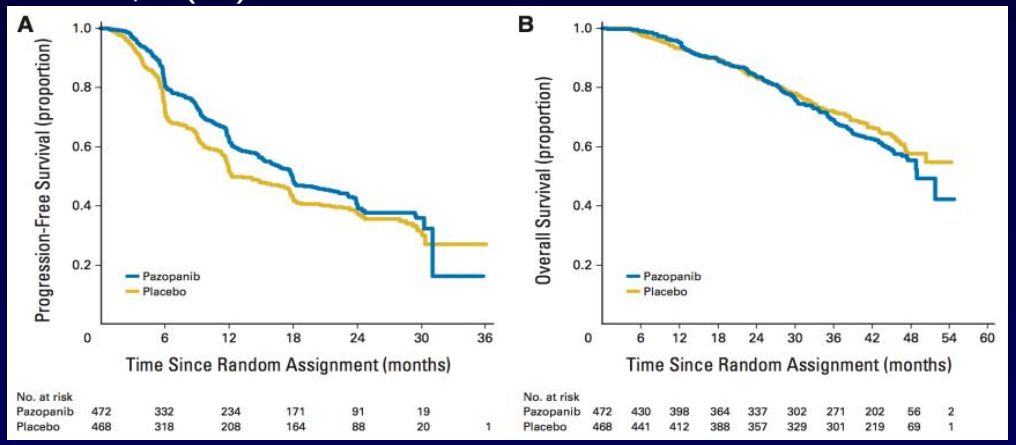
What can we conclude from randomised trials so far?

Image not available

Single-Agent Trials – Antiangiogenic Agents

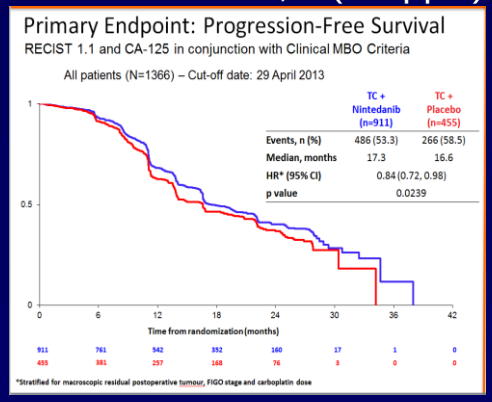
First Line (cont)

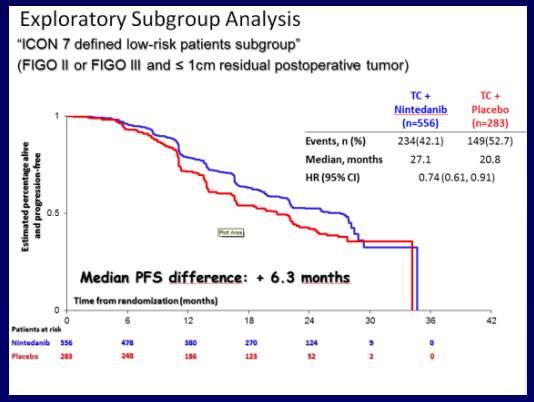
AGO-OVAR 16: DuBois A, et al. *J Clin Oncol.* 2014;32(30):3374-3382.



- Pazopanib (AGO-OVAR 16, n = 940) maintenance only
  - HR 0.77 for PFS benefit
  - significant toxicity at 800 mg bd (<50% patients received 12 months therapy)
  - no overall survival benefit
  - not being pursued in first line

AGO-OVAR 12: DuBois A, et al. *Int J Gynecol Cancer.* 2013;23(8suppl1): Abstract LBA1.

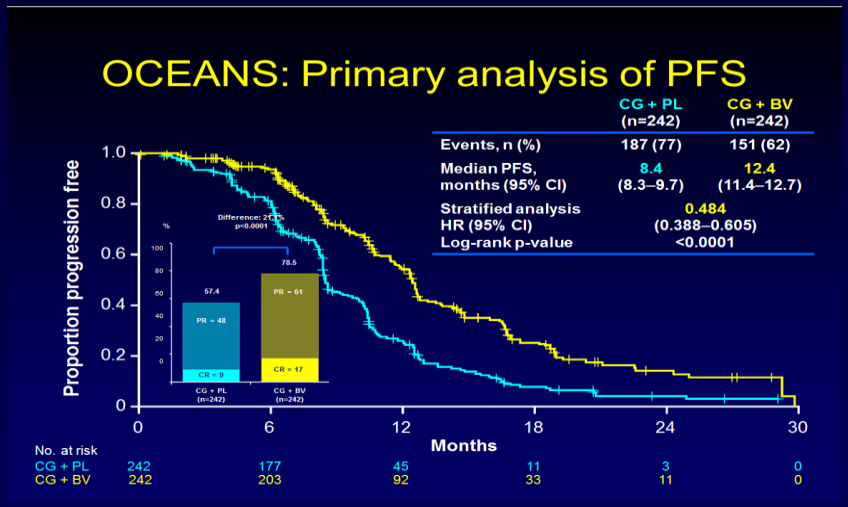


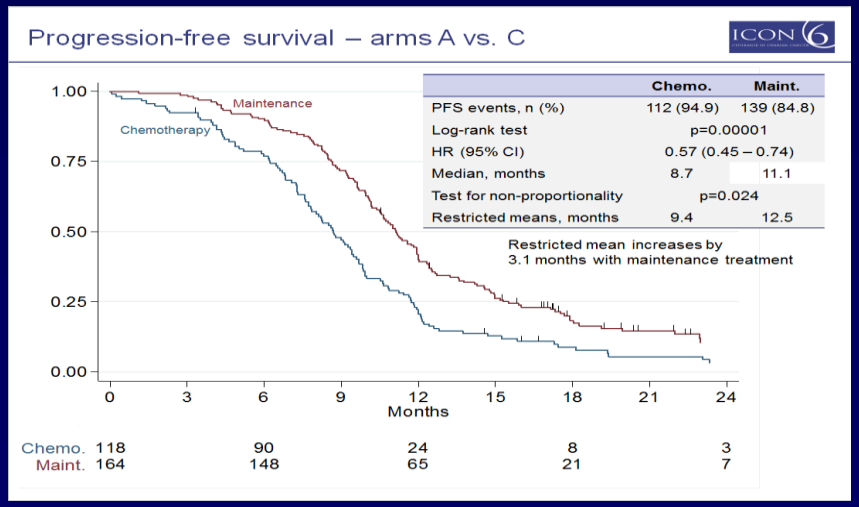


- Nintedanib (AGO-OVAR 12, n = 1366) concurrent and maintenance
  - modest PFS benefit (HR 0.84), best seen in “low-risk” patients
  - further plans for first line studies unclear

Single-Agent Trial – Antiangiogenic Agents

Second Line (platinum sensitive)





- Bevacizumab (OCEANS)
  - As concurrent and maintenance, PFS benefit, HR = 0.48
  - May be preferred option for patients optimally debulked at initial surgery

Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.

- Cediranib (ICON6)
  - As concurrent and maintenance, similar PFS benefit to OCEANS (HR of 0.57) with trend to OS benefit (HR 0.75)
  - Would efficacy be retained in patients previously treated with bevacizumab?

Ledermann JA, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract LBA10.

Open questions:

- Is there a rational patient selection strategy, eg, genomic profile
- What about patients with *BRCA* mutations?
- What is the impact of prior antiangiogenic treatment?

Single-Agent Trials – Antiangiogenic Agents

Platinum-Resistant Disease

– Assume standard treatment is weekly paclitaxel

- Bevacizumab (AURELIA, n = 115)[1]
  median PFS 3.9 m -> 10.4 m
- Trebaninib (TRINOVA-1, n = 919)[2]
  median PFS 5.4 m -> 7.2 m
- Pazopanib (MITO 11, n = 74)[3]
  median PFS 3.5 m -> 6.3 m

- Is there any evidence of survival benefit?
- Which would you choose?
- What is the impact of prior antiangiogenic treatment?

1. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-1308.
2. Monk BJ, et al. *Lancet Oncol.* 2014;15(8):799-808.
3. Pignata S, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5503.

Summary of PFS and OS in AURELIA Trial

	PAC	PAC-B	PLD	PLD-B	TOPO	TOPO-B
PFS (m)	3.9	10.4	3.5	5.4	2.1	5.8
HR	0.46 (0.3-0.71)		0.57 (0.39-0.83)		0.32 (0.21-0.49)	
OS (m)	13.2	22.4	13.7	14.1	13.3	13.8
HR	0.65 (0.42-1.02)		0.91 (0.62-1.36)		1.09 (0.72-1.67)	

PAC, Paclitaxel
PLD, Pegylated liposomal doxorubicin
TOPO, Topotecan

- **Best results seen with paclitaxel**

Poveda AM, et al. *Ann Oncol.* 2012;23(Suppl 9): Abstract LBA26.
Witteveen P, et al. Presented at ESGO 2013.
Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-1308.

Antiangiogenic Inhibitors in 2015

Issues: what if the patient has a *BRCA* mutation?

- **She should receive maintenance PARP inhibitor at some point, either before or after antiangiogenic, depending on regulatory environment**
- **Will a combination be more appropriate? (eg, olaparib/cediranib)**

Impact of Prior Antiangiogenic on Repeat Antiangiogenic Therapy

- **Published / presented data very limited**
  - **Total around 100 cases previously treated with bevacizumab (or other antiangiogenic)**
  - **Includes:**
    - **TRINOVA I – up to 72, (where addition of trebaninib to weekly taxol still carried some (not significant) PFS benefit in patients previously treated with bevacizumab).**
    - **AURELIA – 26 (numbers too small to draw conclusion)**
    - **PHASE II trials of TKIs, inhibiting VEGFR, FGFR, etc,**

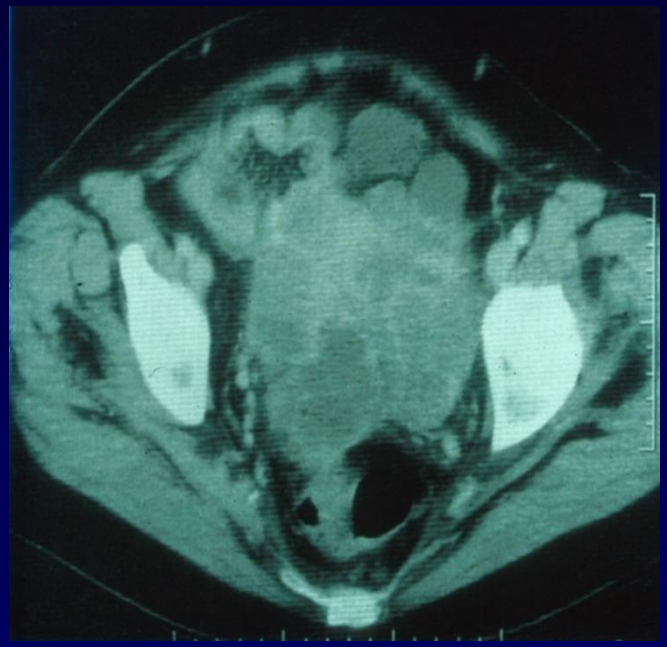
    eg, brivanib where n = 25 for prior antiangiogenic – response rate 23% in this subgroup.

Therefore, more data needed!

- **Is it appropriate to give bevacizumab more than once? – in my view, not until clinical data support this**

Monk BJ, et al. *Lancet Oncol.* 2014;15(8):799-808.
Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-1306.
Kaye S, et al. *Ann Oncol.* 2012;23(Suppl 9): Abstract 9660.

Rational Targets in Ovarian Cancer - Agents Now in the Clinic



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2015 update on:

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- **Combination strategies**

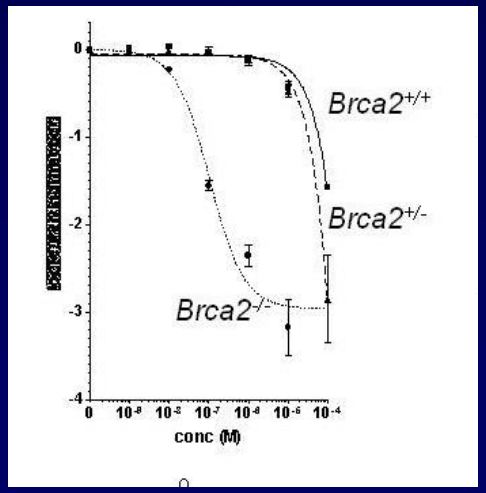
Single-Agent Trials PARP Inhibitors

Based on “tumour synthetic lethality” targeting cells with homologous recombination deficiency (HRD) – is this a new treatment for *BRCA*-mutation associated ovarian cancer?

Preclinical → Early Clinical Trials (Phase I, incl. IB) → Randomised Clinical Trials (Phase II and III)

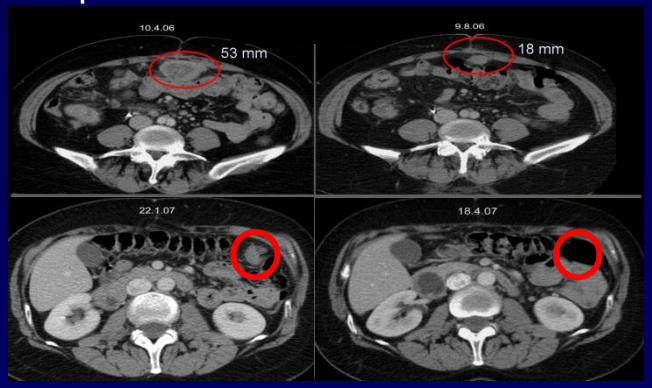
PARP: poly(ADP) ribose polymerase

Exquisite preclinical efficacy of PARPi



Farmer H, et al. *Nature.* 2005;434(7035):917-921.

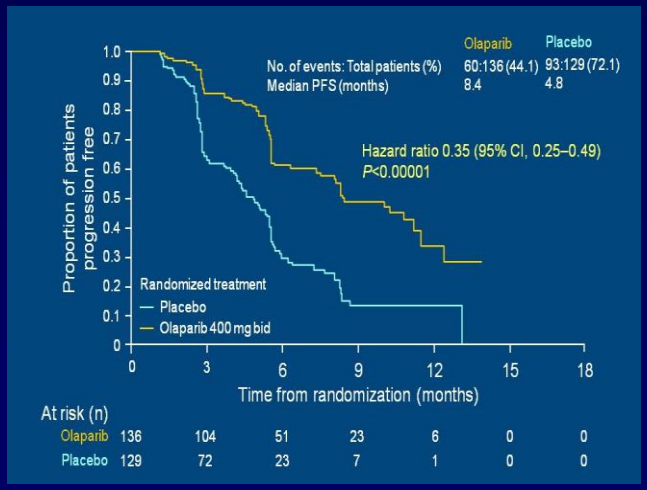
Phase I trial confirms excellent tolerance and expansion in 50 *BRCA* patients showed 46% response.



This is nothing like chemotherapy

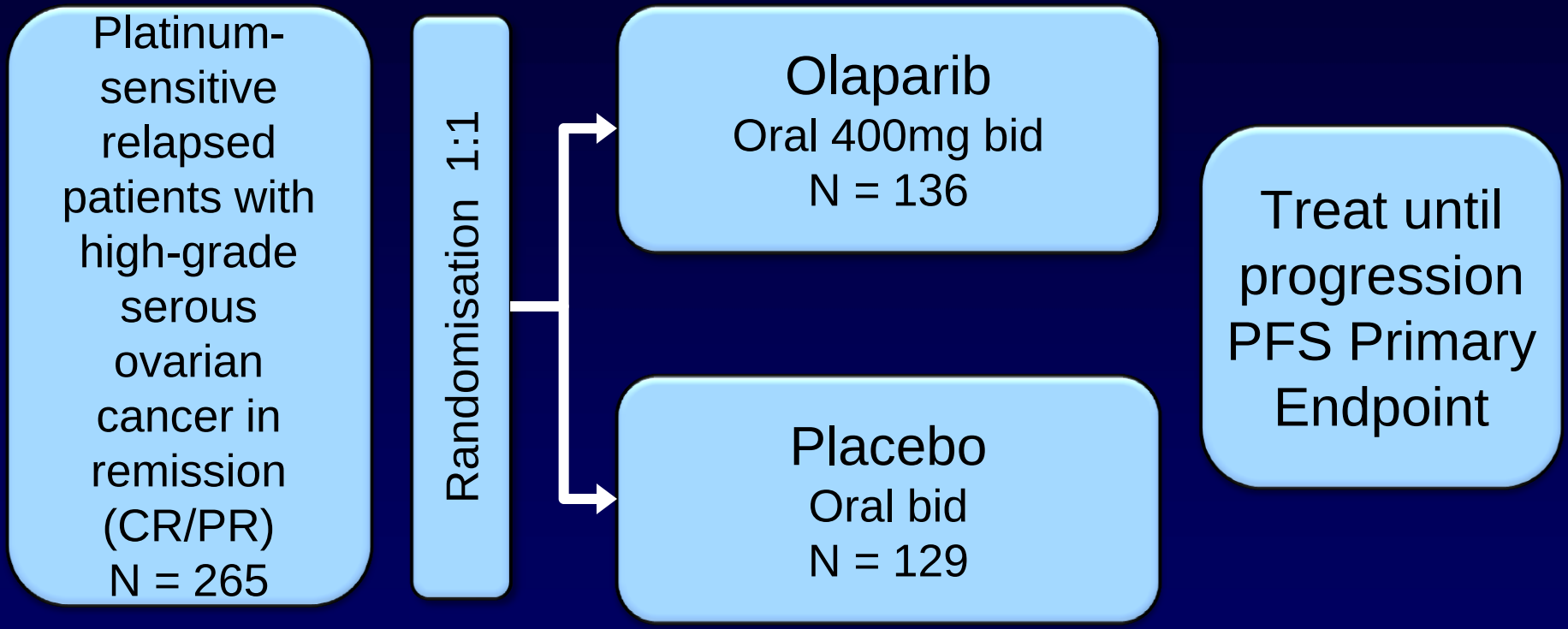
Fong PC, et al. *N Engl J Med*. 2009; 361(2):123-134.
Fong PC, et al. *J Clin Oncol*. 2010; 28(15):2512-2519.

Randomised trial (maintenance therapy) showed marked PFS benefit



Ledermann JA, et al. *N Engl J Med.* 2012;366(15):1382-1392.

Randomised Maintenance Study 19: Design

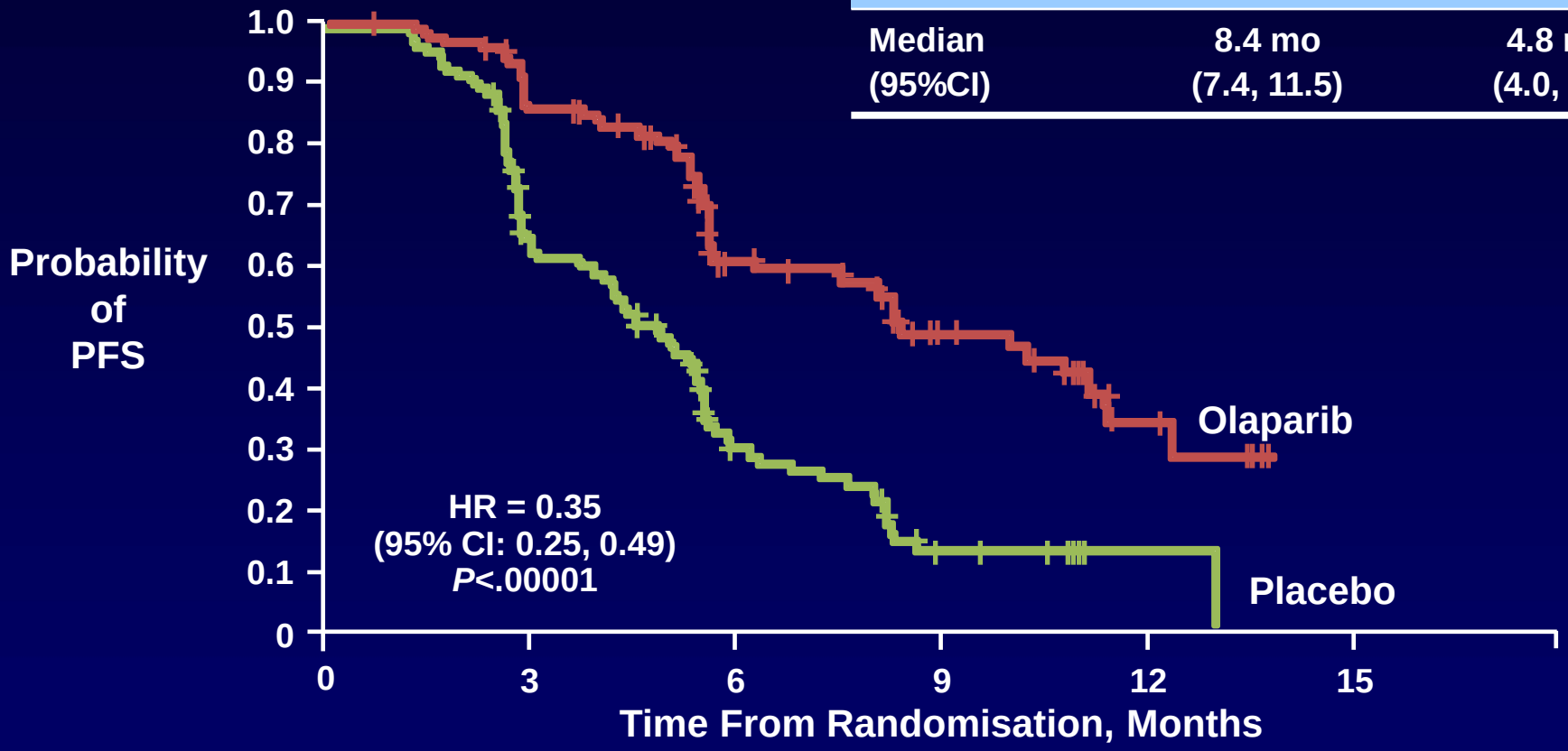


Initially *BRCA*m status known for only 36% of patients; subsequent analysis increased this to 96%

Ledermann JA, et al. *N Engl J Med.* 2012;366(15):1382-1392.

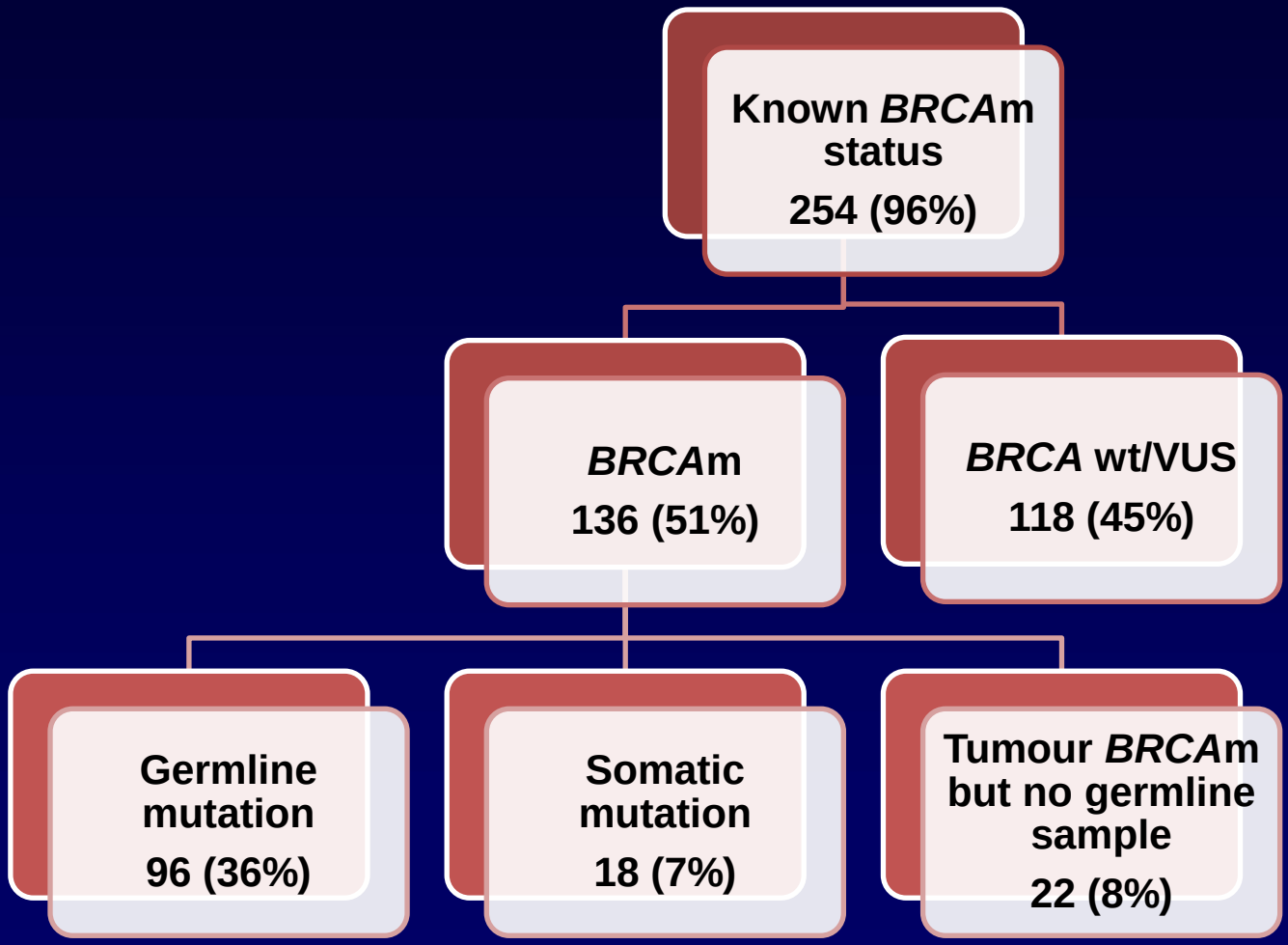
Study 19 (ITT): Met PFS Primary Endpoint

	Olaparib N = 136	Placebo N = 129
Median (95%CI)	8.4 mo (7.4, 11.5)	4.8 mo (4.0, 5.5)

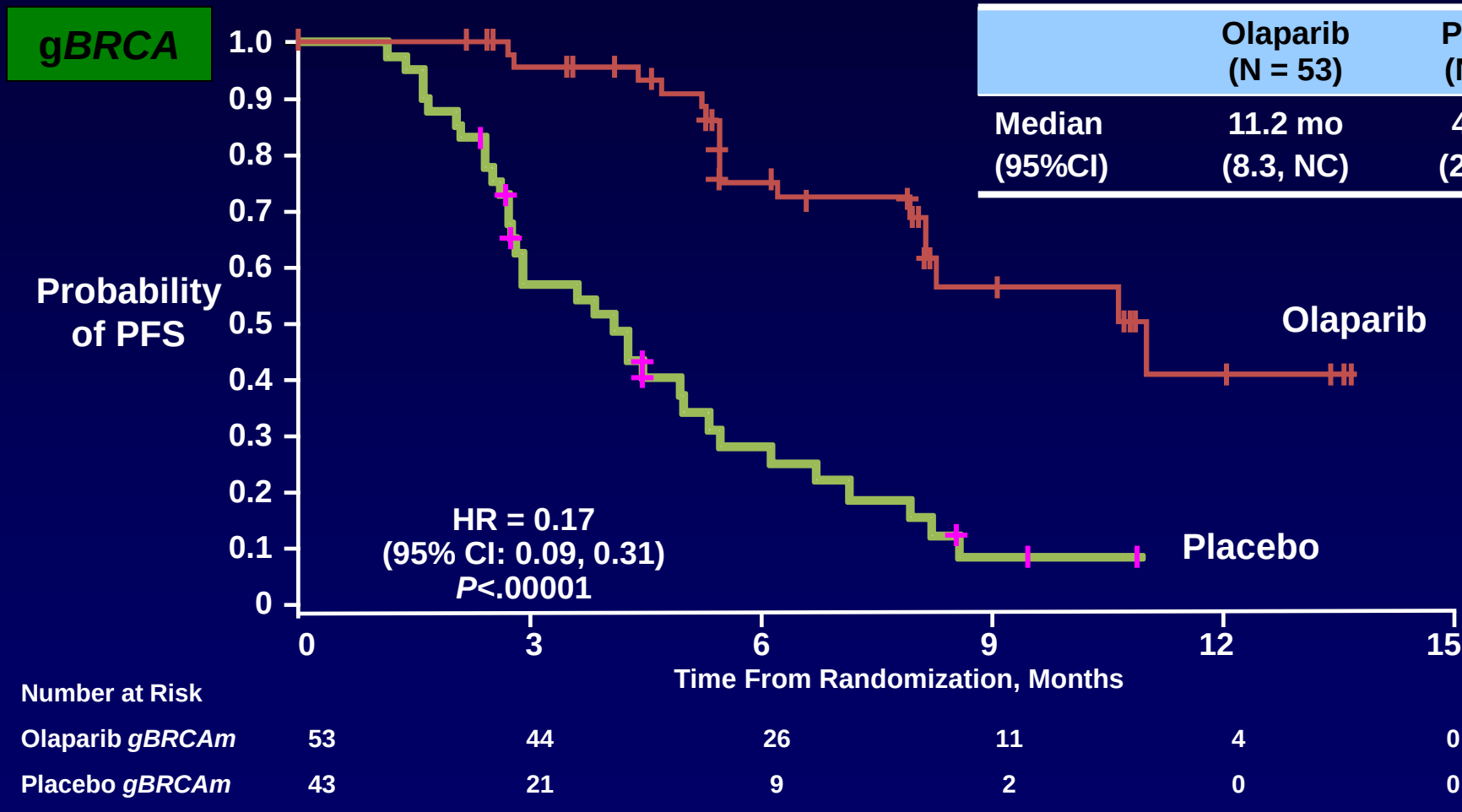


Number at Risk						
Olaparib	136	106	53	24	7	0
Placebo	129	72	24	7	1	0

BRCAm Status Summary



g*BRCAm* Patients Derive Greater PFS Benefit: 7.1 Months Median PFS Improvement



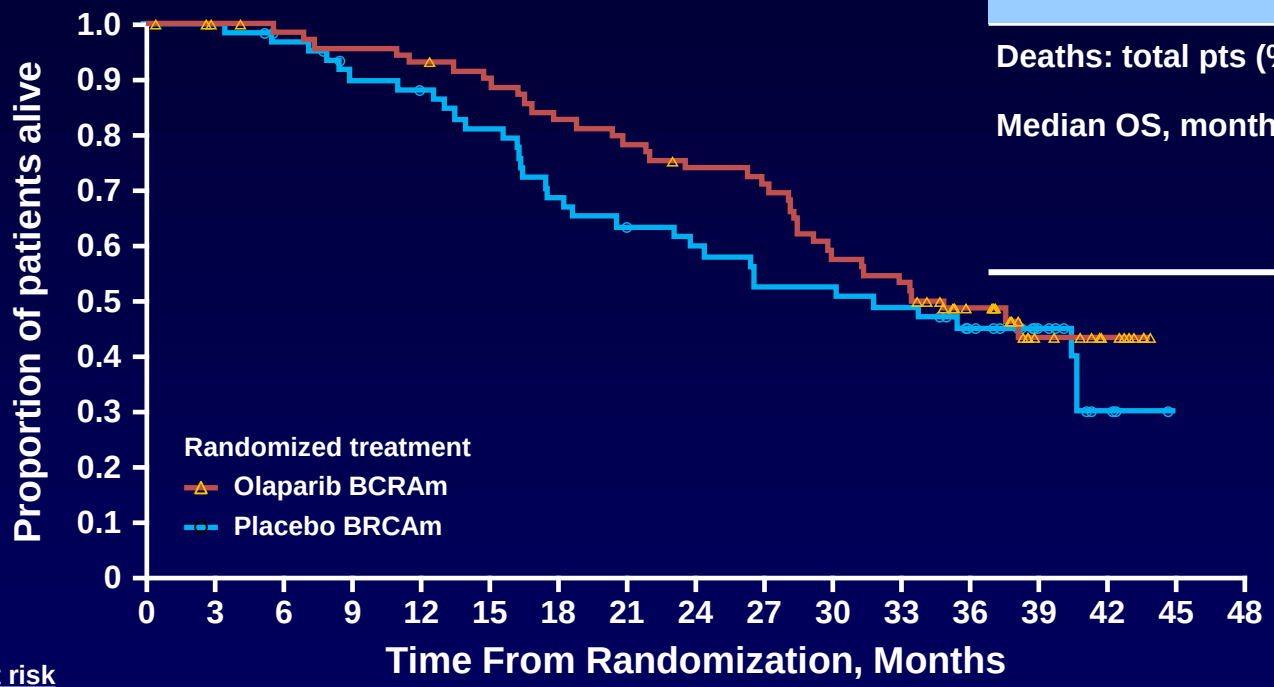
	Olaparib (N = 53)	Placebo (N = 43)
Median (95%CI)	11.2 mo (8.3, NC)	4.1 mo (2.9, 5.1)

Number at Risk						
Olaparib *gBRCAm*	53	44	26	11	4	0
Placebo *gBRCAm*	43	21	9	2	0	0

Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852- 861.

Overall Survival in Patients With *BRCA* Mutation

	BRCA mut (n = 136)	
	Olaparib	Placebo
Deaths: total pts (%)	37:74 (50.0)	34:62 (54.8)
Median OS, months	34.9	31.9
	HR = 0.74 95% CI (0.46, 1.19) *P* = .208	



Number at risk

Olaparib *BRCA*m	74	71	69	67	65	62	57	54	50	48	39	36	26	12	7
Placebo *BRCA*m	62	62	58	52	50	46	39	36	33	29	29	27	21	12	4

- 14/62 (22.6%) placebo patients switched to a PARP inhibitor
- OS in *BRCA WT* patients: HR = 0.98; 95% CI, 0.62–1.55; *P* = .946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months

Ledermann JA, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 5505.

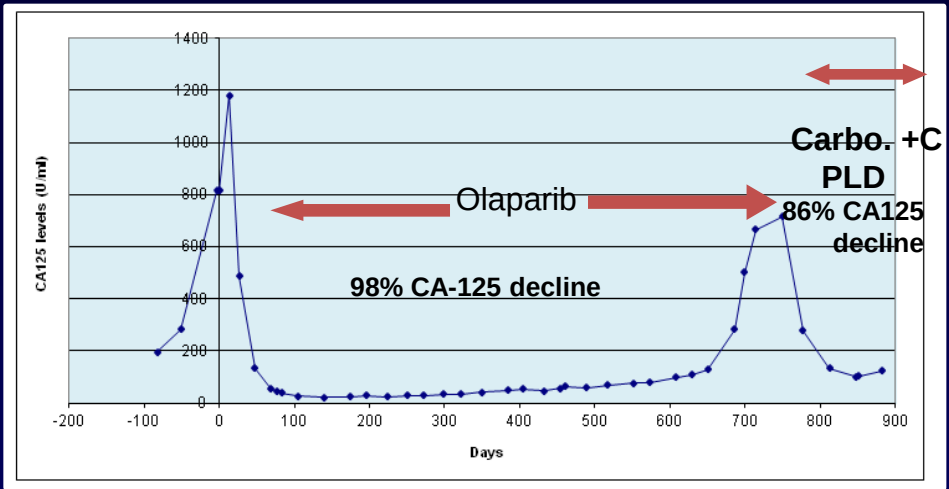
Randomized Trial of Olaparib As Maintenance Therapy in Platinum-Sensitive Sporadic Ovarian Cancer

Trial positive for primary endpoint (PFS).
But overall survival impact less clear.

Does this reflect crossover (23%), or is there an impact of olaparib on subsequent response to chemo, and will this depend on *BRCA* mutation status?

What do we know about olaparib (and platinum) resistance?

Chemosensitivity Post Olaparib in *BRCA*-Mutated Ovarian Cancer



- For platinum-based treatment:
  - RECIST response in 19/48 (40%)
  - RECIST and/or CA-125 response in 26/53 (50%)
  - Median PFS: 22 weeks
  - Median OS: 45 weeks

- In 78 evaluable olaparib-treated patients, response to subsequent chemotherapy seen in 36% (24/67) by RECIST and in 45% (35/78) by CA125 and/or RECIST

- ORR/OS significantly associated with interval since last (pre-olaparib) platinum
- Molecular analysis of tumor resected post-olaparib: No evidence of secondary mutations in 6 cases

Ang JE, et al. *Clin Cancer Res.* 2013;19(19):5485-5493.

PARP Inhibitors – What Are the Next Steps?

- **Anticipate registration of olaparib as maintenance therapy in germline *BRCA*m patients in 2015. Is there also a role in recurrent advanced disease?**
- **Define activity in sporadic ovarian cancer and other cancers, eg, prostate**
- **Develop robust predictive biomarker**
- **Assess PARP inhibitors other than olaparib (rucaparib, niraparib, BMN-673)**
- **Test novel combinations (with P13K or angiogenesis inhibitors, etc)**
- **Monitor long-term toxicity**
- **Understand mechanisms of PARPi resistance – probably multifactorial**

Is There a Role for PARP Inhibitors in Recurrent *BRCA*m Ovarian Cancer?

Primary objective: compare efficacy of 2 dose levels of olaparib (300 mg and 400 mg bd) with liposomal doxorubicin

Patients:
Those with advanced *BRCA1*- or *BRCA2*-mutated ovarian cancer who had progressive or recurrent disease <12 months after previous platinum-based chemotherapy

Randomized 1:1:1

- **Olaparib 200 mg bid in 28-day cycles**
- **Olaparib 400 mg bid in 28-day cycles**
- **Liposomal DOX 50 mg/m^2 iv every 4 weeks**

Sample size:
Total 90 (30 per arm)

- **Efficacy of olaparib (400 mg bd) was as predicted, with response (RECIST/CA125) in 59% and median PFS of 8.8 m**
- **PLD was more effective than anticipated (response 39%; median PFS 7.1 m); thus no significant difference in primary end-point**
- **HR 0.88 *P* = .66**
- **Overall, both treatments well tolerated (<10% discontinuation)**

- **Further studies certainly warranted, including pts previously treated with PLD, eg Study 42, showing 31% response in 193 pts with platinum-resistant *BRCA*m ovarian cancer – Kaufman et al, JCO 2014**

Kaye SB, et al. *J Clin Oncol.* 2012;30(4):372-379.

Olaparib for Recurrent *BRCA*m Ovarian Cancer

Recent Developments

- Ongoing pooled analysis of 300 patients who received olaparib in 6 studies involving *BRCA*m recurrent disease (273 with measurable disease)
- All but one study nonrandomised
- Data on subgroup of 137 patients who received ≥3 lines of chemo presented to FDA for accelerated approval
  - response rate 34%; response duration 7.9 m

→ **Accelerated Approval Granted**

Status of Olaparib – January 2015

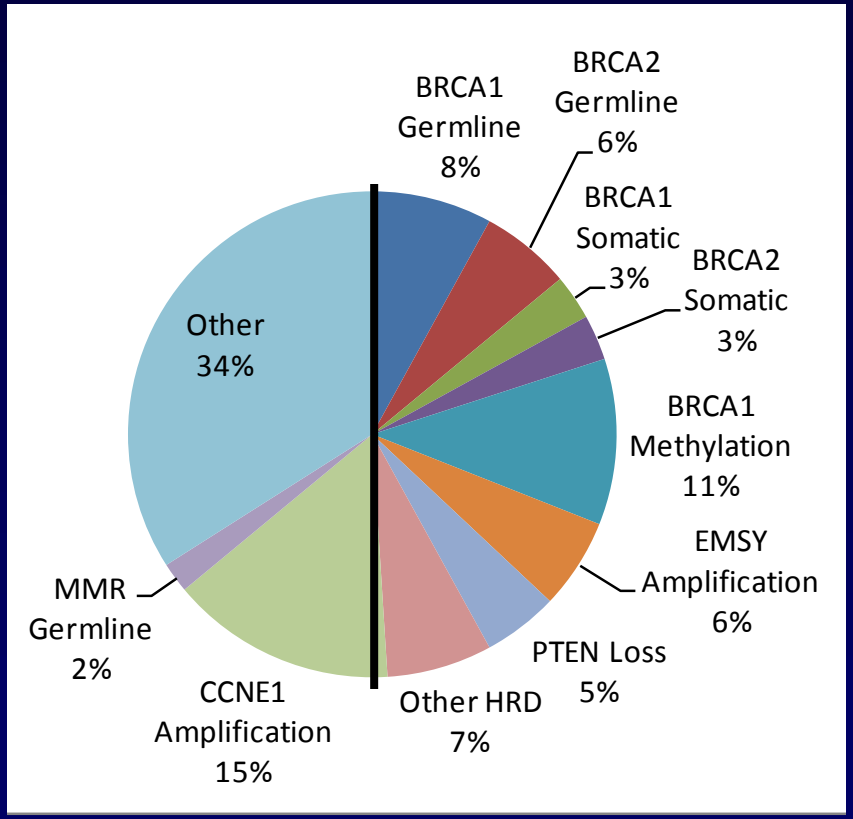
Europe – approved as maintenance treatment for platinum-sensitive relapsed *BRCA*m ovarian cancer – patients in remission following platinum-based therapy

USA – approved as monotherapy for patients who have received ≥3 lines of chemotherapy

- Not approved as maintenance therapy
- Approval also for companion diagnostic (Myriad Genetics *BRCA* analysis CDx)

PARP Inhibitors – What Are the Next Steps?

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011



What is the role of PARPi in sporadic ovarian cancer?

Patient Selection for Treatment with PARP Inhibitors

Germline/somatic *BRCA 1/2* mutation is "a standard of care"

Predictive biomarker for sporadic ovarian ca pts, possibilities include:

- **functional test for loss of HR (RAD 51 foci-formation)[1,2]**
- **molecular signature (gene array) [3]**
- **immunohistochemistry for BRCA 1 protein[4]**

Circumstantially:

- **repeated response to platinum-based chemotherapy**
- **prolonged survival (>5 yrs)**
- **high-grade serous histology**

1. Mukhopadhyay A, et al. *Clin Cancer Res.* 2010;16(8):2344-2351; 2. Graeser M, et al. *Clin Cancer Res.* 2010;16(24):6159-6168; 3. Konstantinopoulos PA, et al. *J Clin Oncol.* 2010;28(22):3555-3561; 4. Garg K, et al. *Am J Surg Pathol.* 2013;37(1):138-146.

Homologous Recombination Deficiency Assay

Myriad Genetics, presented at NCI/EORTC/AACR meeting 2014

DNA-based assay aimed at detecting HRD independent of cause, incorporating 3 algorithms:

- **Loss of heterozygosity (LOH)**
- **Telomeric allelic imbalance (TAI)**
- **Large-scale state transitions (LST)**

HRD score is sum of LOH + TAI + LST scores

- **106 high-grade ovarian samples evaluated for HRD score and correlation with *in vitro/in vivo* PARPi (niraparib) sensitivity.**
- **Initial results support further exploration of HRD score.**

Haluska P, et al. *Eur J Cancer.* 2014;50(suppl 6): Abstract 214.

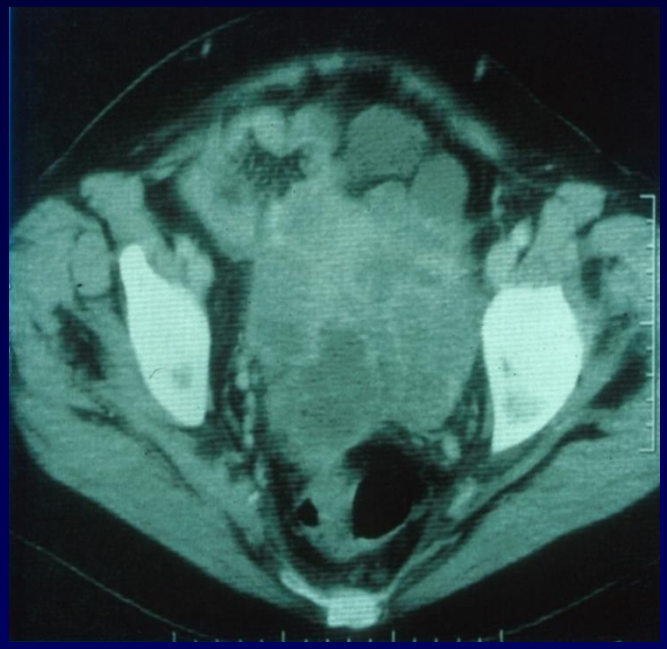
Single-Agent Activity for PARP Inhibitors in Ovarian Cancer

Drug	*BRCA* Mutation Positive			*BRCA* Wildtype and Unknown		
	n	% Resp	Resp duration	n	% Resp	Resp duration
Olaparib[1,2,3]	> 100 (most plat resist)	30%-60%	7-10 m	46	24%	7 m
Rucaparib[4]	23 (all plat sens)	61%	>6 m	38	24%	>6 m
Niraparib[5]	20 (9 plat sens)	45%	11 m	20	15%	5 m
BMN 673[6]	28 (22 plat sens)	68%	>6 m			

* Preliminary genomic data for rucaparib	BRCA-like signature (LOH)	No BRCA–like signature
n	25	13
resp %	32%	8%

1. Fong PC, et al. *J Clin Oncol*. 2010; 28(15):2512-2519.
2. Kaye SB, et al. *J Clin Oncol.* 2012;30(4):372-379.
3. Gelmon KA, et al. *Lancet Oncol.* 2011;12(9):852-861.
4. Swisher E, et al. . *Eur J Cancer.* 2014;50(suppl 6): Abstract 215.
5. Sandhu SK, et al. *Lancet Oncol.* 2013;14(9):882-892.
6. Ramanathan R, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract LBA29.

Rational Targets in Ovarian Cancer - Agents Now in the Clinic



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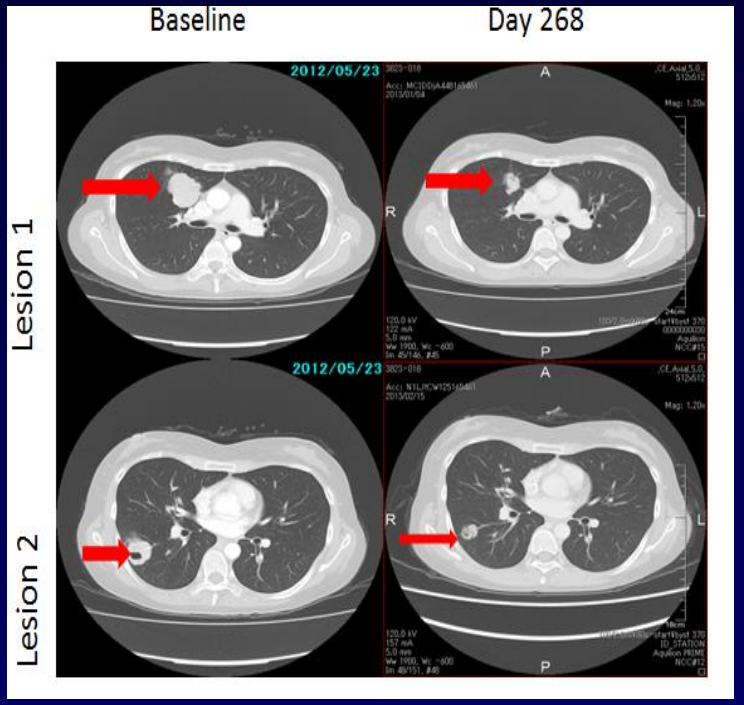
Single-Agent Trials – Other Agents

P13Kinase/AKT inhibitors

- Mutations in 25%-30% clear cell/endometrial
- Responses seen in phase I, eg, AZD 5363



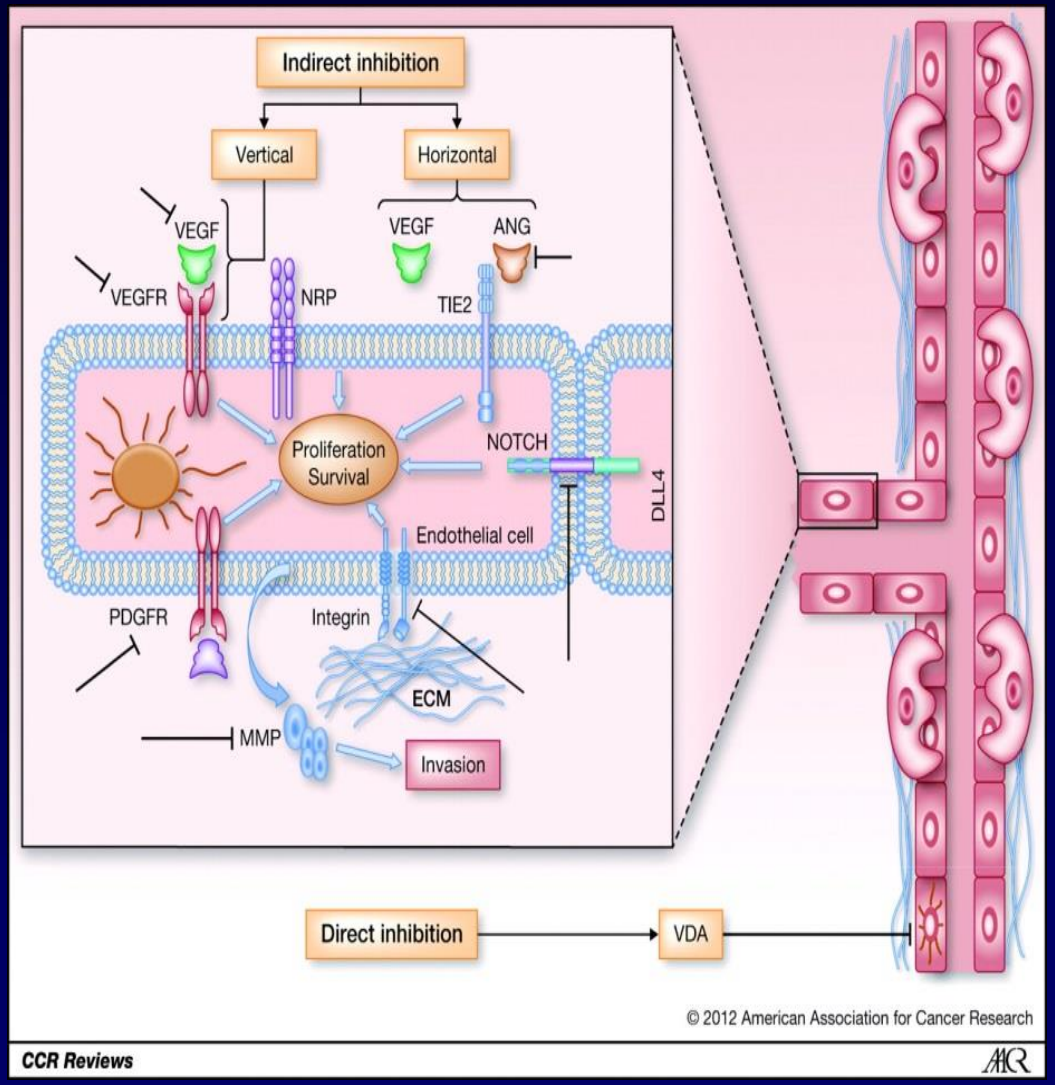
MEK Inhibitors

- RAS mutations in up to 50% low-grade serous
- Single-agent efficacy seen with selumetinib
- Randomised studies underway with more potent MEK inhibitors

Combination Strategies

- Antiangiogenic / antiangiogenic
  - vertical / horizontal
- Antiangiogenic / PARP inhibitor
  - cediranib / olaparib
- PARP inhibitor / P13K inhibitor
- P13K / MEK inhibitor
- PI3K / chemotherapy
- Not PARPi/chemotherapy!

Combination of 2 Antiangiogenic Agents



Moreno Garcia V, et al. *Clin Cancer Res.* 2012;18(14):3750-3761.

a) vertical

ie, bevacizumab plus VEGFR-TKI, eg, sorafenib

- Increased toxicity leads to dose modifications of both drugs, albeit with potential increased efficacy
- (47% RR in 19 patients)

Lee JM, et al. *Br J Cancer.* 2010;102(3):495-499.

b) horizontal

ie, vascular disrupting agent (VDA) plus VEGF inhibitor

- Fosbretabulin (CA4 pro-drug) plus bevacizumab. Potential synergy since VDA leads to blood-flow reduction and release of VEGFR
- Randomised trial recently reported

Monk BJ, et al. Presented at: 15th Biennial Meeting of the International Gynecologic Cancer Society; November 8-11, 2014: Melbourne, Australia.

Bevacizumab/Fosbretabulin vs Bevacizumab

Recurrent epithelial ovarian cancer

RANDOMISED

- Bevacizumab 15 mg/kg q3w n = 54
- Bevacizumab 15 mg/kg + fosbretabulin 60 mg/kg q3w n = 53

Response	Median PFS	Toxicity – G3 hypertension
28.2%	4.8m	19.6%
35.7%	7.3m	32.7%
	HR 0.68 *P* = .049	

Conclusion: combination "warrants further evaluation in ovarian cancer"

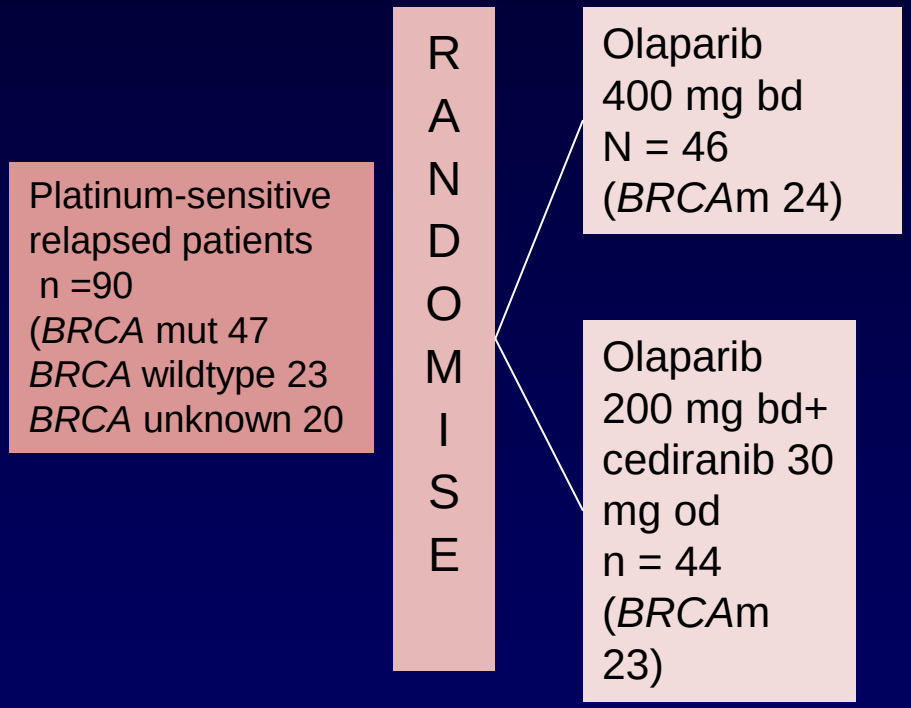
Monk BJ, et al. Presented at: 15th Biennial Meeting of the International Gynecologic Cancer Society; November 8-11, 2014: Melbourne, Australia.

Antiangiogenic/PARP Inhibitors

- Complementary targets/mechanisms of action
- Potential enhancement of sensitivity to PARPi by increasing HRD through changes in oxygenation caused by antiangiogenic agent
- Bevacizumab/olaparib – phase I trials confirmed feasibility
- Cediranib/olaparib – randomised trial presented at ASCO 2014

Dean E, et al. *Br J Cancer.* 2012;106(3):468-474.
Liu JF, et al. *Lancet Oncol.* 2014;15(11):1207-1214.

Olaparib/Cediranib in Ovarian Cancer



Response (%)	Med PFS
22 (48%) Including 2 CR	9 m (*BRCA*mut 16.5 m *BRCA* other 5.7 m)
35 (80%) Including 5 CR	17.7m (*BRCA*mut 19.4 m *BRCA* other 16.5 m)

Main toxicity: h/t, diarrhoea, fatigue, leading to dose reduction n 34/44 (77%) and 4 pts discontinued treatment on olaparib/cediranib.

	***P* value for PFS difference**
BRCAmut	.16 (ns)
BRCA other	.0008

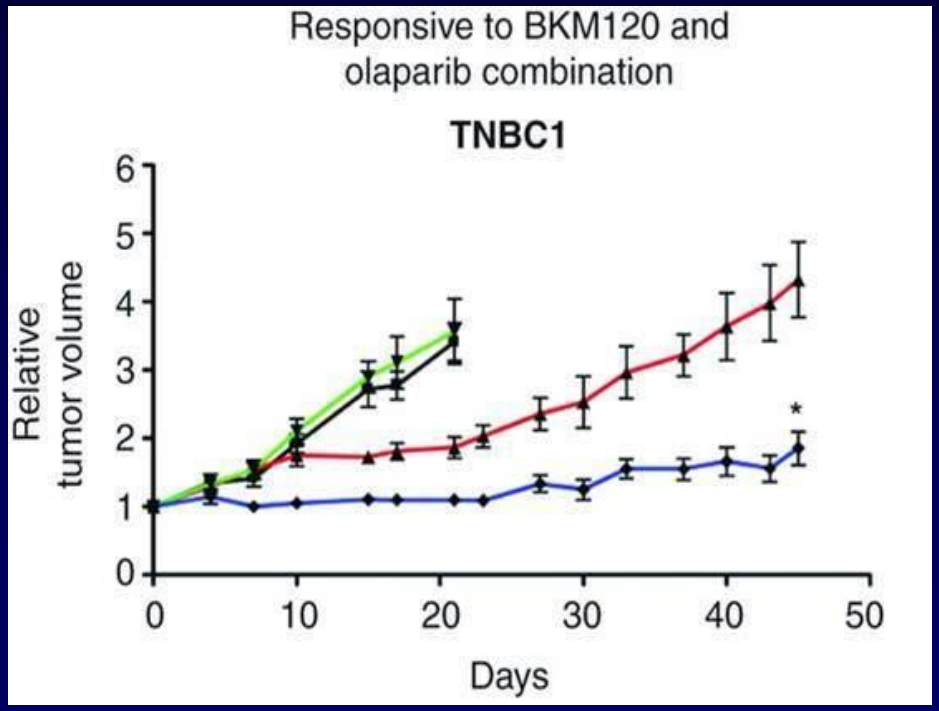
Liu JF, et al. *Lancet Oncol.* 2014;15(11):1207-1214.

Olaparib /Cediranib in Ovarian Cancer

- **Conclusions / concerns**
  - **An open-label study with no placebo may lead to bias**
  - **Nevertheless, most likely a significantly superior efficacy is seen for combination compared to olaparib alone, particularly in *BRCA* "other group"**
  - **At dose of 30 mg od, cediranib toxicity was considerable**
  - **Further studies of this combination are warranted both as maintenance therapy and for recurrent disease**

Liu JF, et al. *Lancet Oncol.* 2014;15(11):1207-1214.

PARP Inhibitor Plus PI3K Inhibitor



Ibrahim YH, et al. *Cancer Discov.* 2012; 2(11):1036-1047.

- With PI3K/AKT inhibitors
  - Preclinical data in TNBC cells demonstrate that P13K inhibition suppresses *BRCA* 1/2 expression and enhances sensitivity to PARP inhibition, partly through activation of ERK and transcription factor ETS1
- Phase I trials now underway, including olaparib plus AZD5363
  - Initial data encouraging with no overlapping toxicity

Juvekar A, et al. *Cancer Discov.* 2012;2(11):1048-1063.
Rehman FL, et al. *Cancer Discov.* 2012;2(11):982-984.

MEK Inhibitor Plus P13K Inhibitor

- **Serous ovarian cancer comprises:**

	Precursor	Mutation	Chromosomal Instability	Response to Chemo	5-Year Survival, %
Low-Grade	Serous borderline	*KRAS, BRAF, HRAS*	Low	Usually poor	50-60
High-Grade	STIC	*TP53*	High	Good but recurs	40-50

In low-grade serous cancer:

- **Responses (PR18%) noted with single-agent MEK inhibitor (selumetinib), but will this be sufficient?** (Farley J, et al. ***Lancet Oncol.*** 2013;14(2):134-140.)
- **Note experience with RAF inhibitors in melanoma**
- **Preclinical data suggest resistance to RAS/RAF/MEK inhibition can be circumvented by P13K/AKT blockade.**
- **Toxicity challenges: diarrhoea / skin rash /fatigue**
- **Randomised studies may be necessary with appropriate dose modifications.**

Looking Ahead……

New targets leading to developments in:

- Immunotherapy (checkpoint inhibitors)
- Antibody-drug targeting

Looking Ahead – Early Results in Platinum-Resistant Ovarian Cancer

PDL-1[1]

- 48/70 +ve for PDL1 expression (Hamanishi J, et al. *Proc Natl Acad Sci U S A.* 2007;27(9):3360-3365.)
- 20 patients with platinum-resistant disease treated with nivolumab (anti PDL1 antibody)
  - 1/10 PR at 1 mg/kg
  - 2/8 CR at 3 mg/kg, including 1 PR lasting 1 year and 1 patient with clear-cell carcinoma

NaPi2b[2]

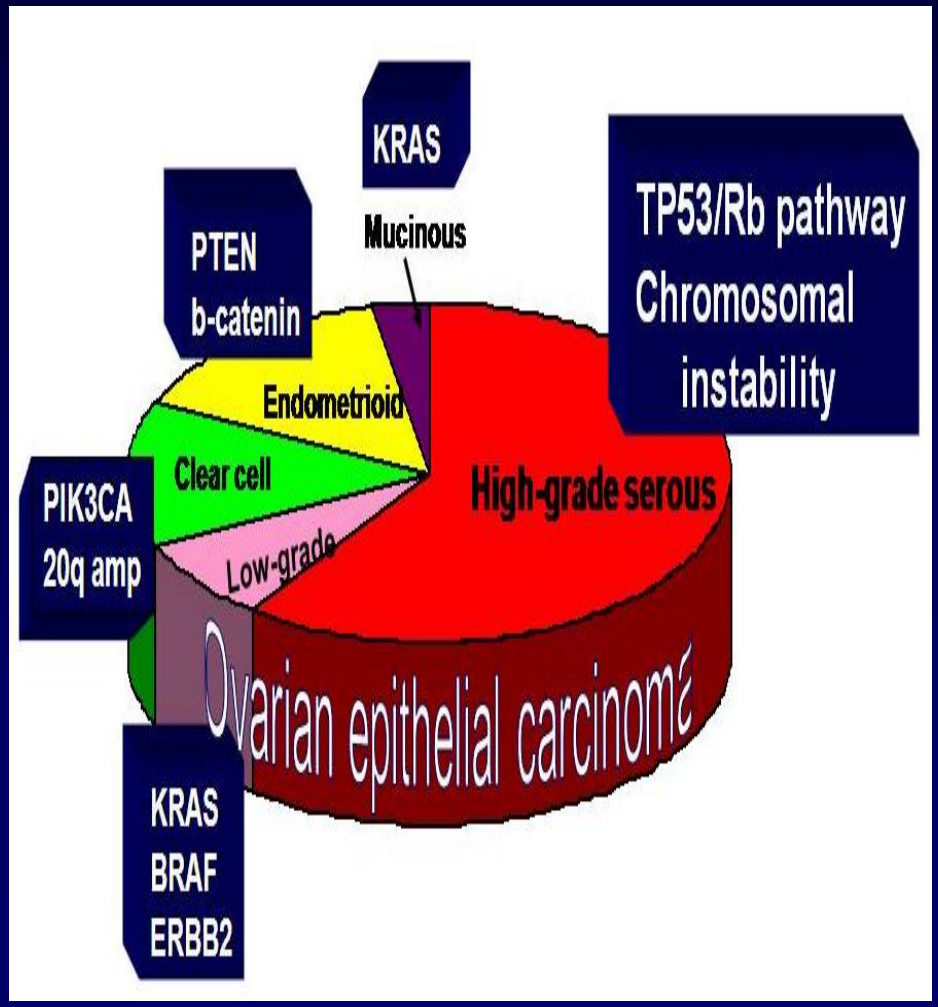
- Highly expressed in ovarian cancer
- Controls transport of inorganic phosphate
- Drug antibody conjugate comprising anti-NaPi2b with MMAE iv q3 weekly
- 7/17 PR (41%) in IHC-positive patients with platinum-resistant disease

Folate receptor[3]

- Highly expressed in ovarian cancer
- IMGN853 is a drug-antibody conjugate comprising anti-FRα with DM4 iv q 2 weekly
- 10/24 PR (42%) in platinum-resistant patients receiving >3.3 mg/kg

1. Hamanishi J, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5511.
2. Burris HA, et al. *J Clin Oncol.* 2014;32(5S): Abstract 2504.
3. Moore KN, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5571.

Targeted Therapy in Ovarian Cancer



Summary:

- **Real optimism surrounding new treatments for first time in 20 years**
- **Antiangiogenesis and PARP inhibition are most promising, with positive randomized trial data**
- **Other targeted approaches, particularly involving novel combinations, are being actively pursued**
- **Patient selection, using robust predictive biomarkers, will be key to success**

2015

Progress and Controversies in Gynecologic Oncology Conference