Targeted therapy of ovarian cancer: beyond angiogenesis

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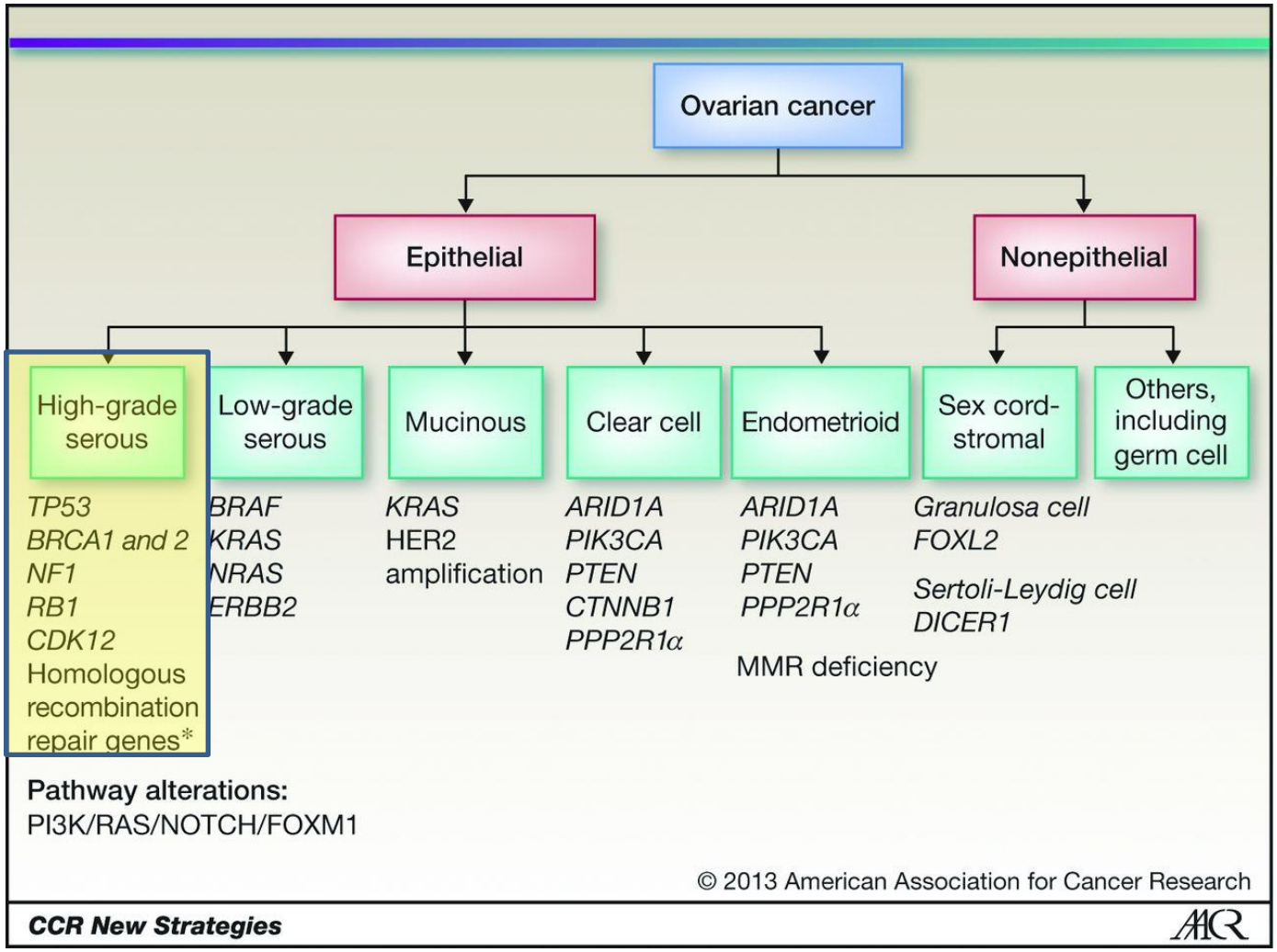
Disclosure slide

- Advisory board participation: Roche, Astra Zeneca, Pharmamar, MSD, Amgen, Oxigene, Endocyte
- Participation in sponsored trials: Astra Zeneca, Roche

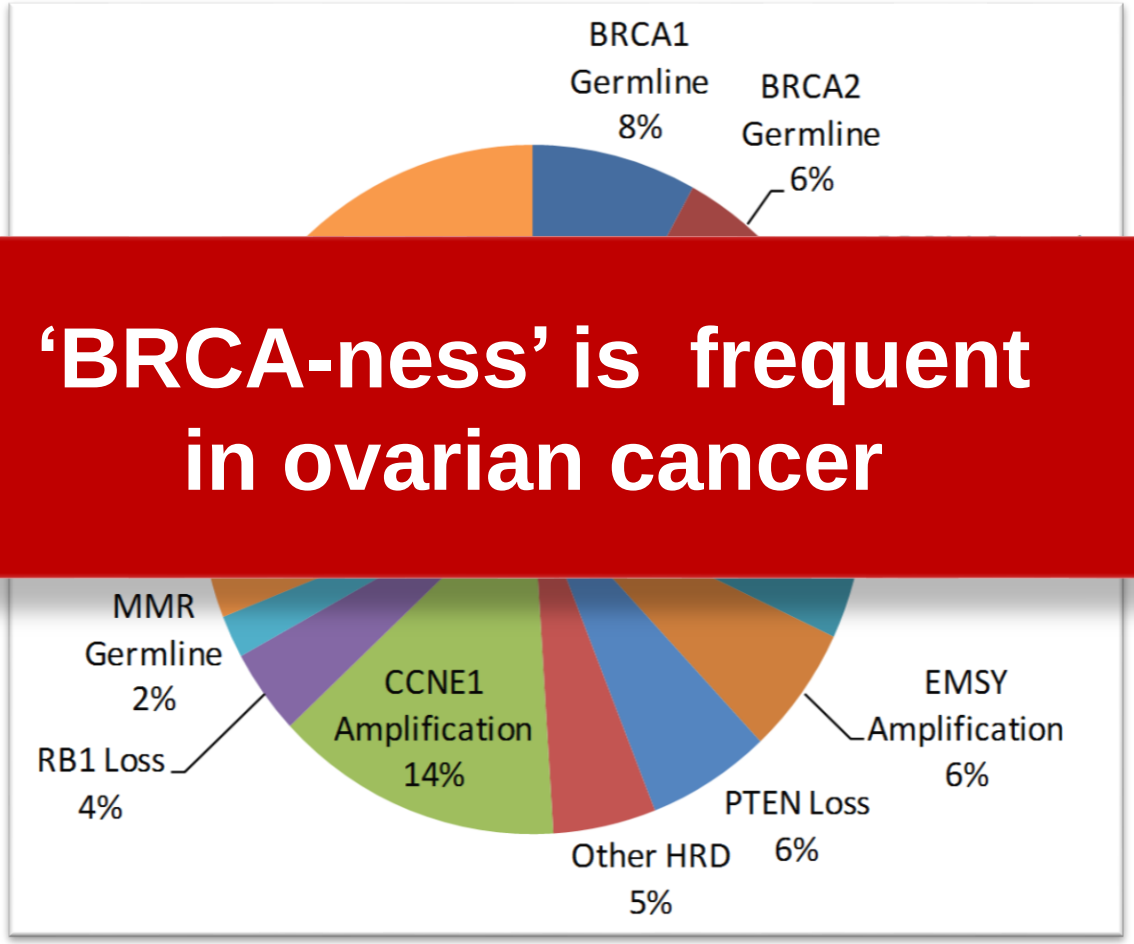
Beyond angiogenesis

Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.



Banerjee S , and Kaye S B Clin Cancer Res 2013;19:961-968

High grade serous ovarian cancer: Potential benefit of PARP inhibition in 50%



'BRCA-ness' is frequent in ovarian cancer

Not I… HR

Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615.

Mechanisms of Action of PARP-Inhibitors

DNA SSBs occur all the time in cells and PARP detects and repairs them

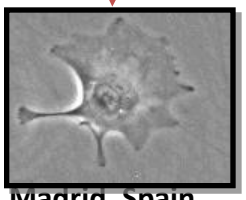
During the replication process unrepaired SSBs are converted into DSBs

Replicating cells

Normal cell

Repair by Homologous Recombination

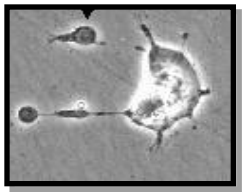
Survival



Tumor specific killing by Olaparib

Cancer cell with HRD

No effective repair (No HR pathway)



Cell death

Randomized Trial of Maintenance Olaparib in Platinum-Sensitive High Grade Serous Relapsed Ovarian Cancer - 'Study 19'

Study aim and design

265 patients

Patients:

- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

Olaparib 400 mg PO bid

Randomized 1:1

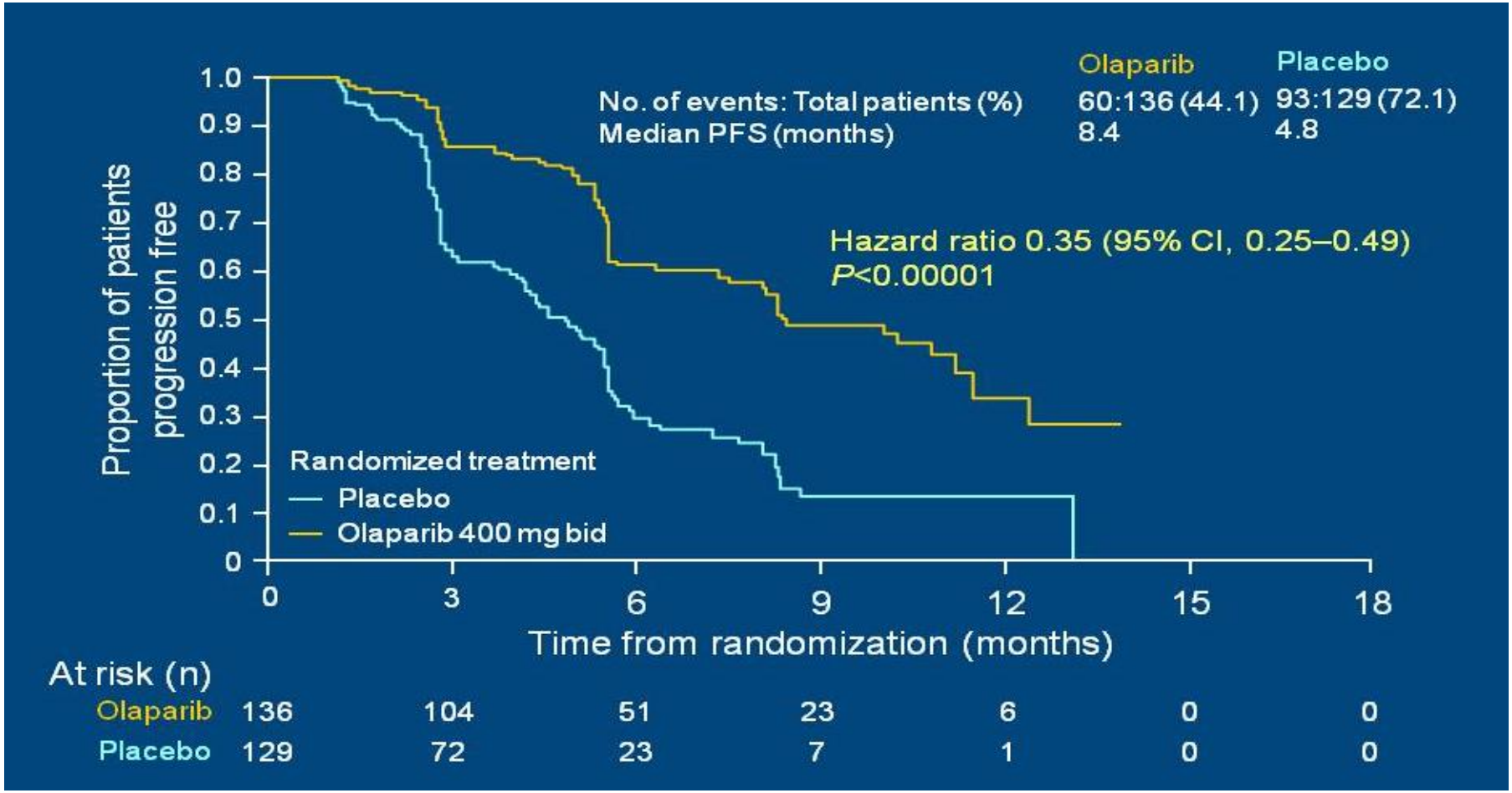
Placebo PO bid

Treatment until disease Progression

Primary endpoint : PFS

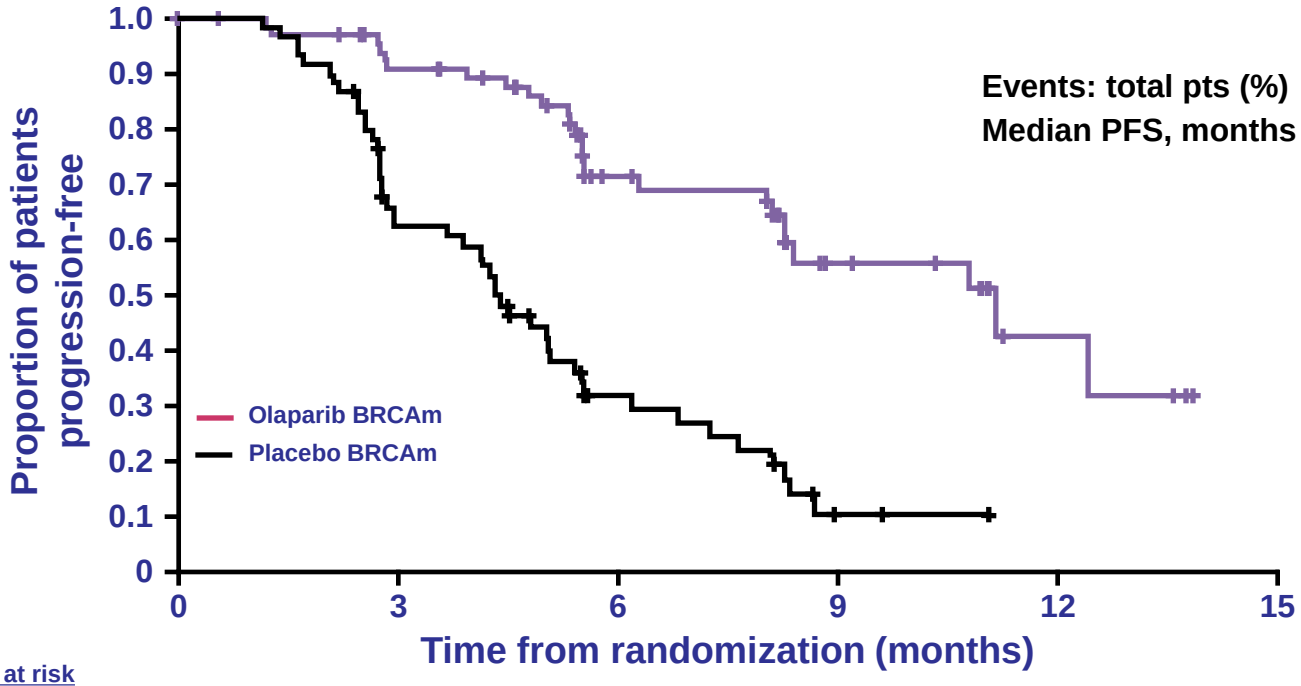
Ledermann J, et al. *N Engl J Med.* 2012;366(15):1382-1392. Ledermann JA, et al. *J Clin Oncol.* 2013;31(suppl): Ledermann J, et al. *Lancet Oncol*. 2014;15(8):852-861.

Progression-Free Survival in Randomized Trial of Maintenance Olaparib



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

PFS in relation to BRCA mutation



Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

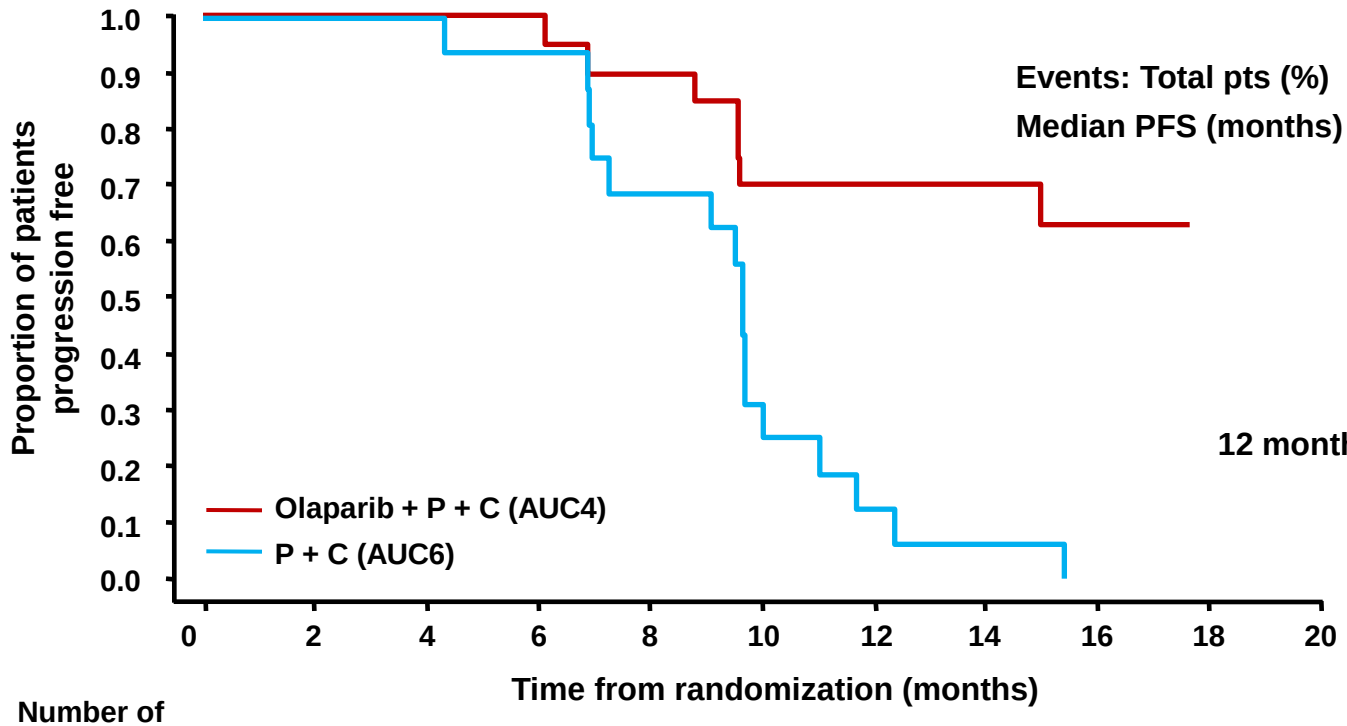
BRCAm (n=136)		
	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)
Median PFS, months	11.2	4.3

HR=0.18
95% CI (0.11, 0.31);
P<0.00001

- 82% riduzione nel rischio di progressione di malattia o morte con olaparib

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

Adding Olaparib to Carboplatin and Paclitaxel Improves PFS* in *BRCAm* Patients



Number of patients at risk											
O/P/C	20	20	20	20	18	14	14	10	1	0	0
P/C	21	18	17	15	11	4	2	1	0	0	0

BRCAm (n=41)	O/P/C	P/C
Events: Total pts (%)	7:20 (35.0)	16:21 (76.2)
Median PFS (months)	NR	9.7

HR=0.21
95% CI (0.08, 0.55);
P=0.0015

Percentage event free	O/P/C	P/C
12 months	70%	12.5%

- 79% reduction in risk of disease progression with olaparib in BRCAm patients
- Clear separation between treatment arms observed at 7 months

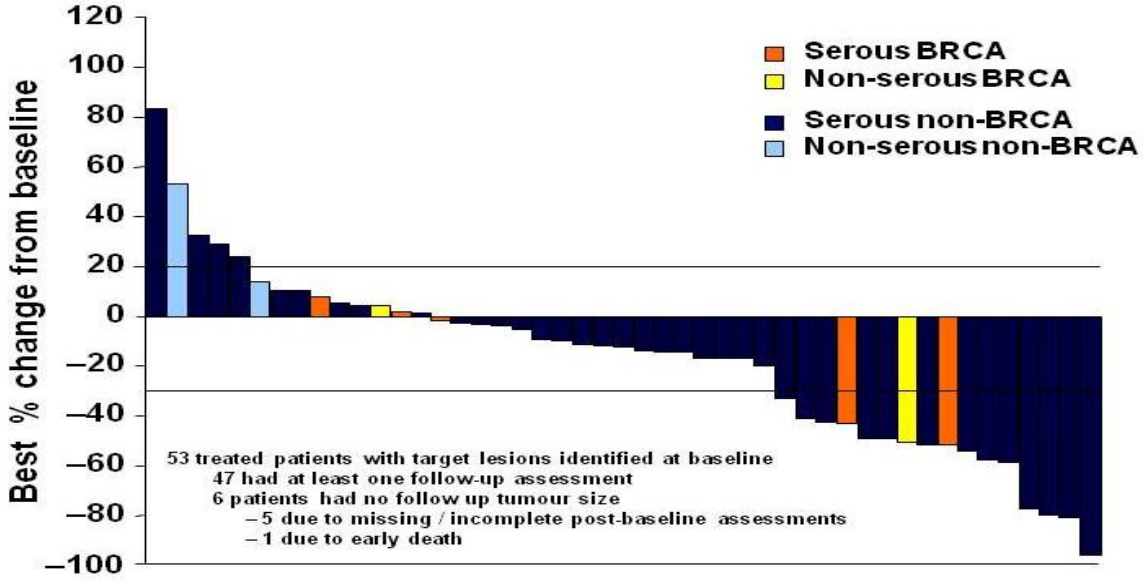
Amit Oza et al. ECC 2013

Tolerability of Olaparib—Longterm Use

- Fatigue, nausea, and anemia—main adverse effects- generally low grade
- 30% patients on olaparib had a dose interruption (9% on placebo)
- 19% needed dose reduction (2% with placebo)

Potential of PARP Inhibitors in Sporadic Ovarian Cancer

Best % change in target lesion size: high grade serous ovarian/undifferentiated tubo-ovarian; unknown or *BRCA* –ve at entry

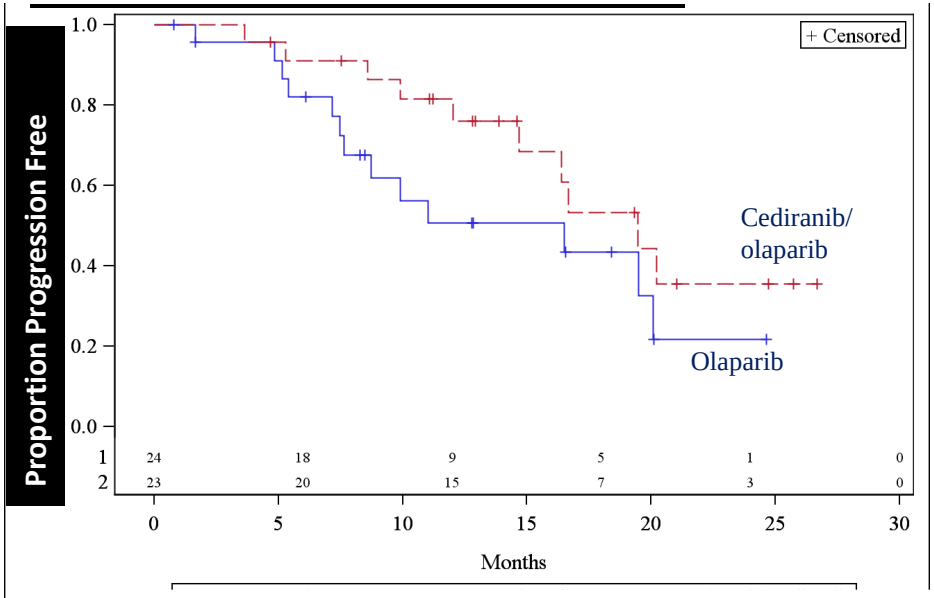


Single-agent olaparib 400 mg BID cont. in 48 cases of relapsed ovarian cancer

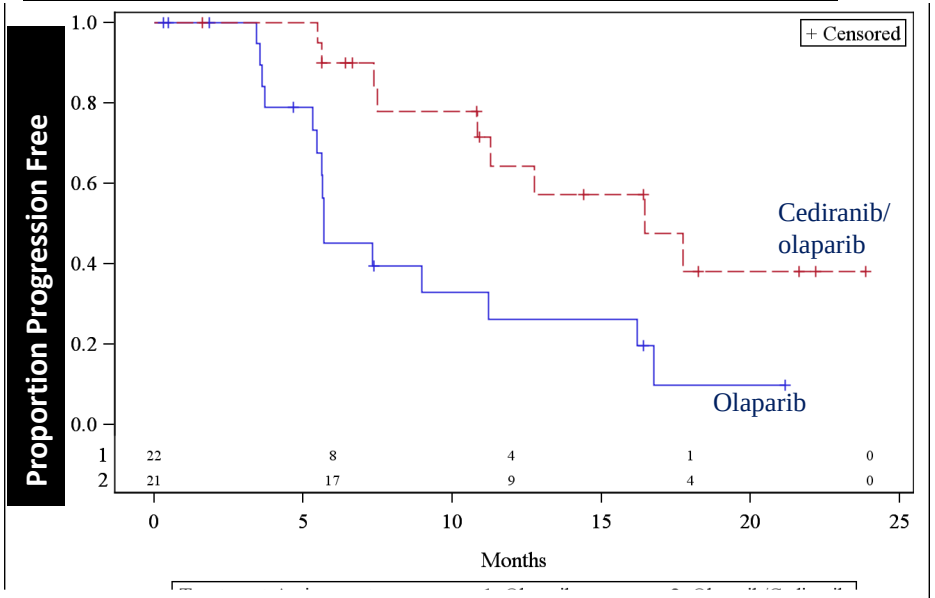
Gelmon KA, et al. *Lancet Oncol*. 2011;12(9):852-861.

Cediranib/Olaparib Significantly Increased PFS in Patients Without a *BRCA* Mutation

BRCA Mutation Carrier



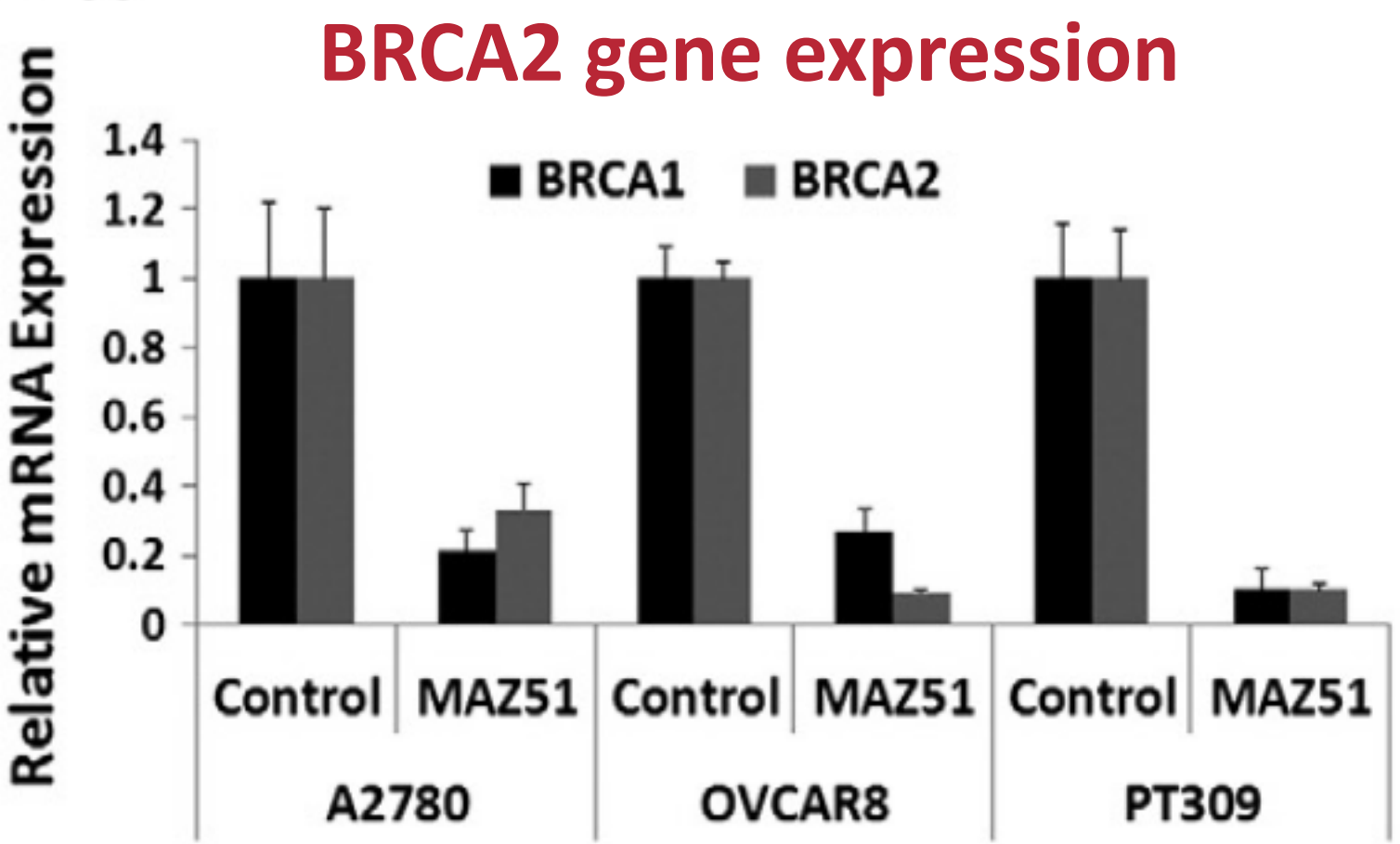
BRCA Non-Carrier/Unknown



Olaparib	Ced/Olap	Olaparib	Ced/Olap
13	10	15	9
16.5 months	19.4 months	5.7 months	16.5 months
P = .16		*P* = .008	
HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

Liu J, et al. *Lancet Oncol 2014* Published **Online** September 11, 2014

VEGFR3 inhibition decreases BRCA1 and BRCA2 gene expression



Jaeyoung J.Lim et al. Neoplasia (2014) 16, 343–353.e2

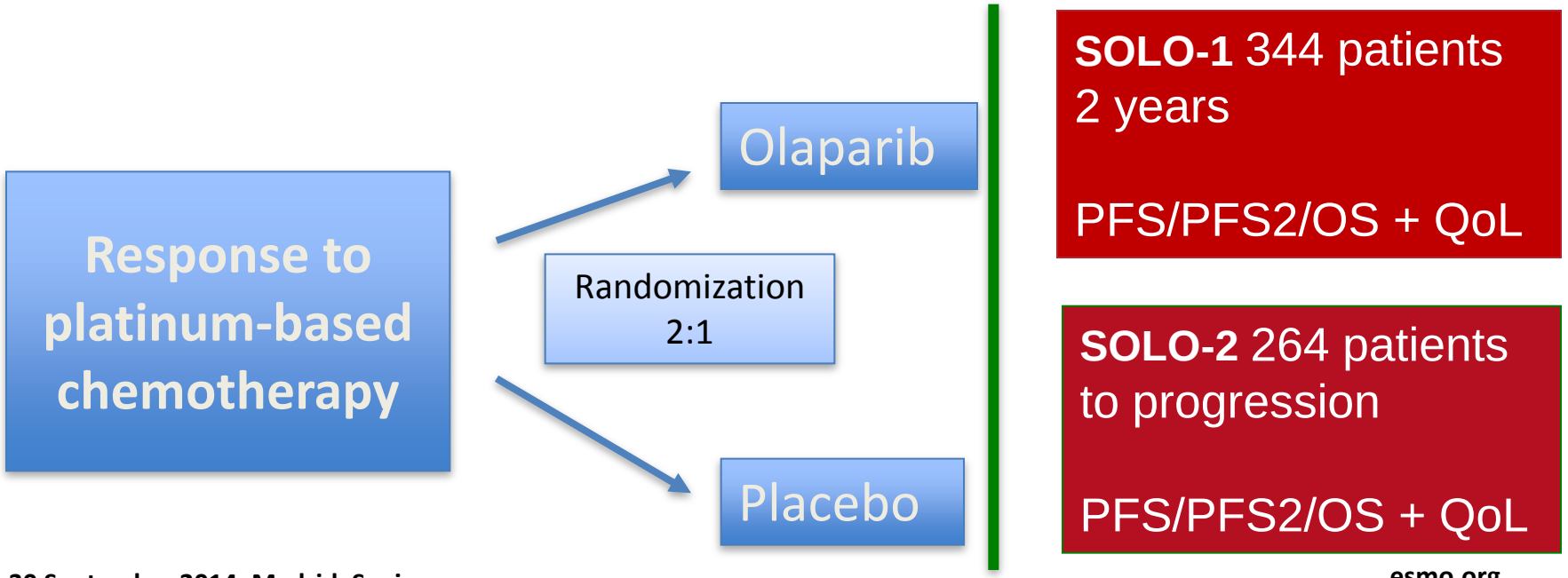
PARP Inhibitors in Clinical Trials

PF-01367 (Rucaparib)	Clovis/Pfizer	IV/oral
Olaparib	AZ	Oral
MK 4827 (Niraparib)	Tesaro	Oral
BMN 673	BioMarin	Oral
ABT 888 (Veliparib)	Abbott	Oral
INO-1001	Inotek	IV
GP1201	Eisai	Oral
CEP 9722	Cephalon	Oral

Consistent feature at highest doses is myelosupression affecting WBC and/or platelets.

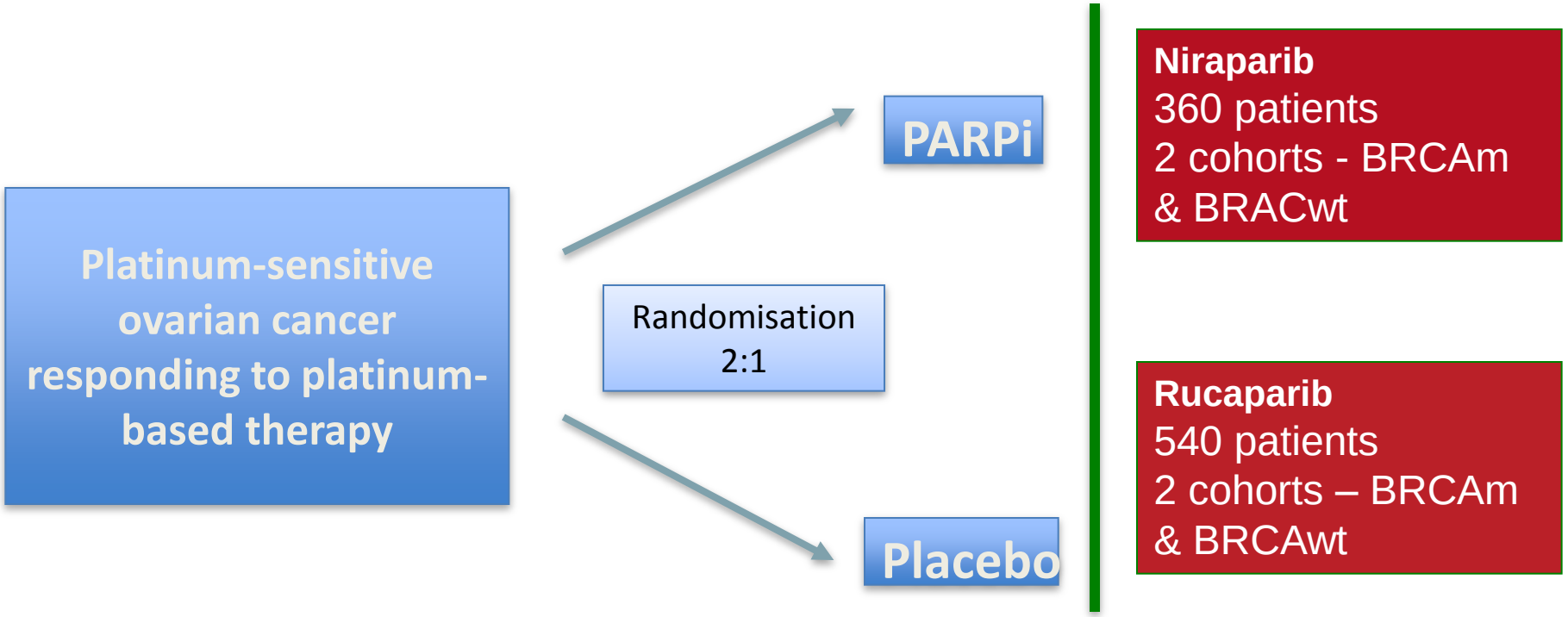
SOLO-1 & SOLO 2 Program
BRCAm Population Only

First-line maintenance or maintenance in 'platinum-sensitive' setting



NOVA and ARIEL3 Programmes

Both studies include a BRCAm and High Grade Serous wild type subsets



Identification of companion diagnostic marker to select patients with HRD, most likely to benefit

Key issues for future development

- Combination approach?
  - Chemotherapy not worth and too toxic
  - **With antiangiogenic agents (hypoxia increased HRD in preclinical model; VEGFR3 inhibition decreased BRCA expression)**
  - With P13K/AKT inhibitors (preclinical data on suppression of BRCA1/2 expression)
- How frequent are secondary (revertant) mutations, restoring *BCRA* function?
- Will PARPi impact response and tolerance to subsequent therapy?
- What is the activity in other HR-deficiency profiles ?

p53 is an attractive target for new therapeutic approaches

Loss of function
by mutation

Reactivaton *of the*
Tumor-suppressor function

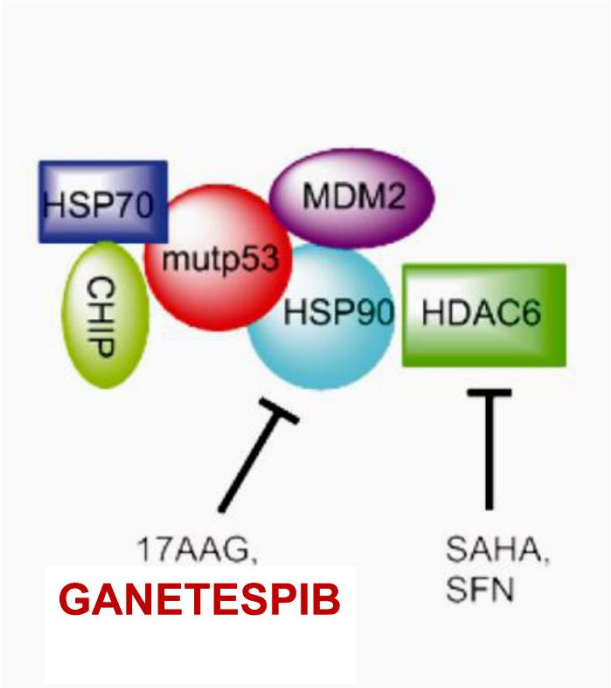
Gain-of function
by the mutant protein

Inhibition *of the*
oncoprotein function

HSP90 interaction

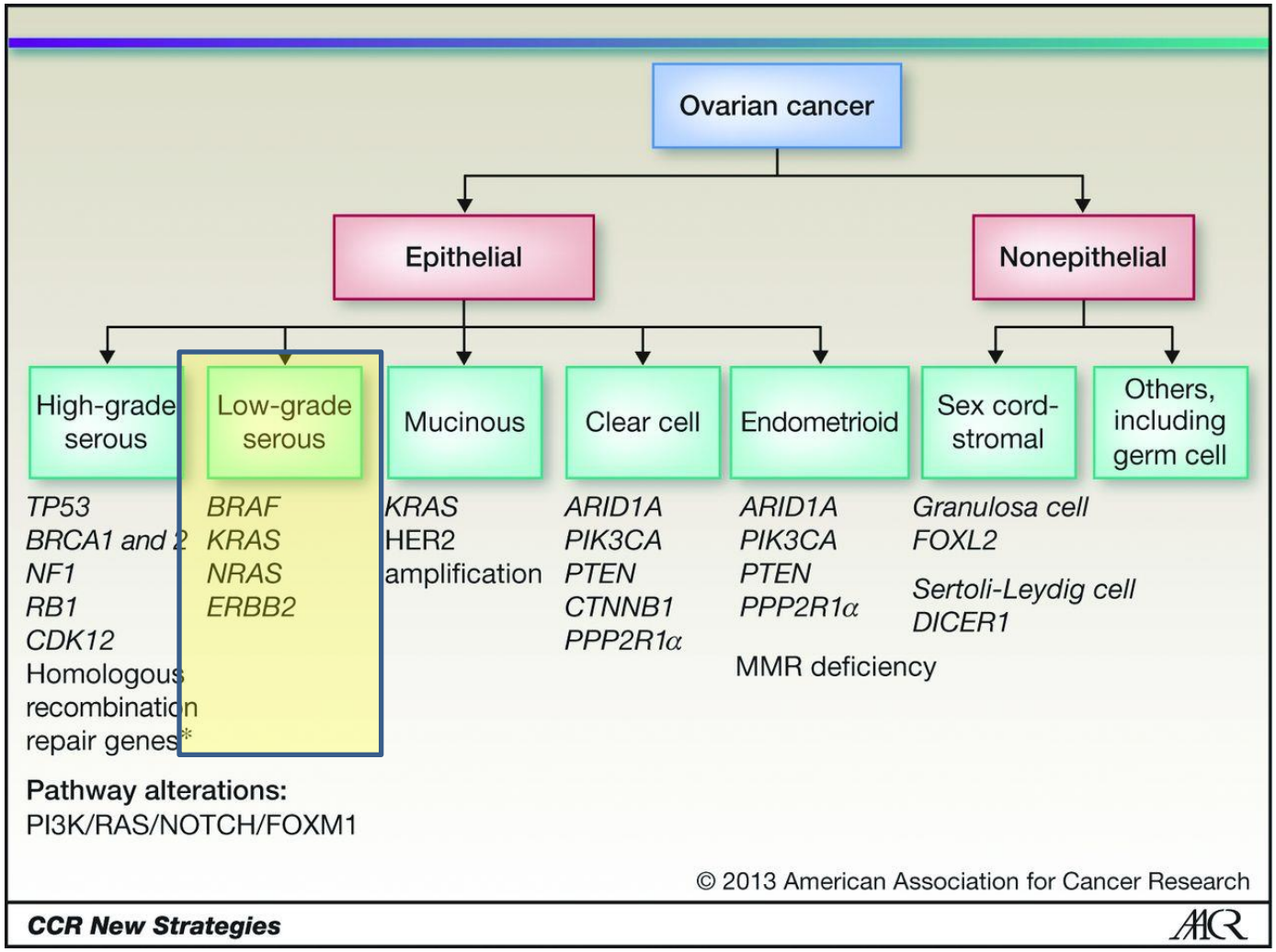
mutp53 proteins **depend on permanent folding support by the multi-component HSP90 chaperone**

Staple chaperone complex with mutp53



Li et al, Mol Cancer Res 2011
Li et al, Cell Death & Diff 2011

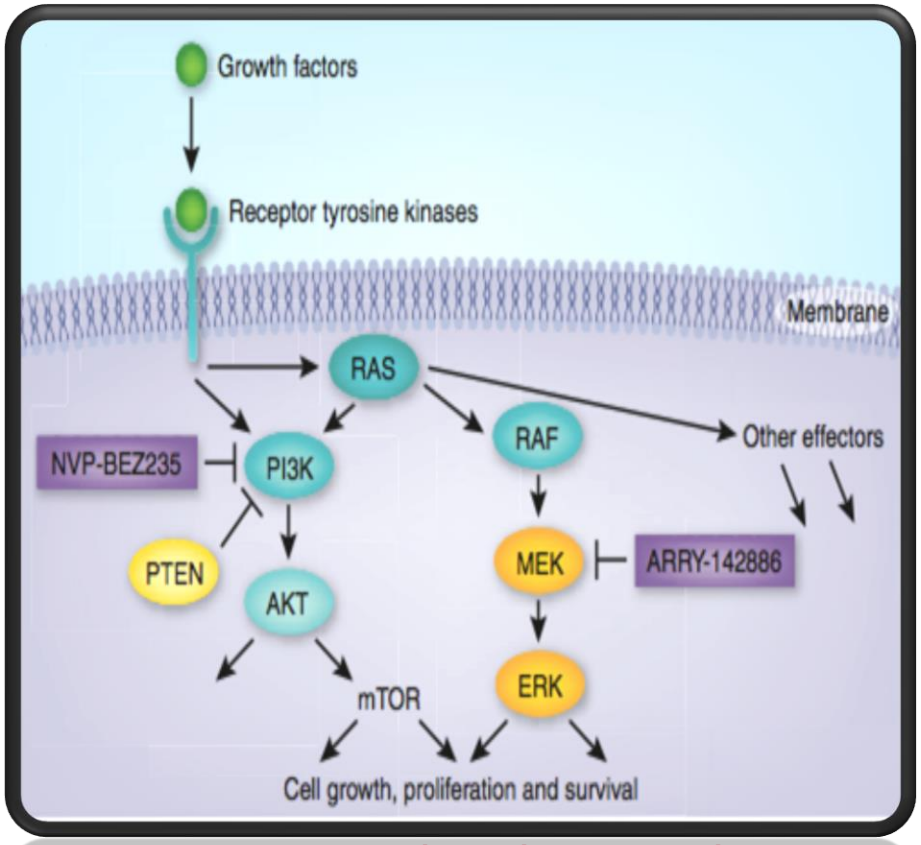
Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.



Banerjee S , and Kaye S B Clin Cancer Res 2013;19:961-968

GOG 239: AZD6244

- Phase II
- Recurrent low-grade serous carcinoma of the ovary
  - Central pathology review for eligibility
- AZD6244 (ARRY-142886) small molecule inhibitor of the MEK-1/2
  - 68% of low-grade serous tumors have mutations in *BRAF* or *KRAS* genes



Farley et al Lancet Oncol 2013

MADRID 2014 ESMO congress

MEK-inhibition shows Promising clinical data in Recurrent low-grade Serous Carcinoma

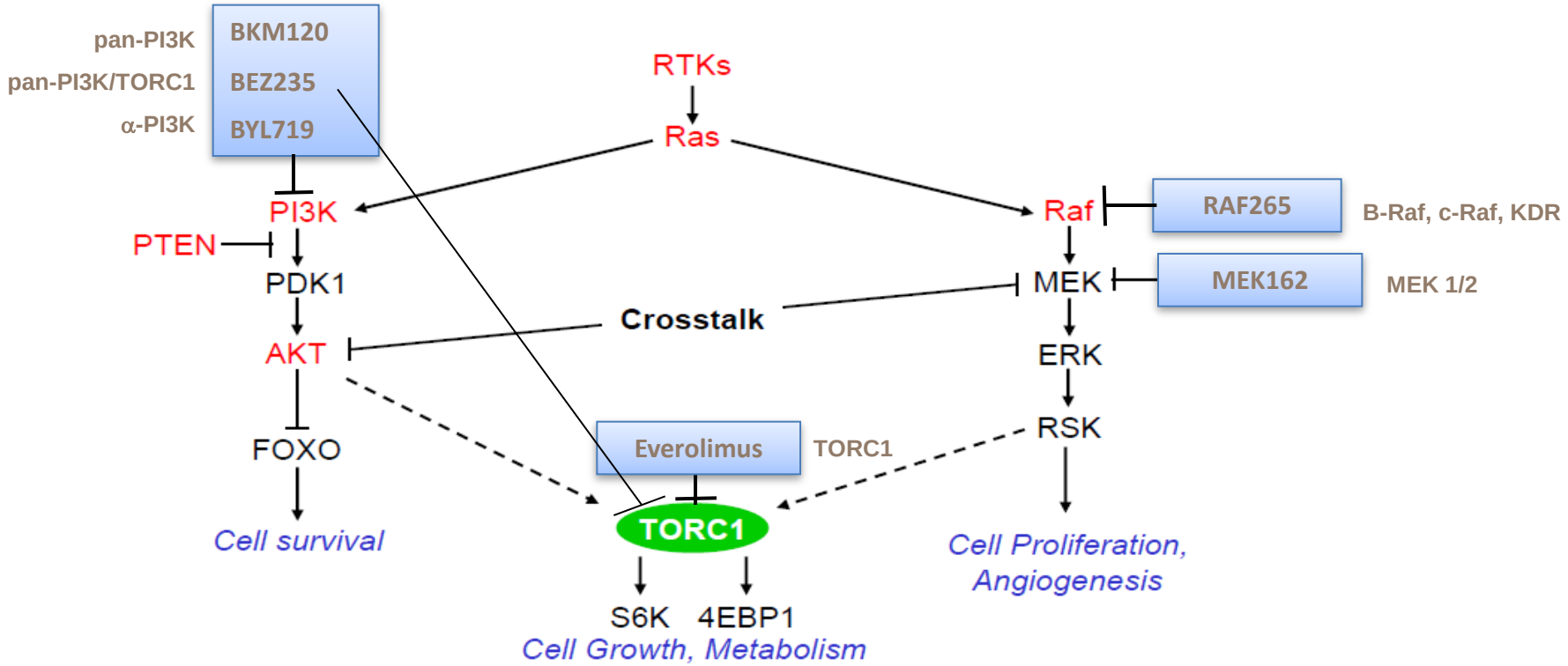
Parameter	Chemotherapy	Hormonal therapy	Selumetinib
N. Patients	58	64	**52**
N			
C			
P			
SD(%)	60	62	**65**
% Clinical benefit	64	71	**80.5**
Median PFS	7.3 mo	7.4 mo	**11 mo**
% PFS>6 mos	58	61	**63**

No correlation between response and BRAF/KRAS mutation

Gershenson et al, Gynecol Oncol 2009
Gershenson et al Gynecol Oncol 2012
Farley et al Lancet Oncol 2013

Interaction of the MAPK and PI3K Pathways in Cancer Combination-Targeted Therapy with PI3K Inhibitors

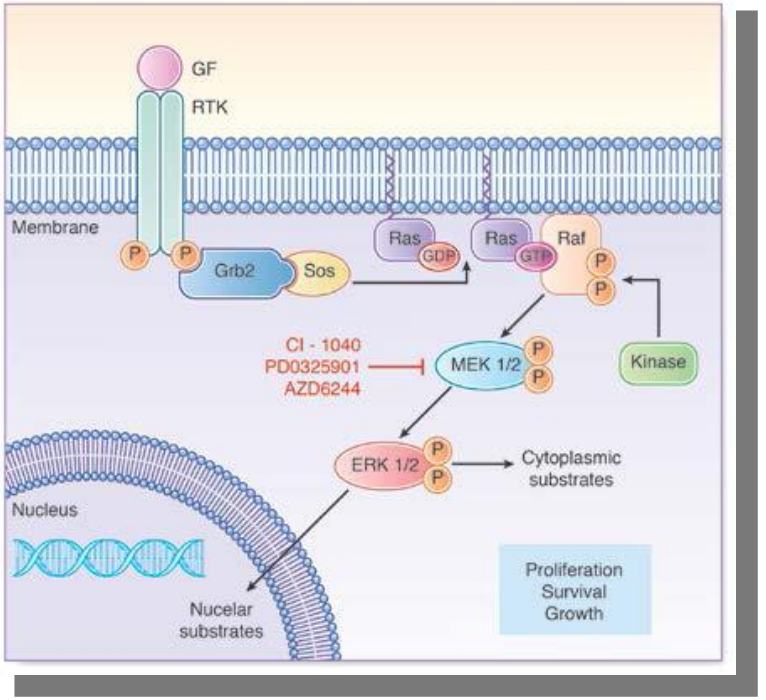
- **Sharing common upstream activators (eg, EGFR)**
- **Common activation by oncogenic Ras**
- **Cross-talking at various levels (eg, Akt on MEK)**
- **Providing compensatory signaling when one or the other is inhibited**



frequently mutated in cancers

Clinical Trial Protocol EMR 200066_012

Phase II Randomized Double Blind Placebo Controlled Trial of Combination of **Pimasertib** with **SAR245409** or of **Pimasertib** with **SAR245409 Placebo** in Subjects with **Previously Treated Unresectable Low Grade Ovarian Cancer**

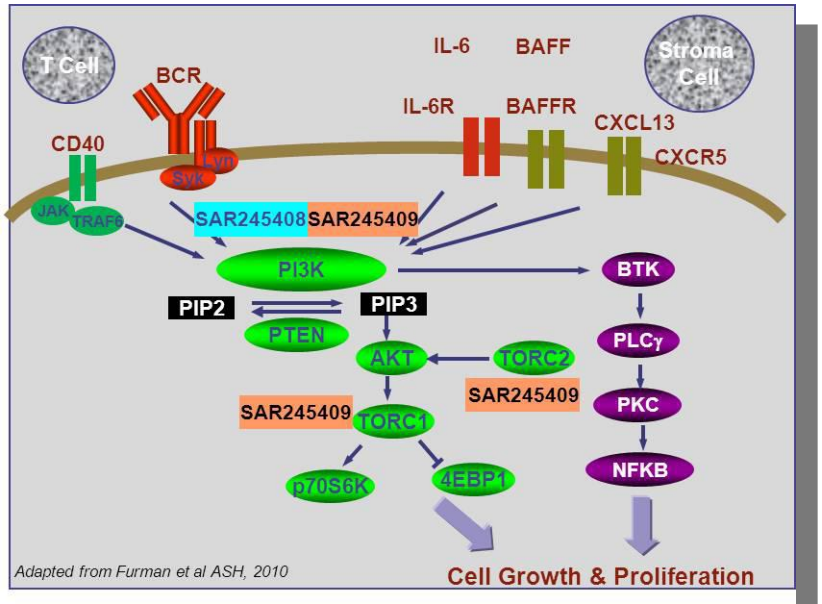


Pimasertib

Selective uncompetitive MEK1/2 inhibitor

Induces G1 cell-cycle arrest and apoptosis

Efficacy in solid tumor with activating mutations in the MAPK signaling pathway (mainly *BRAF and NRAS)*

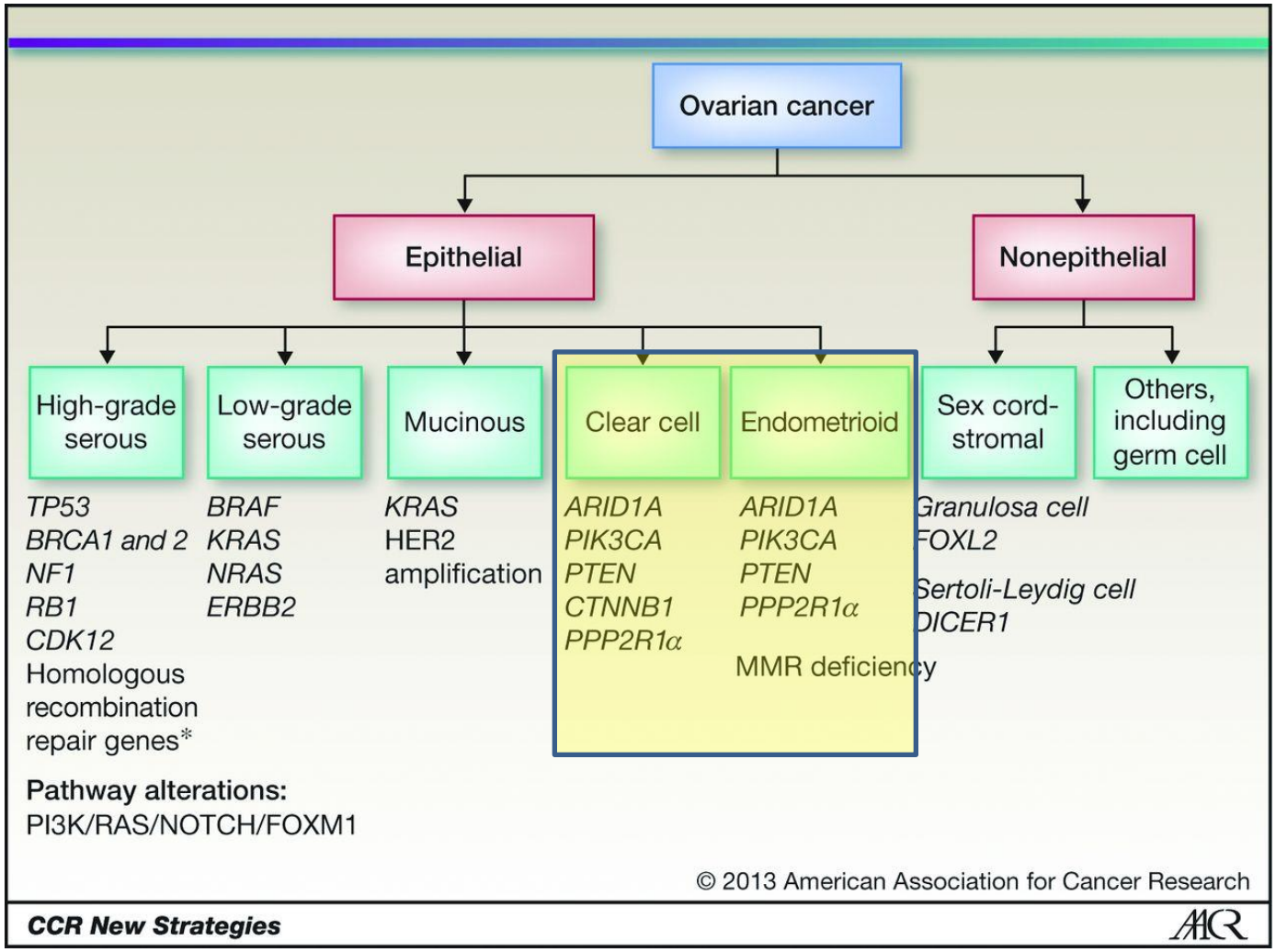


SAR245409

PI3K and ERK pathway inhibition with TORC1/C2 activity

Anti-proliferative and pro-apoptotic effect

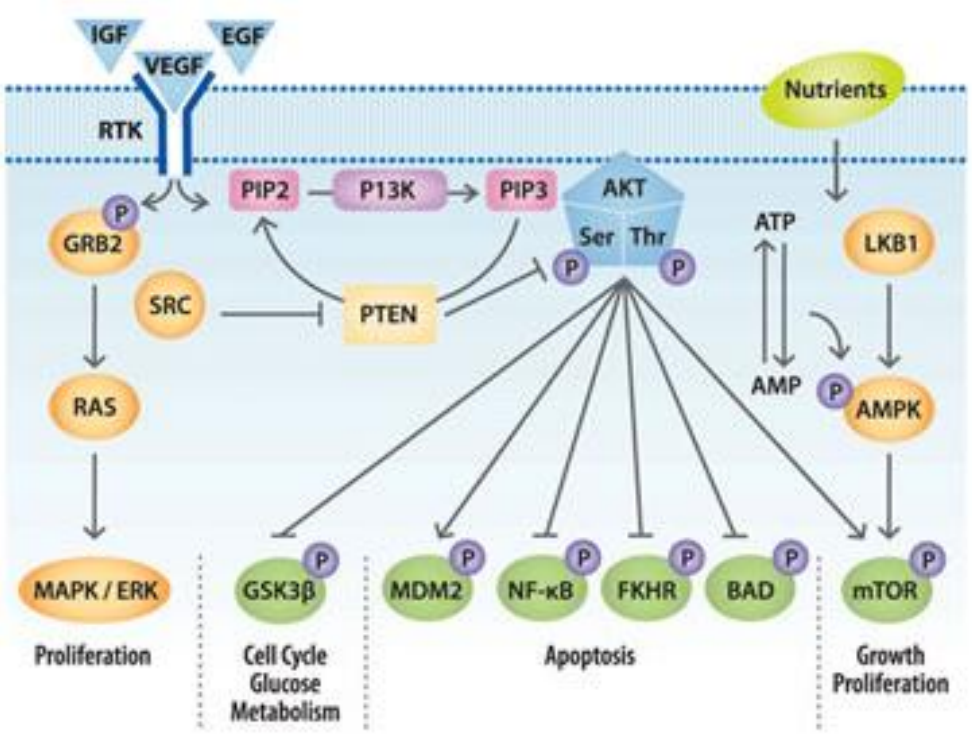
Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, CHK2, BARD1, BRIP1, PALB2, RAD50, RAD51C, ATM, ATR, EMSY, Fanconi anemia genes.



Banerjee S , and Kaye S B Clin Cancer Res 2013;19:961-968

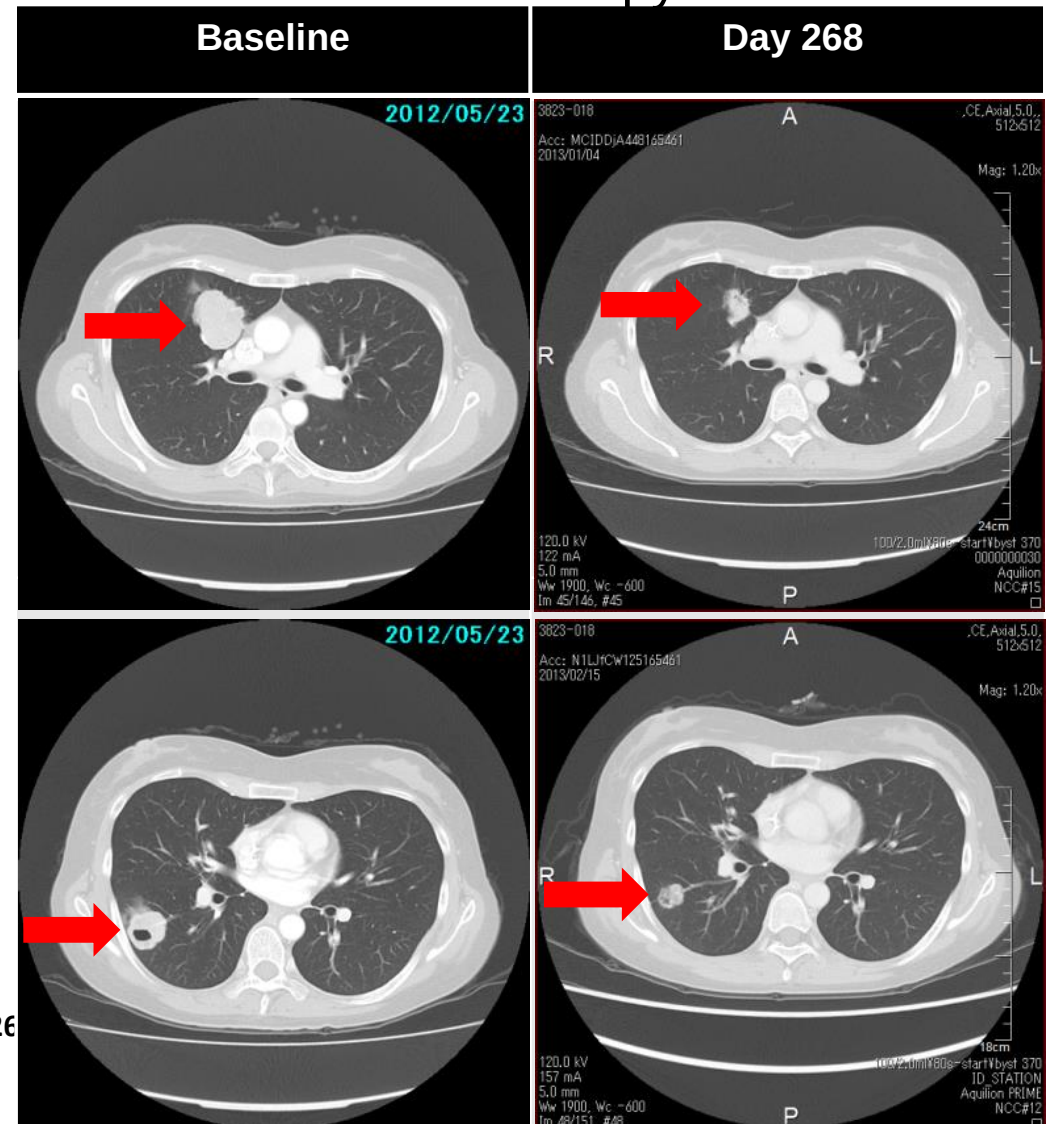
PI3K/AKT Pathway in Ovarian Cancer

- *PI3K* mutation :5% to 6%
- *PI3K–AKT* amplification: 20% to 40%; higher frequency in clear cell and endometroid
- In experimental models PI3K/AKT inhibitors may revert paclitaxel/platinum resistance
- Various pathway-specific inhibitors in phase I clinical trials



AZD5363

38 y-old asian female with endometrioid ovarian cancer after 8 lines of chemotherapy

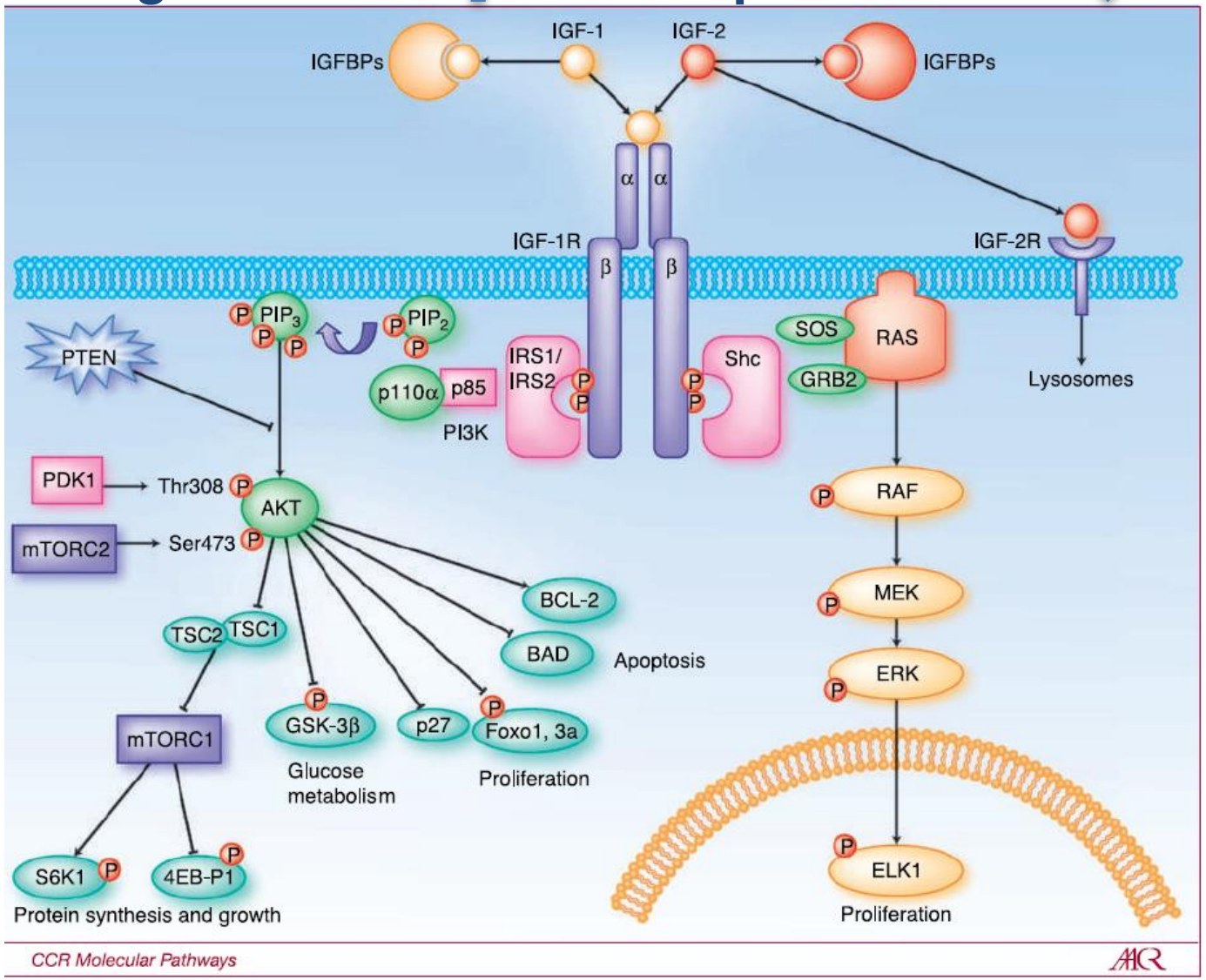


AZD5363 is an orally active, selective protein kinase B inhibitor (Pan-AKT : AKT1, AKT2 and AKT3)

AZD5363 inhibits phosphorylation of AKT substrates and downstream pathway proteins in cells

IGF-1R Signaling Pathway

Gynecological cancer: ↑IGF1R expression and ↓PFS



Zha J, et al. *Clin Cancer Res.* 2010;16(9):2512-2517.

OSI-906 (Oral IGF-1R and IR dual kinase inhibitor) and Weekly Paclitaxel in Ovarian Cancer

Phase I:

58 patients, 55% with ovarian cancer

Main toxicities: Fatigue (45%), nausea (33%), rash (28%), diarrhea (26%)

In 32 ovarian cancer patients, 4PR, 6SD and 10 PD

Phase II : just completed in DDP refractory/resistant

ARM A intermittent OSI906 600 mg QD + weekly P

ARM B continuous OSI906 150 mg BID + weekly P

ARM C weekly P alone

Harb WA, et al. *J Clin Oncol.* 2011;29(Suppl): Abstract 3099.

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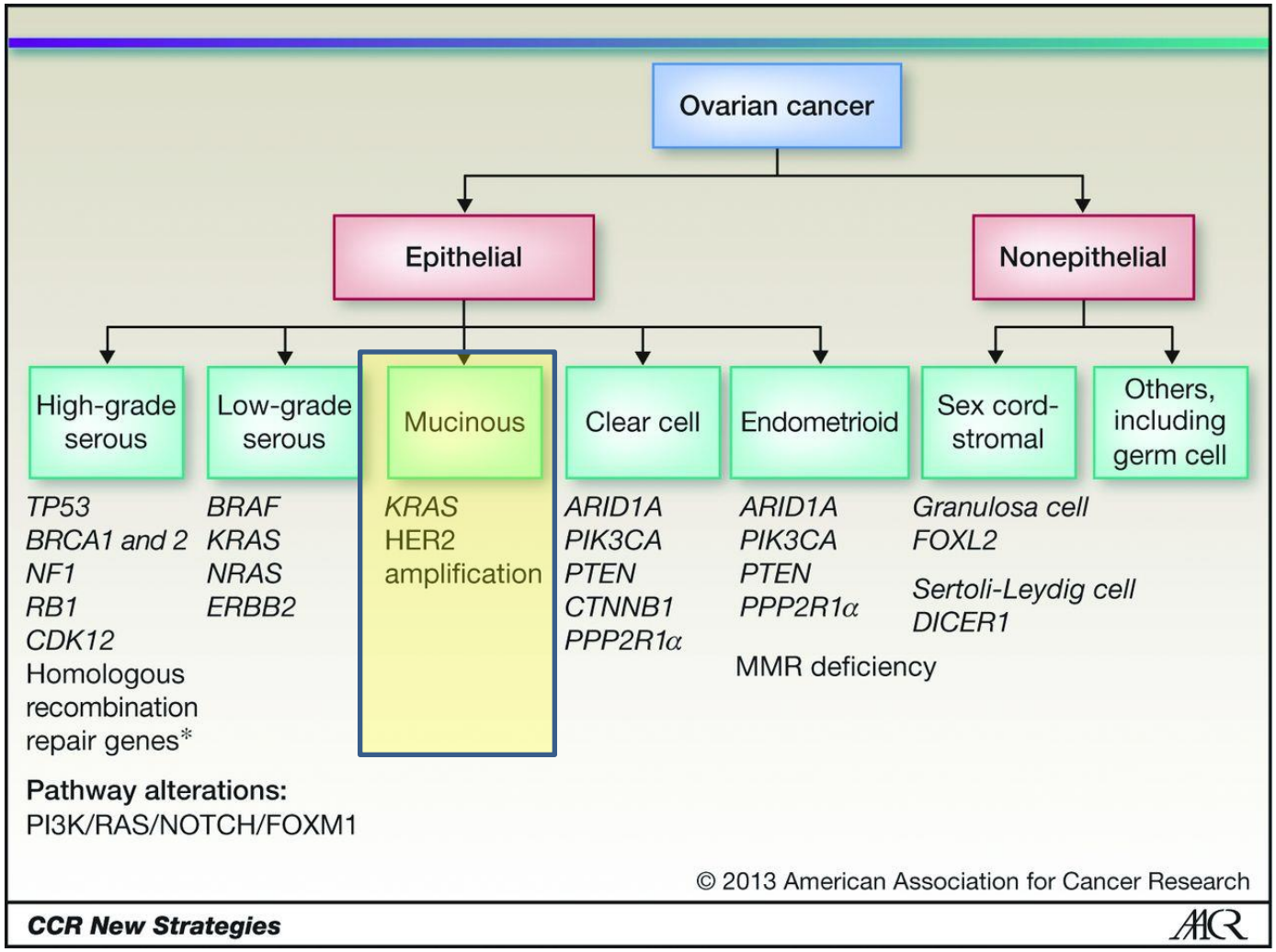
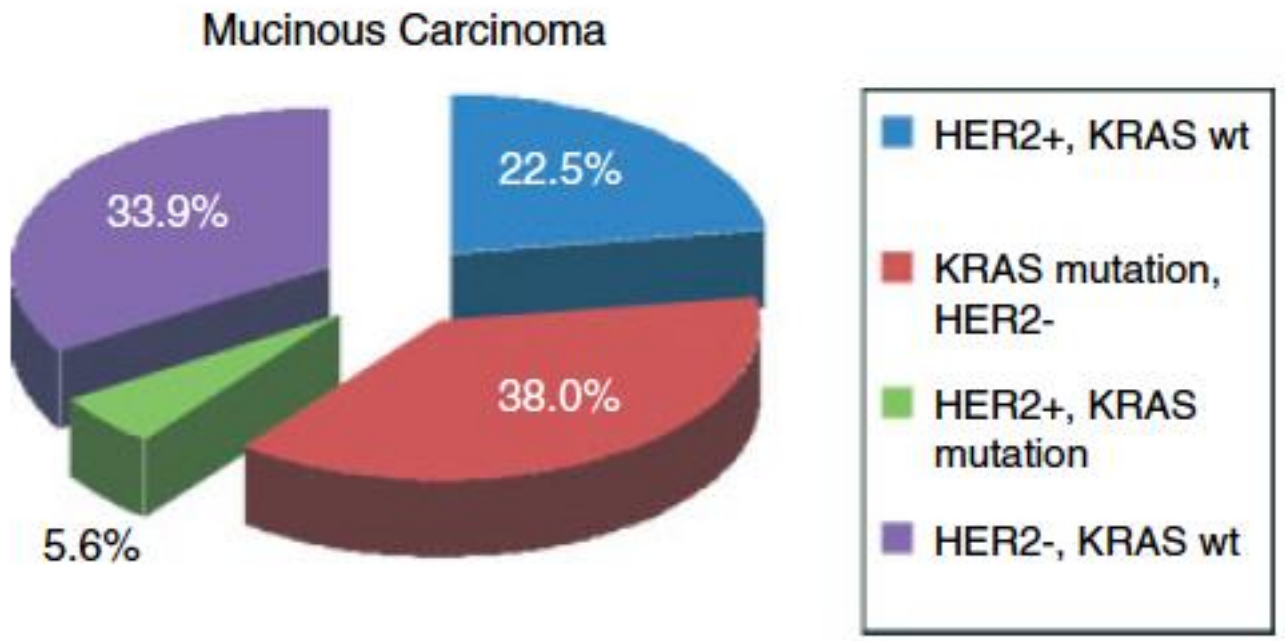


Banerjee S , and Kaye S B Clin Cancer Res 2013;19:961-968

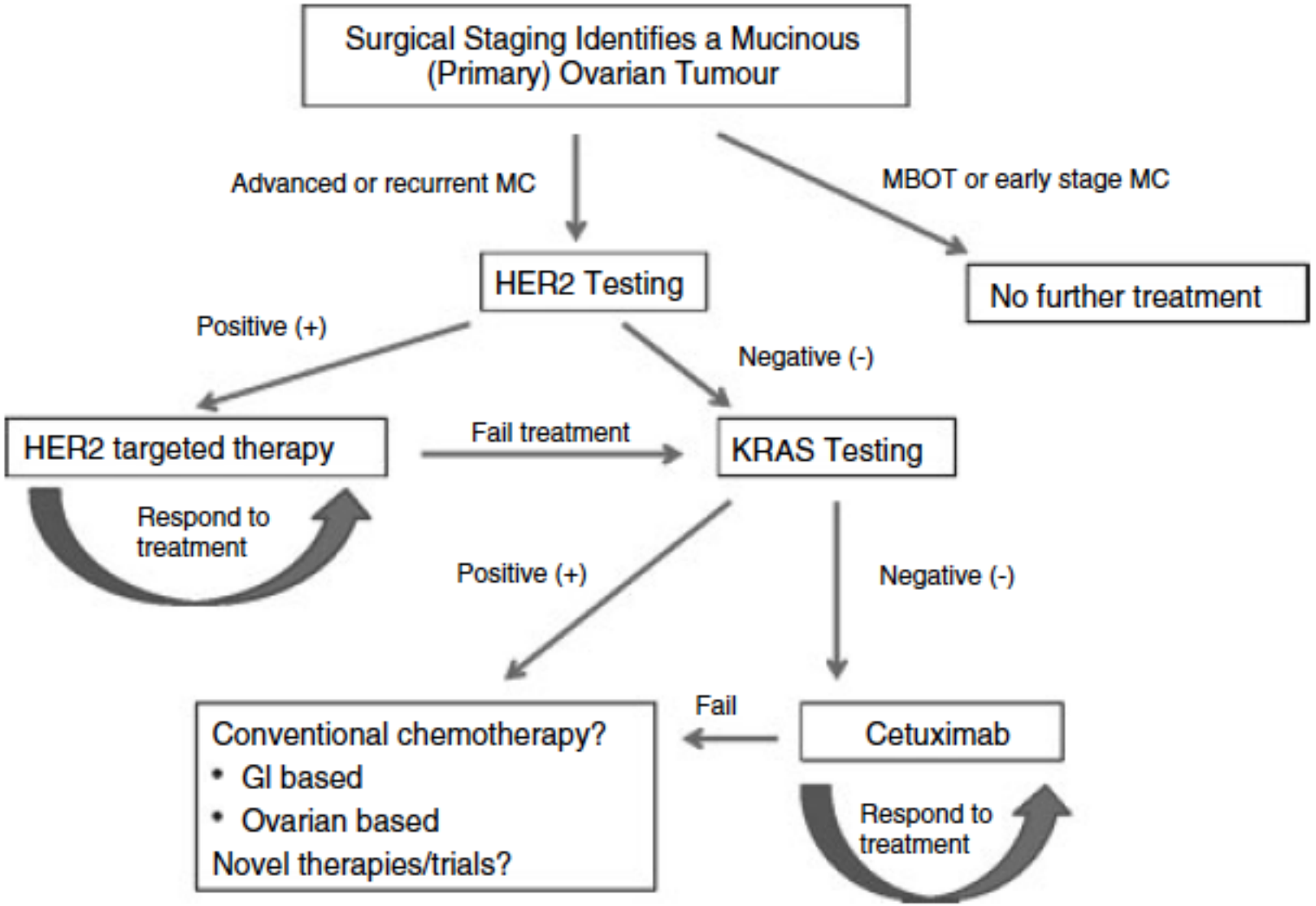
Molecular characterization of mucinous ovarian tumors supports a stratified treatment approach with HER2 targeting in 19% of carcinomas

189 mucinous ovarian cancers



Anglesio et al. J Pathol 2013;229:111-120

Molecular characterization of mucinous ovarian tumors supports a stratified treatment approach with HER2 targeting in 19% of carcinomas

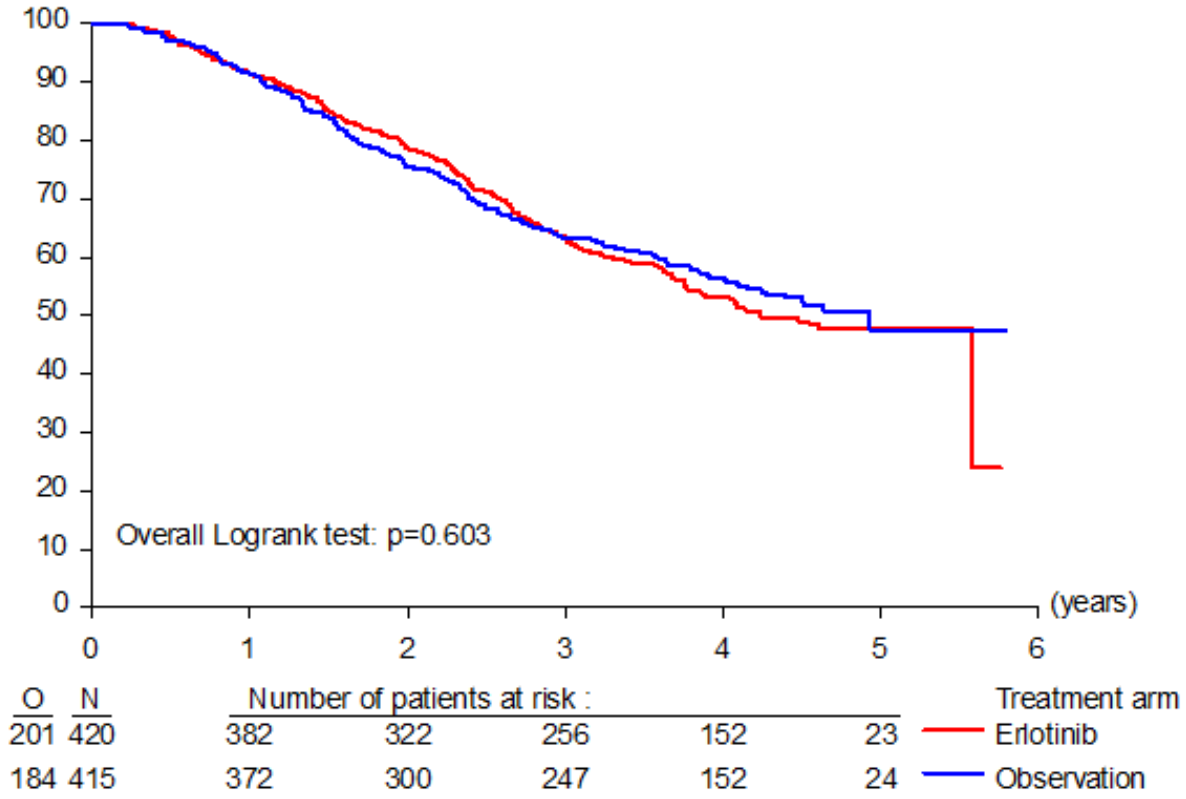


Anglesio et al. J Pathol 2013;229:111-120

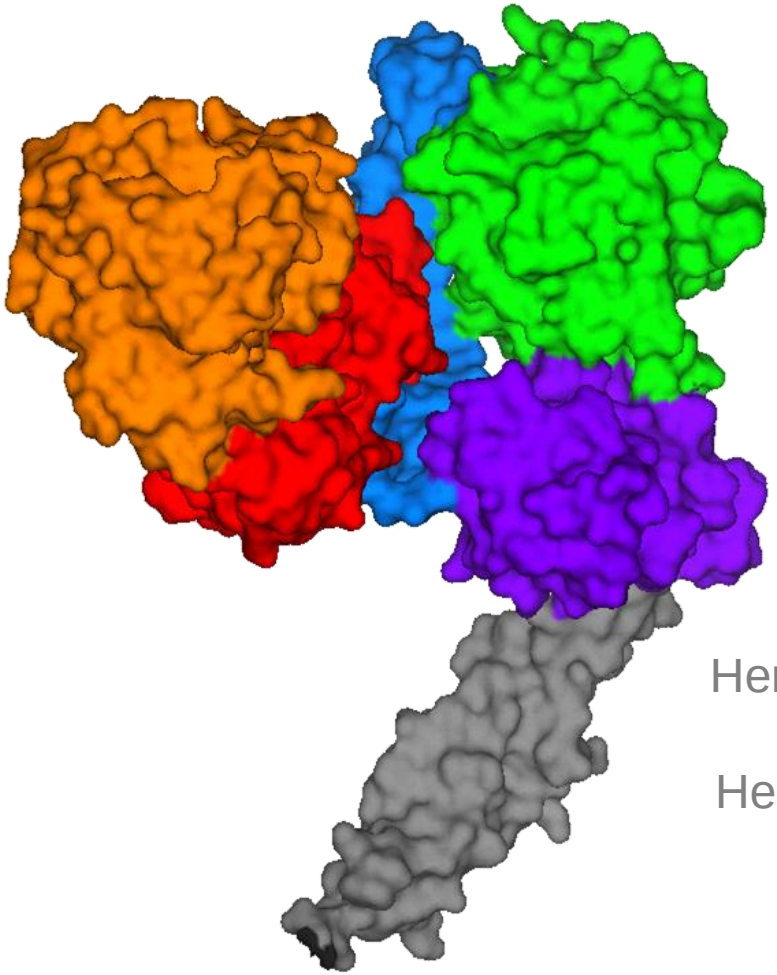
Epidermal growth factor receptor (HER) targeting: disappointing results in ovarian cancer

Randomised trial on Erlotinib vs observation in first-line ovarian cancer:

Overall Survival



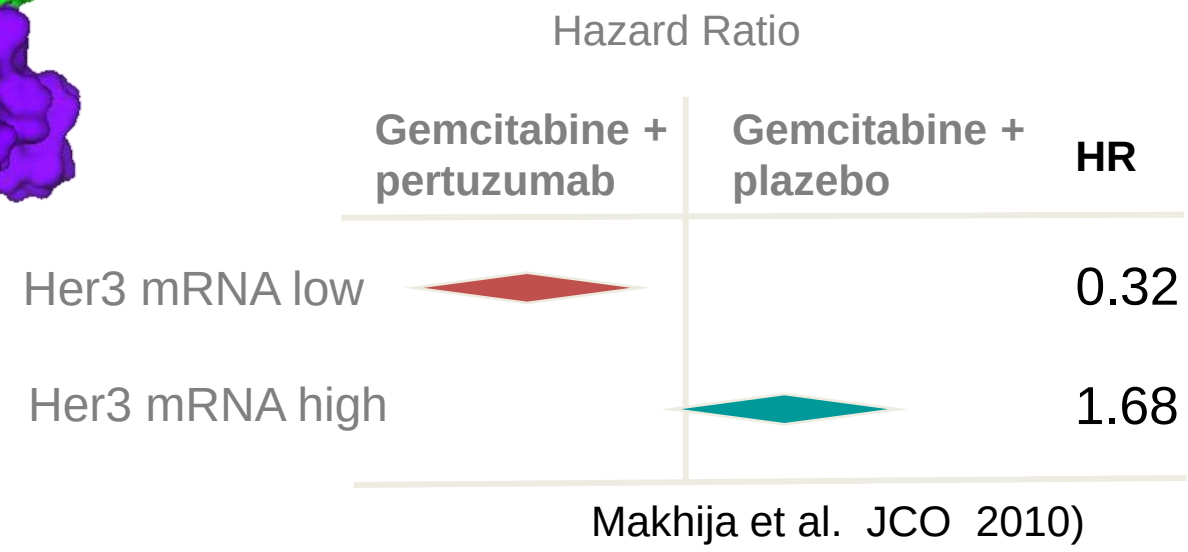
Next generation epidermal receptor inhibitors: Pertuzumab: Recombinant humanised monoclonal antibody, HER2 dimerisation inhibitor



Compound: Pertuzumab

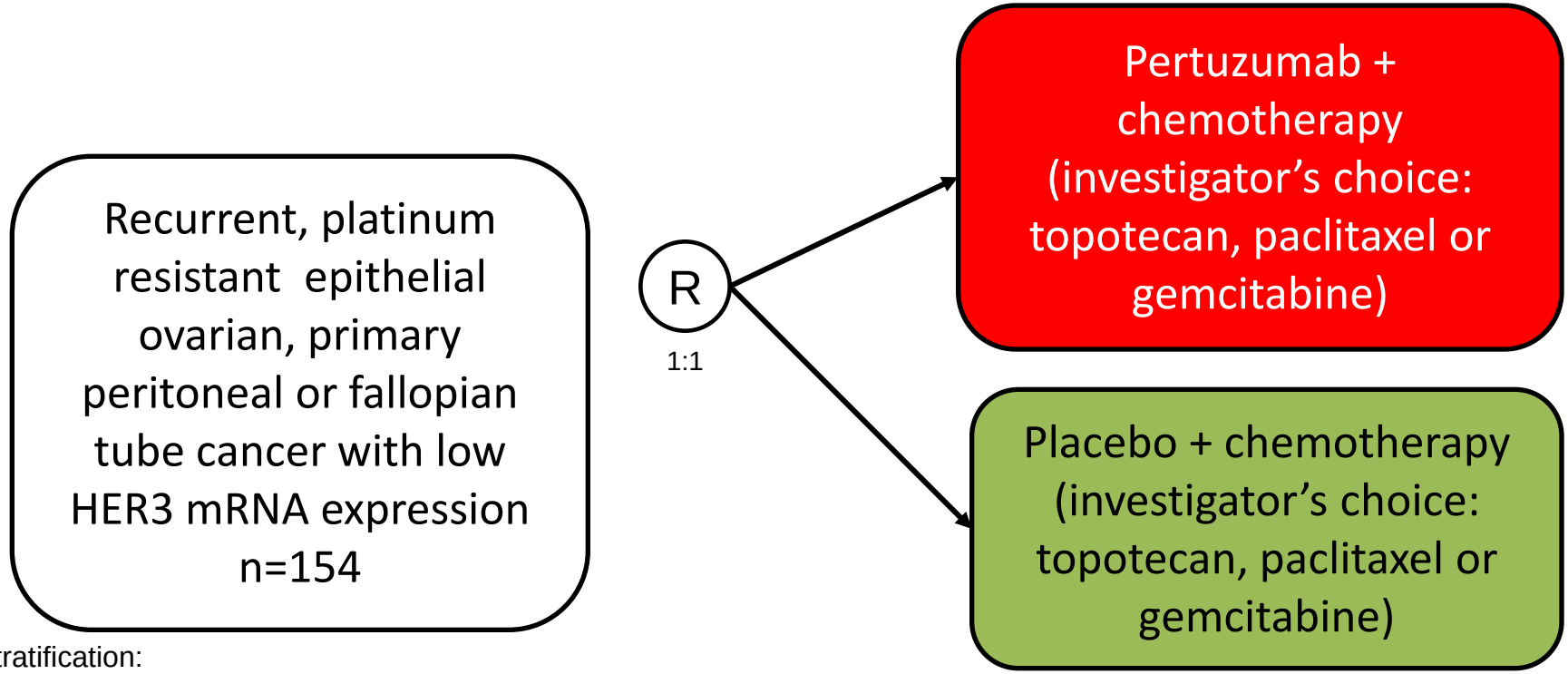
Patient population: Platinum-resistant OC

Marker: HER3 mRNA expression



Makhija et al. JCO 2010)

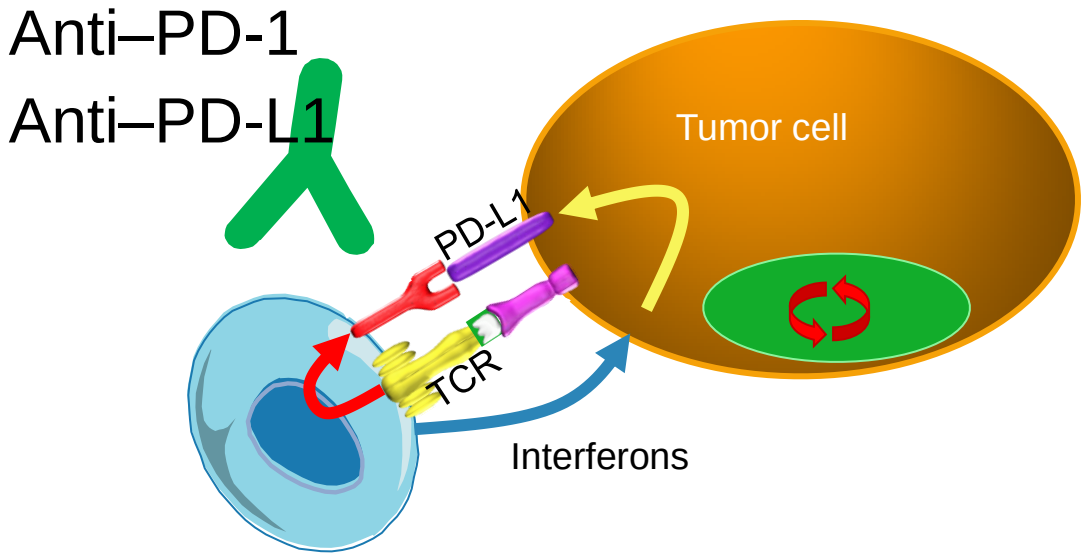
Penelope Trial design



Stratification:
- Chemotherapy cohort (topotecan vs paclitaxel vs gemcitabine)
- Prior anti-angiogenic therapy (yes vs no)
- Platinum-free interval (<3 vs 3–6 months)

AGO-OVAR 2.20 (ENGOT OV.14)

Targeting the PD-L1/PD-1 Immune Checkpoint in Ovarian Cancer



- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)[1,2]
  - PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, death)
- In ovarian cancer and other tumors, PD-L1 expression has been shown to be associated with shorter survival[3]

1. Topalian SL, et al. Curr Opin Immunol. 2012;24:207-212. 2. Taube JM, et al. Sci Transl Med. 2012;4:127ra37. 3. Hamanishi et al. Proc Natl Acad Sci vol.104 no. 9: 3360–3365, 2007

Efficacy and safety of anti-PD-1 antibody (Nivolumab: BMS-936558, ONO-4538) in patients with platinum-resistant ovarian cancer

Junzo Hamanishi, MD, PhD
Kyoto University, Japan

Junzo Hamanishi, Masaki Mandai*, Takafumi Ikeda, Manabu Minami, Atsushi Kawaguchi, , Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Toshinori Murayama, Shunsuke Chikuma, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, Ikuo Konishi

Kyoto University, Japan , *Kinki University, Japan

Presented By Junzo Hamanishi at 2014 ASCO Annual Meeting, **Abstract No:** 5511

Clinical Effect : Best Overall Response

Dose	total (n)	CR	PR	SD	PD	NE	RR	DCR
1 mg/kg	10	0	1	2	6	1	1/10 (10%)	3/10 (30%)
3 mg/kg	8	2	0	3	3	0	2/8 (25%)	5/8 (63%)
Total	*18	2	1	5	9	1	3/18 (17%)	8/18 (44%)

*Cutoff date 2014/3/31

Presented by: **Junzo Hamanishi, MD, PhD**

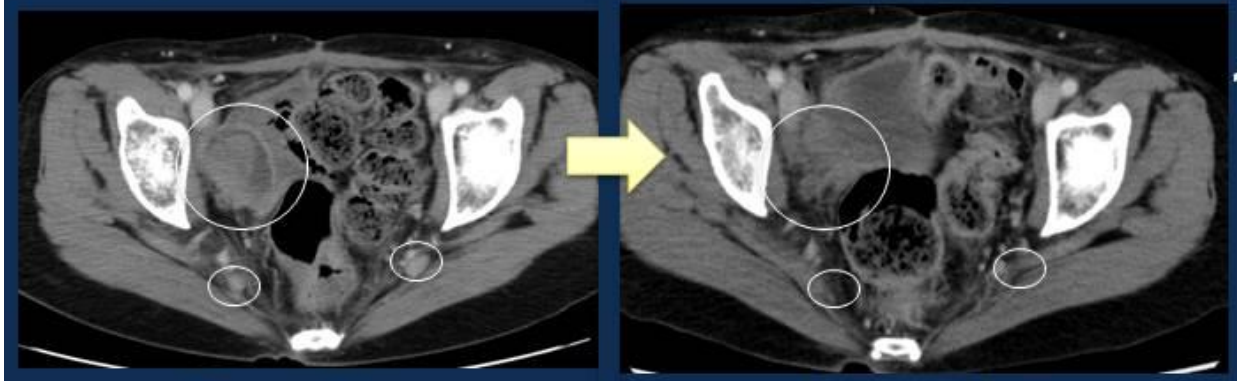
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Junzo Hamanishi at 2014 ASCO Annual Meeting, **Abstract No:** 5511

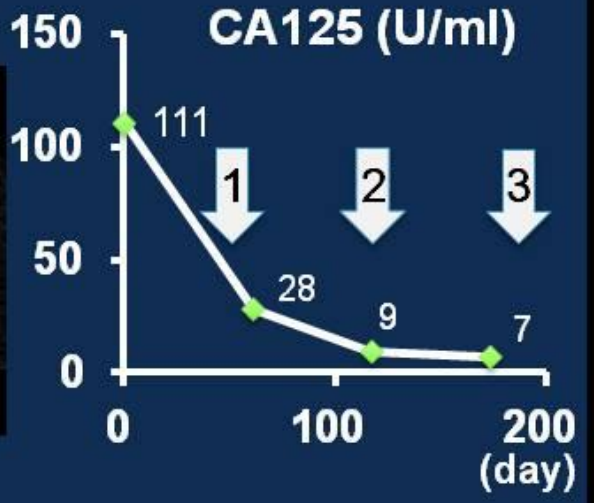
A Responder with Serous adenoca : Nivolumab 3mg/kg

History: 59 yr. Stage Ic with progressive disease after TAH+BSO+pOM+PeN, CAP*5 and DC*9

Multiple pelvic LN meta. ⇒ disappeared



Baseline 4 months



Outcome: CR for > 3months, at cutoff

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PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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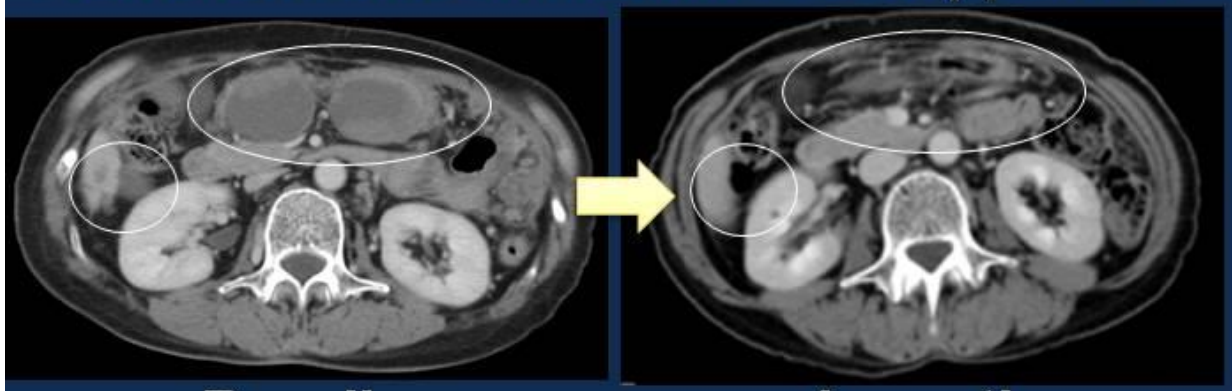
A Responder with Clear cell carcinoma : Nivolumab 3mg/kg

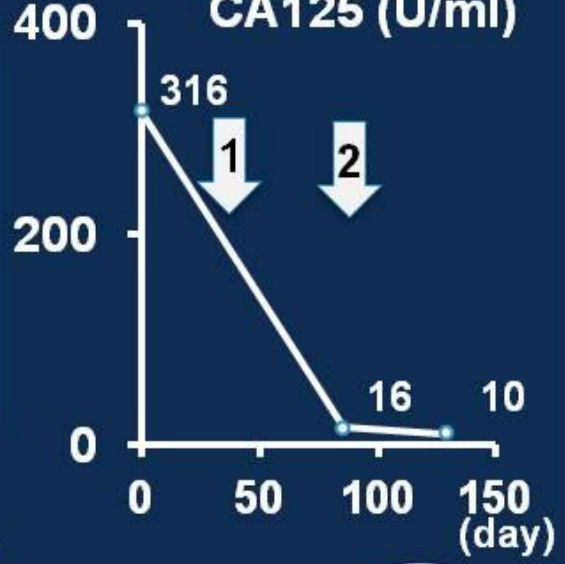
History: 60 yr. Stage Ic with progressive disease after RSO, MMC/CPT11*3, SCH+BSO, CPT/CDDP*5, TC*2

SAE with Fever

Peritoneal dissemination ⇒ disappeared



Baseline 4 months



Outcome: CR for > 44days, at cutoff

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Conclusions

- Real optimism surrounding targeted therapy for first time in 20 years
- Besides angiogenesis, homologous recombination deficiency is the second most promising target in high grade serous ovarian cancer : PARP inhibition has given positive results in randomized clinical trials for ovarian cancer.
- Phase III studies ongoing in both first line and II line

Conclusions

- Other approaches, such us targeting specific pathways should take into consideration that the term ovarian cancer encomprises a number of diseases with different natural history, prognosis and molecular make up
  - Low-grade serous → MEK inhibitors
  - Mucinous → Src / Her2 / MEK inhibitors
  - Clear cell → PI3K pathway / HIF-1$^{\alpha}$ / MET inhibitors
  - Endometrioid → PI3K pathway / aromatase inhibitors

Patient selection, using robust predictive biomarkers, will be key to success