Biomarqueurs moléculaires dans les cancers de l'ovaire

Juin 2017

Alexandra Leary, MD, PhD

Gynecology Unit
& Translational Research Laboratory INSERM U981
Gustave Roussy Cancer Center

Liens d’intérêt

- Board : Clovis, AstraZeneca
- Transports : AstraZeneca
- Investigator in clinical trial sponsorized by : Clovis, AstraZeneca

Outline

- **Predictive biomarkers in High Grade Serous Ovarian Cancer (HGSOC)**
  - Homologous recombination deficiency for PARP inhibitors: ready for prime-time?
    - BRCA mutations: germline and somatic, BRCA hypermethylation
    - Mutations or SCNAs in HR genes
    - HRD scar

  - When do we need this HRD information? Relapse?
  - Diagnosis?
  - Resistance mutations

- **Predictive biomarkers in other rare epithelial OC**

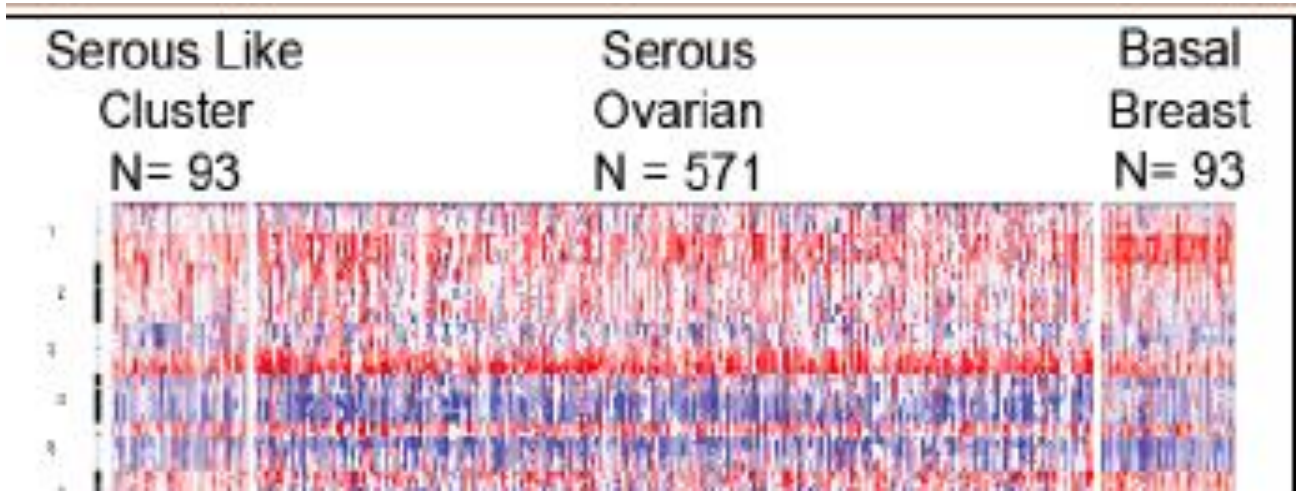
- **Diagnostic value** of genomic alterations in **rare** non-epithelial ovarian cancers

- **Endometrial Cancers**

Molecular subtypes of epithelial ovarian cancer

High grade serous ovarian cancer (75%)

- High Ki67
- Genomically unstable
- Chemosensitive but poor prognosis
- Universal TP53 mutation – few other mutations
- Associated with BRCA1/2 germline mutations (12-15%)
- Genomic homology with triple negative BC



TCGA Nature, 2011; Kurman et al, 2011

Rare subtypes (25-30%)

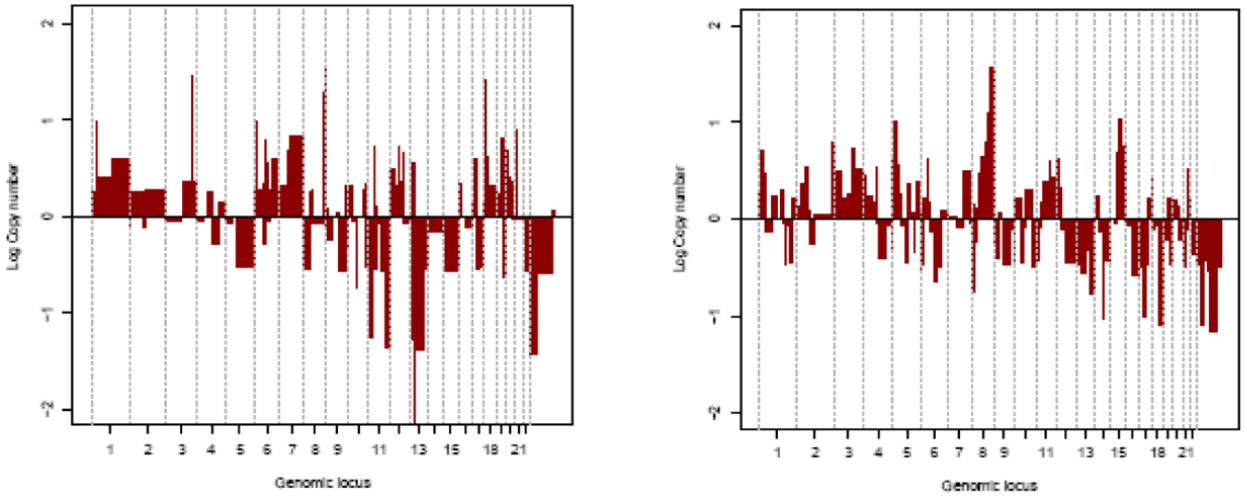
- Histologic similarities with other primary tumors
- Chemotherapy resistance
- Frequent oncogenic mutations

Subtypes of rare OC

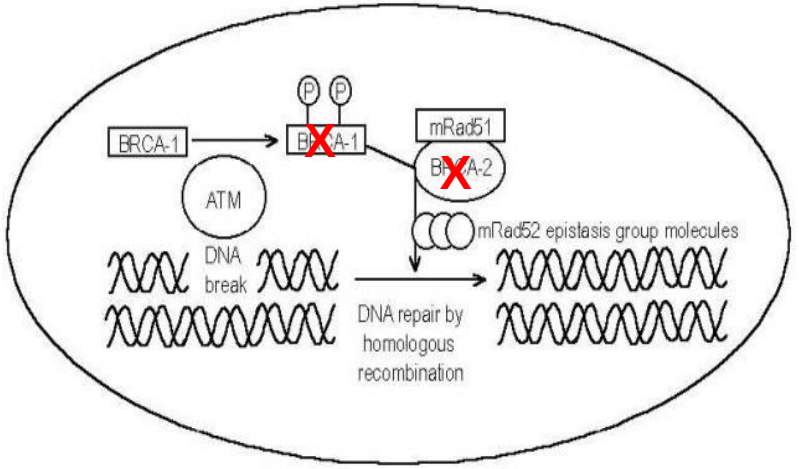
Invasive histology	Histological similarities
Low grade serous	
Mucinous	Colorectal cancer
Endometrioid	Endometrial cancer
Clear cell	Renal cell cancer
Transitional cell/Brenners	Urothelial tumors

HGSOC genomically unstable – attributable to DNA repair deficiency

Genomically unstable HGSOC



12-15% of HGSOC have DNA repair deficiency via homologous recombination from germline inactivating mutation in BRCA

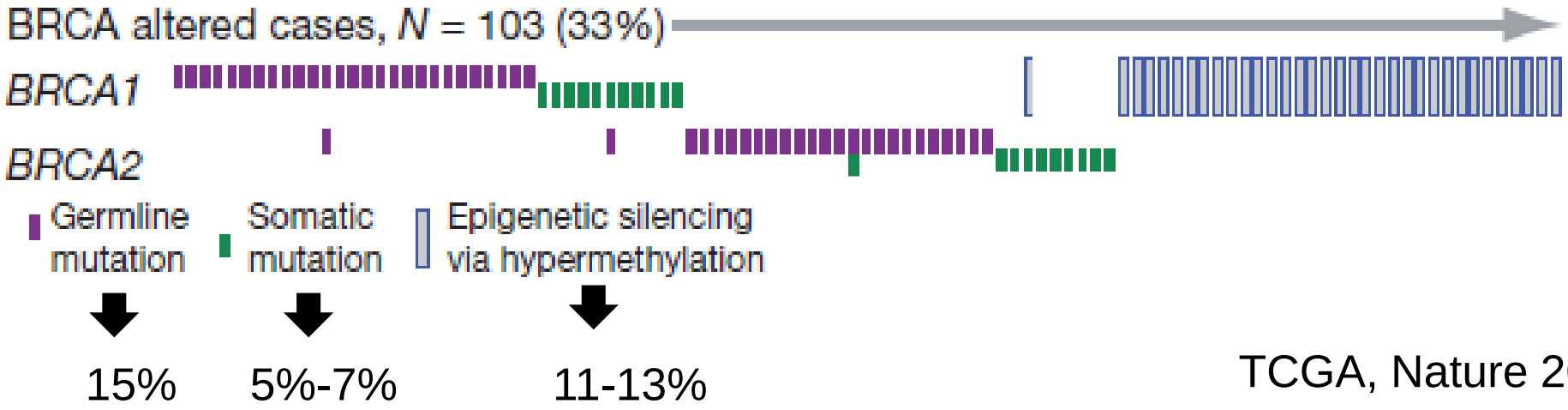


Reis-Filho et al 2011 Cell Cycle

Results in genomic instability AND explains chemo-sensitivity

High Grade Serous Ovarian Cancer (HGSOC): DNA repair deficiency

30% of HGSOC demonstrate alterations in BRCA1 or BRCA2

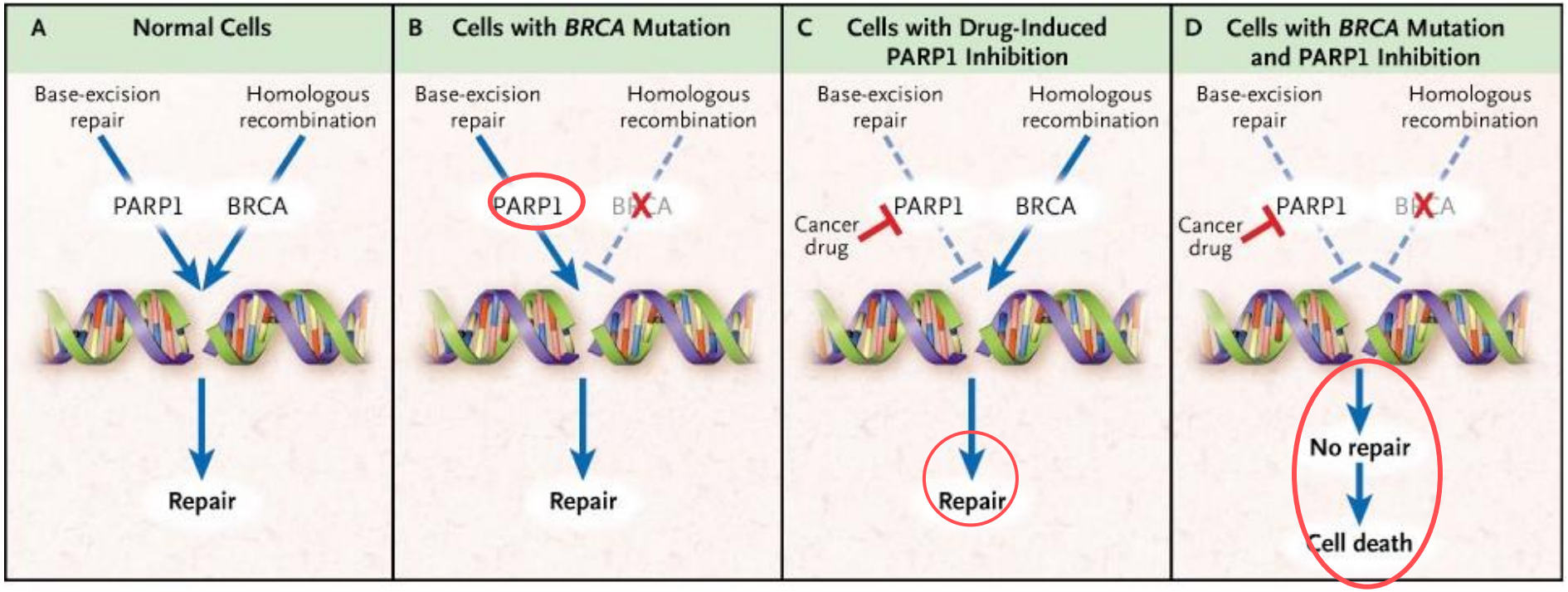


TCGA, Nature 2011

TCGA on >300 HGSOC

Concept of synthetic lethality of PARP inhibitors in BRCA mutated tumors

Healthy tissue BRCA cancer cells Healthy tissue BRCA cancer cells



PARP: Poly-ADP Ribose Polymerase

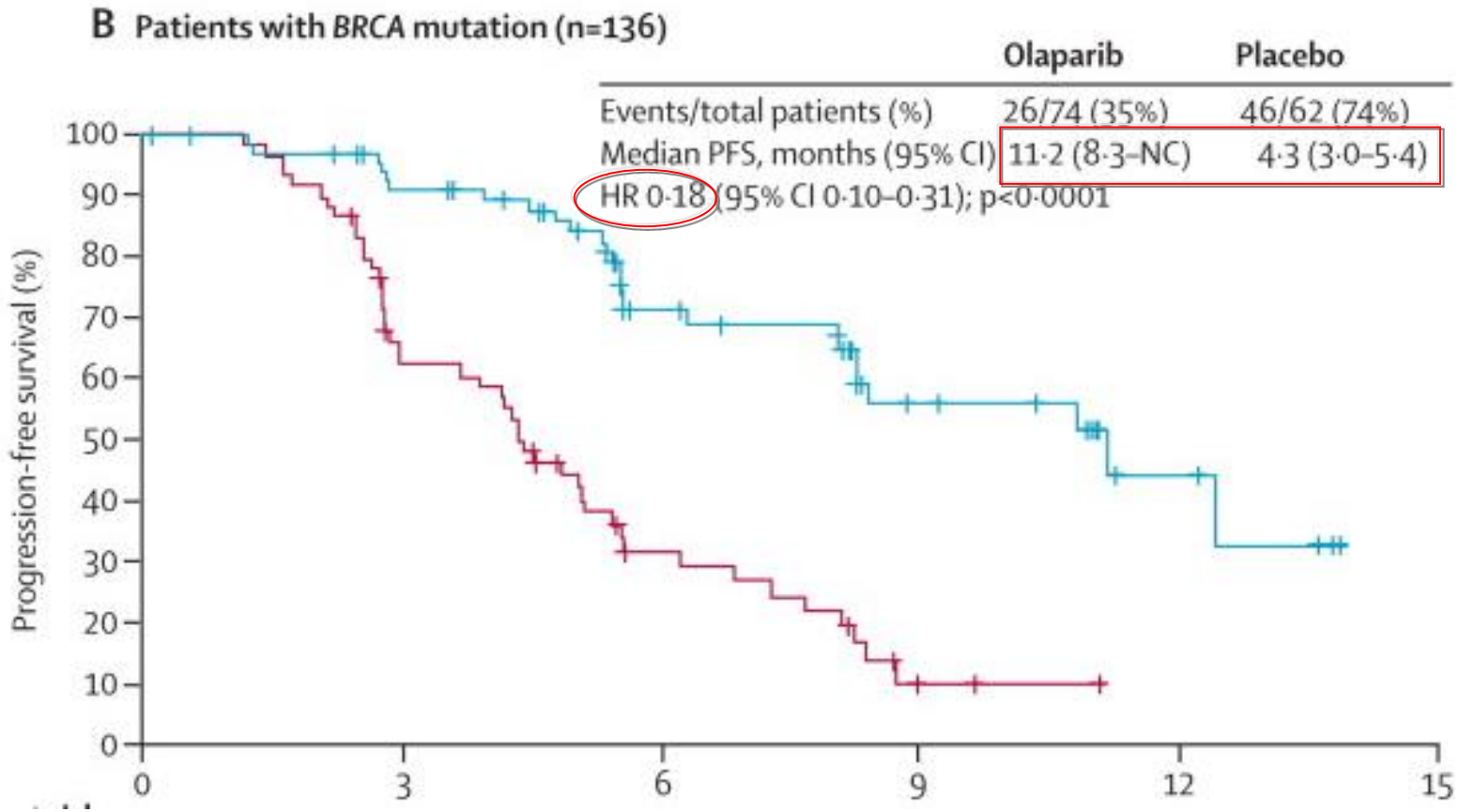
Synthetic lethality: HR defects renders BRCA mutated tumors 'addicted' or essentially dependent on other DNA repair pathways. Inhibition of PARP becomes synthetically lethal in the context of an inactivating BRCA mutation

Iglehart, NEJM 2009

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Greatest benefit of olaparib in BRCA mutated subset (germline or somatic)



NEJM, Ledermann et al 2012

EMA approval for olaparib

- In patients with platinum-sensitive relapsed,
- High grade serous ovarian, fallopian tube or primary peritoneal cancer,
- Associated with a deleterious BRCA1 or 2 mutation (germline or somatic),
- Who are in response (PR or CR) to platinum based chemotherapy

Olaparib maintenance until progression or intolerance

EMA approval for olaparib

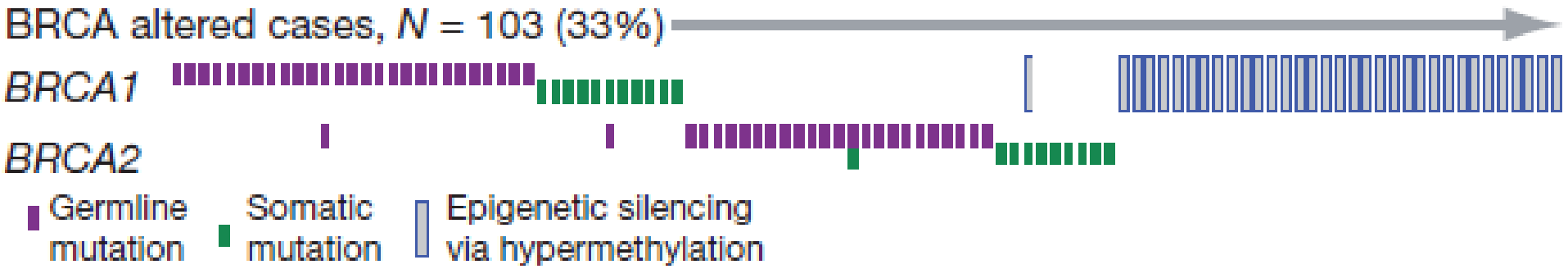
- In patients with platinum-sensitive relapsed,
- High
  prim
- Asso utation
  (germ
- Who are in response (PR or CR) to platinum based chemotherapy

Olaparib maintenance until progression or intolerance

First targeted therapy associated with a genomic predictive biomarker approved in gynecological cancers

PARP inhibitors beyond BRCA mutations in OC?

50% of HGSOC dysfunctional DNA repair homologous recombination (HR) pathway

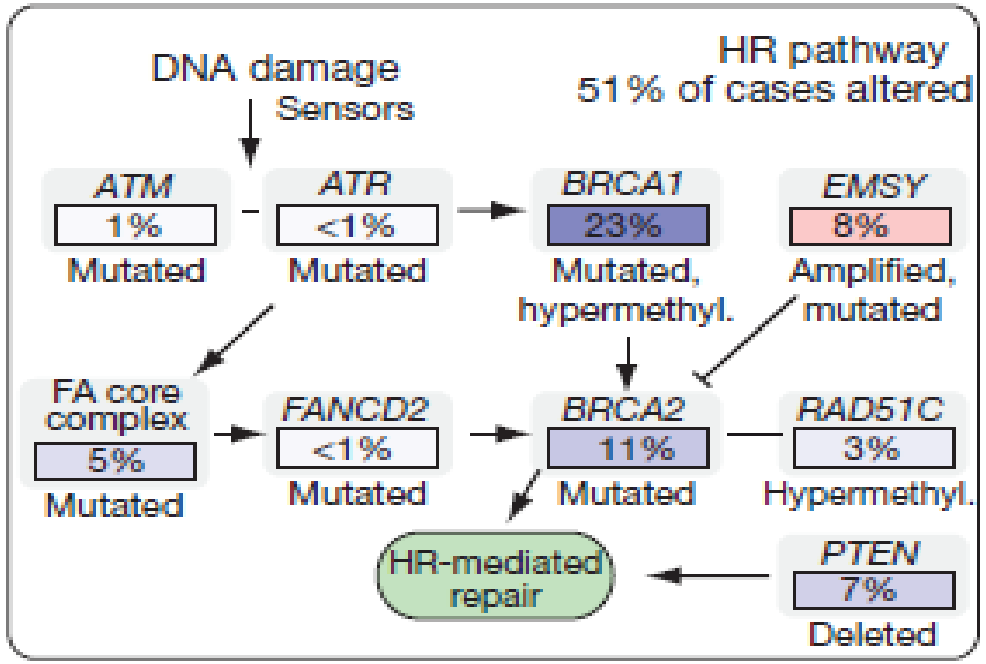


<u>30% BRCA loss</u>

- via germline BRCA-M+
- somatic BRCA-M+
- BRCA hypermethylation

<u>Another 20% with dysfunctional HR-mediated DNA repair:</u>

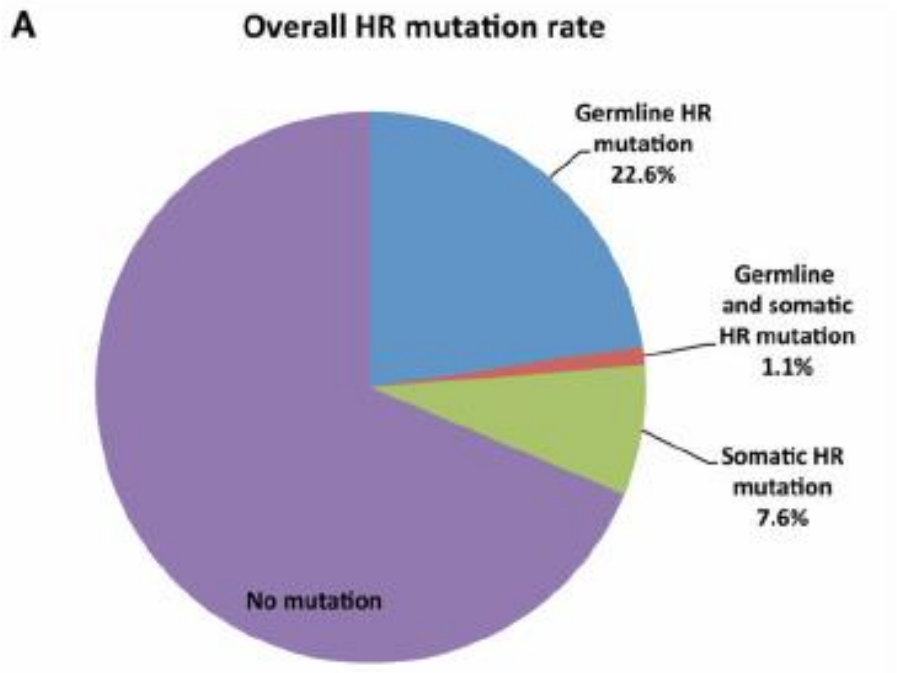
- EMSY amp 5-17%
- RAD51 loss 3-5%
- ATM/ATR M+: 3%
- Fanc M+: 5%
- PTEN loss 7%



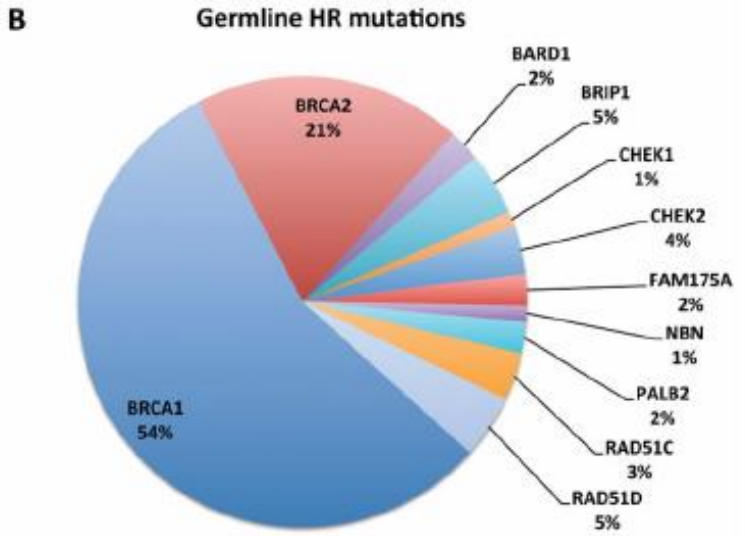
TCGA, Nature 2011

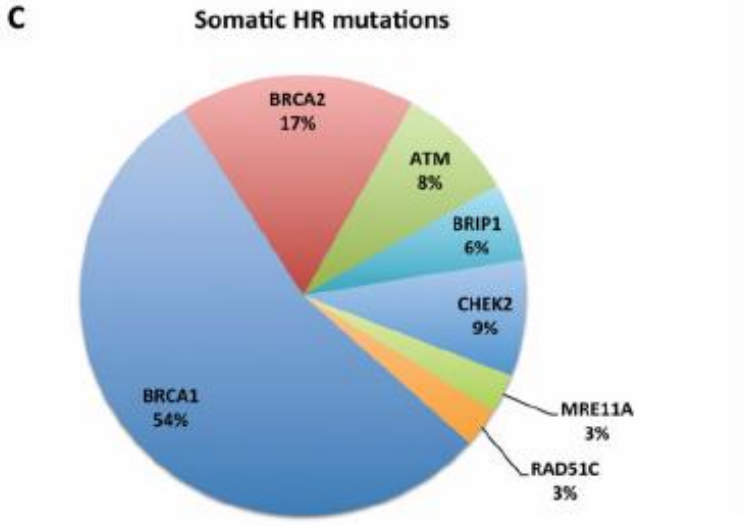
Germline and somatic alterations in non-BRCA HR genes in OC

Identified in 1/3



Mainly M+ BRCA,
other alterations are rare





Pennington et al

Identifying BRCA-WT OC with HR deficiency: One approach: SCNAs or mutations in HR genes

Gene symbol	% mutated/deleted in HGSOC*	HR pathway subgroups
BRCA1	13.4%	BRCA genes
BRCA2	10.5%	BRCA genes
	23.9%	

Gene symbol	% mutated/deleted in HGSOC*	HR pathway subgroups
ATRX	1.1%	Helicase that regulates HR repair
BARD1	0.2%	BRCA1 protein complex
BLM	1.1%	Helicase that regulates HR repair
BRIP1	0.7%	Helicase that regulates HR repair
MRE11A	1.3%	MRN double strand DNA break repair complex
NBN	0.7%	MRN double strand DNA break repair complex
PTEN	4.6%	
RPA1	1.3%	
	11.0%	

Gene symbol	% mutated/deleted in HGSOC*	HR pathway subgroups
ATM	2.6%	DNA damage response genes
ATR	0.7%	DNA damage response genes
CHEK1	1.1%	DNA damage response genes
CHEK2	1.8%	DNA damage response genes
FANCA	5.0%	Fanconi Anemia genes
FANCC	0.9%	Fanconi Anemia genes
FANCD2	0.2%	Fanconi Anemia genes
FANCE	0.2%	Fanconi Anemia genes
FANCF	0.4%	Fanconi Anemia genes
FANCG	0.2%	Fanconi Anemia genes
FANCI	0.7%	Fanconi Anemia genes
FANCL	0.4%	Fanconi Anemia genes
FANCM	1.4%	Fanconi Anemia genes
PALB2	1.1%	Fanconi Anemia genes
RAD50	1.5%	RAD genes
RAD51	3.5%	RAD genes
RAD51B	0.2%	RAD genes
RAD51C	0.0%	RAD genes
RAD51D	0.9%	RAD genes
RAD52	0.2%	RAD genes
RAD54L	0.9%	RAD genes
	23.9%	

*Based on most up to date NGS data of 456 HGSOC tumors in TCGA (Apr 2013)

Note: a small subset of mutations and deletions co-occur, resulting in slightly lower cumulative frequencies for BRCA and nbHRD

Are alterations in non-BRCA genes equally predictive of a response to PARPi?

Chemical Therapeutics

Molecular Cancer Therapeutics

RAD51C-Deficient Cancer Cells Are Highly Sensitive to the PARP Inhibitor Olaparib

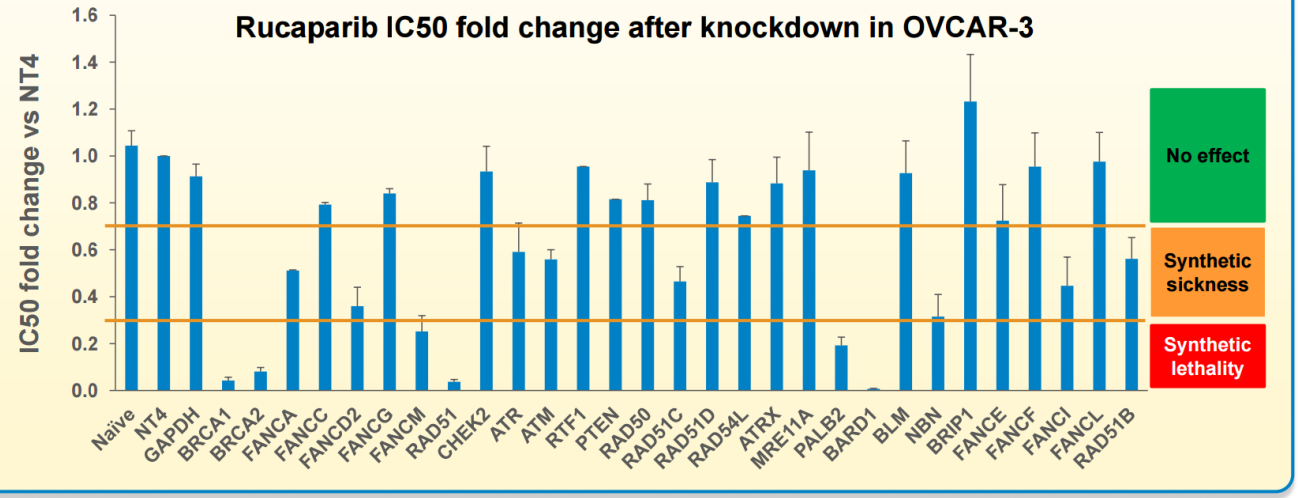
Ahrum Min[1], Seock-Ah Im[1,2], Young-Kwang Yoon[1], Sang-Hyun Song[1], Hyun-Jin Nam[1], Hyung-Seok Hur[1], Hwang-Phill Kim[1], Kyung-Hun Lee[1,2], Sae-Won Han[1,2], Do-Youn Oh[1,2], Tae-You Kim[1,2,4], Mark J. O'Connor[5], Woo-Ho Kim[1,3], and Yung-Jue Bang[1,2]

Differential sensitivity to PARP inhibitor rucaparib (siRNA knockdown)

HRD Genotype Approach

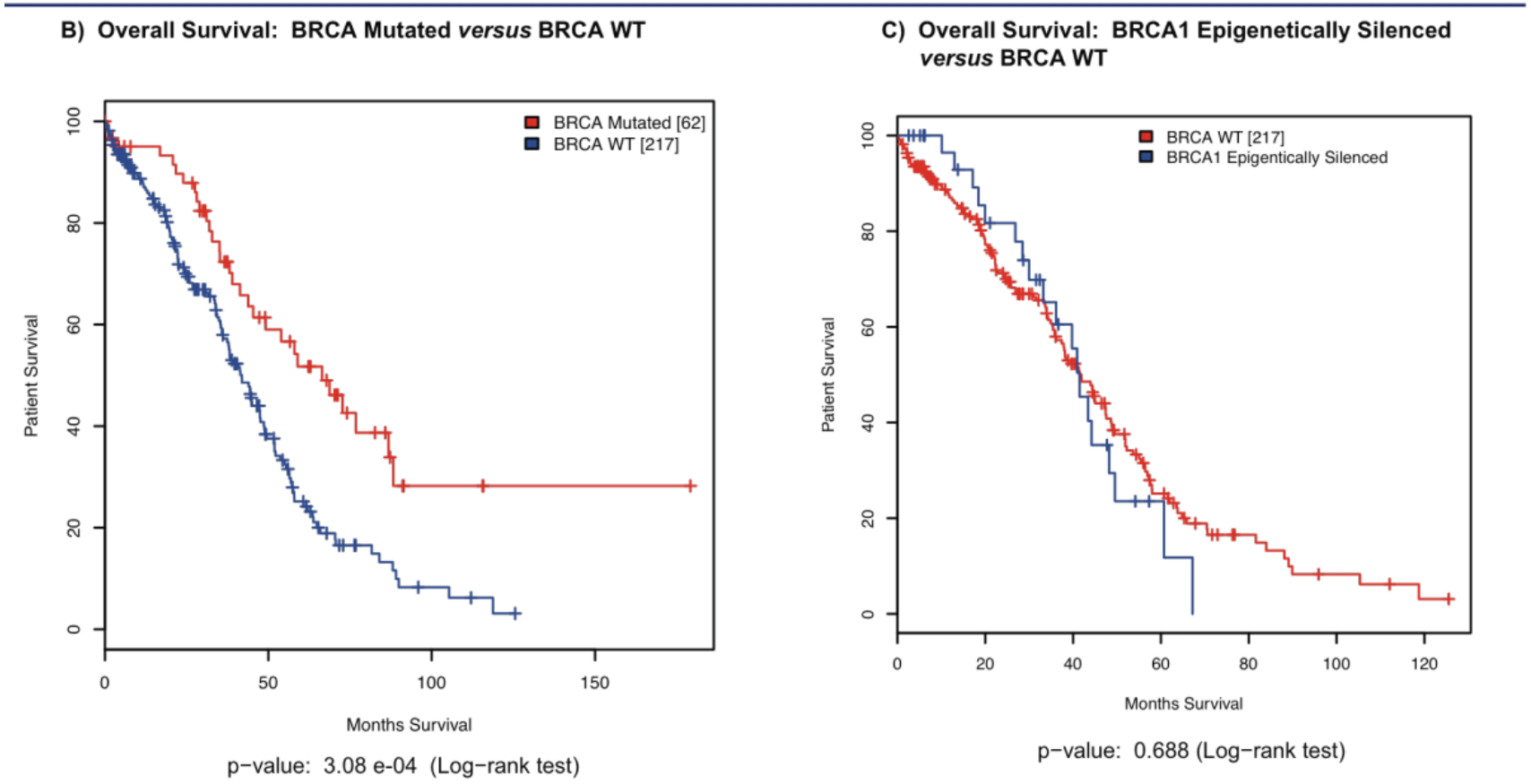
siRNA knockdown of HR pathway genes renders differential sensitivity to rucaparib in ovarian cancer cell lines

- Rucaparib sensitivity was tested in ovarian cancer cell line OVCAR-3 with 29 homologous recombination (HR) pathway genes individually knocked down using siRNA
- Similar findings were observed in SK-OV-3, UWB1.289+*BRCA1*, and OAW-28 cell lines



I McNeish, ESMO, 2014

BRCA hypermethylation does NOT have the same prognostic impact as BRCA mutation



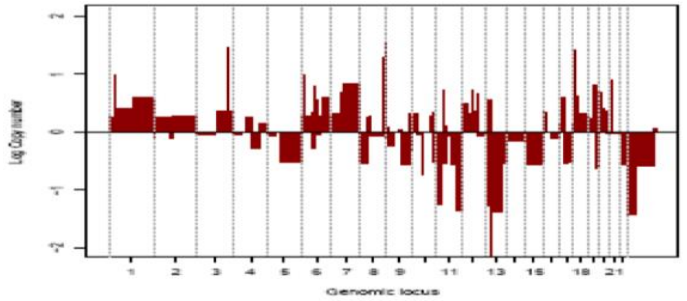
BRCA hypermethylation does not have prognostic value in platinum treated OC

Valid surrogate for HRD?

TCGA, Nature 2011

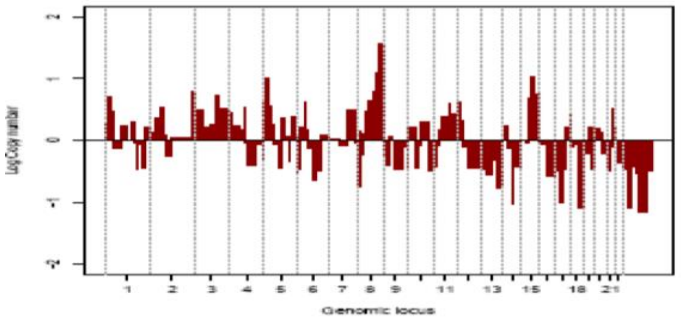
Loss of heterozygosity (LOH) score: deficiency in homologous recombination (HRD)

BRCA^{mut}

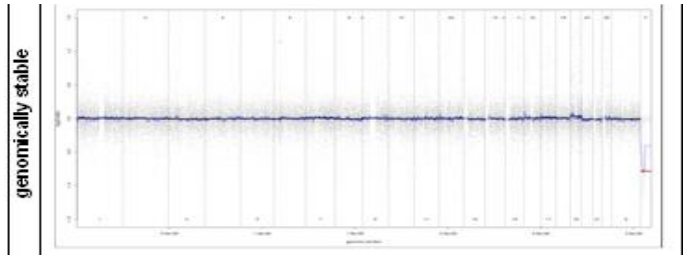


BRCA^{WT}

HRD/BRCA-like

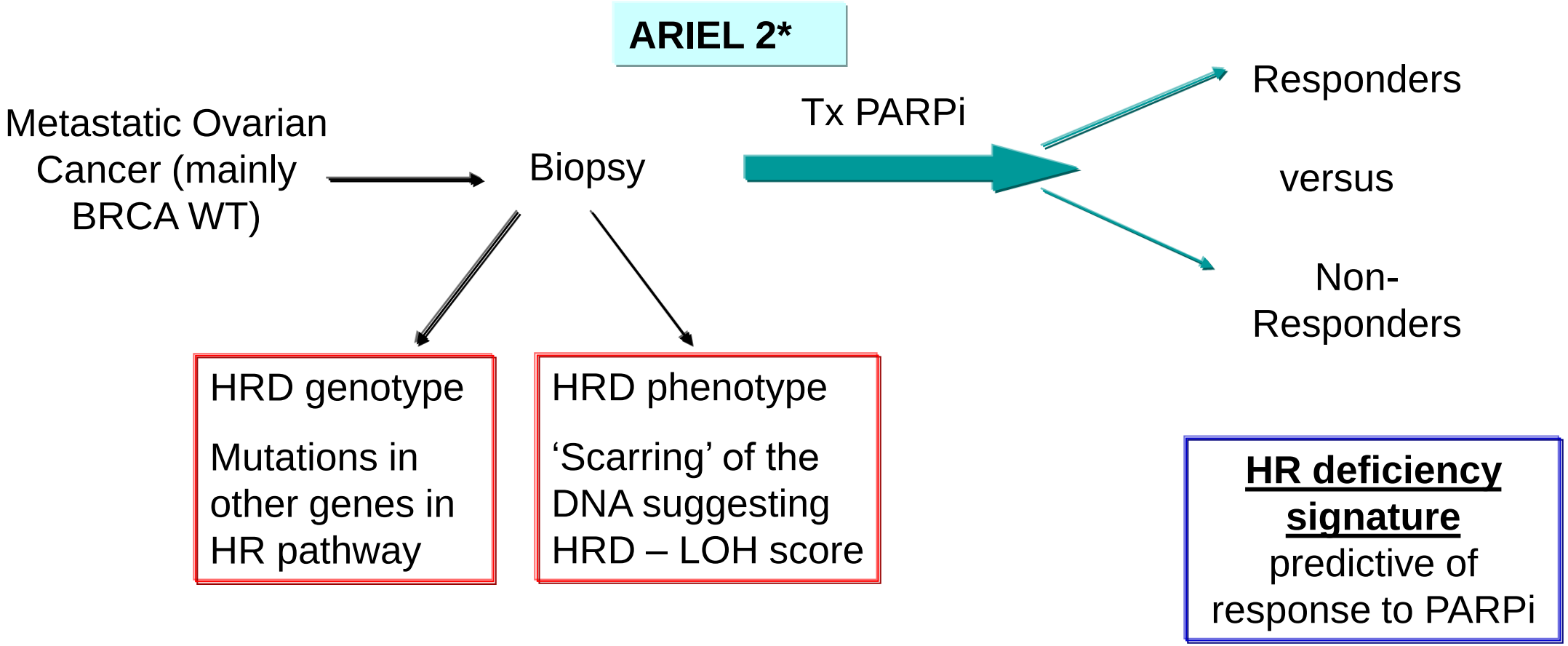


HR competent



High LOH score reflects HRD regardless of the cause BRCA-like➔ predict response to PARPi?

ARIEL studies*: Identify BRCA wild-type tumors with homologous recombination deficiency (HRD) that may benefit from PARP inhibitors



Do mutations in non-BRCA HR genes predict benefit from PARPi?

HR-pathway gene	Genetic alteration type	Germline/somatic inference	HRD molecular subgroup	RECIST response	CA-125 response
NBN	Truncation	Germline	Biomarker-negative	Partial Response	Yes
RAD51C	Truncation	Germline	BRCA-like	Partial Response	Yes
RAD51C	Homozygous Del	Somatic	BRCA-like	Partial Response	Yes
RAD51C	Splice	Germline	BRCA-like	Partial Response	Yes
RAD51C	Splice	Germline	BRCA-like	Stable Disease	Yes
ATM	Homozygous Del	Somatic	Indeterminate	Stable Disease	Yes
RAD51L3	Truncation	Indeterminate	BRCA-like	Stable Disease	Yes
BRIP1	Splice	Germline	Biomarker-negative	Stable Disease	No
BRIP1	Truncation	Germline	Biomarker-negative	Stable Disease	No
CHEK2	Splice	Indeterminate	Biomarker-negative	Stable Disease	No
CHEK2	Truncation	Germline	BRCA-like	Stable Disease	No
RAD51L1	Truncation	Indeterminate	Biomarker-negative	Stable Disease	No
NBN	Truncation	Germline	Indeterminate	Stable Disease	Not evaluable
RAD54L	Truncation	Somatic (subclonal)	Biomarker-negative	Stable Disease	Not evaluable
FANCA	Homozygous Del	Somatic	BRCA-like	Stable Disease	Not evaluable
FANCI	Truncation	Germline	Biomarker-negative	Progressive Disease	No
ATM	Truncation	Somatic	Indeterminate	Not evaluable	Not evaluable

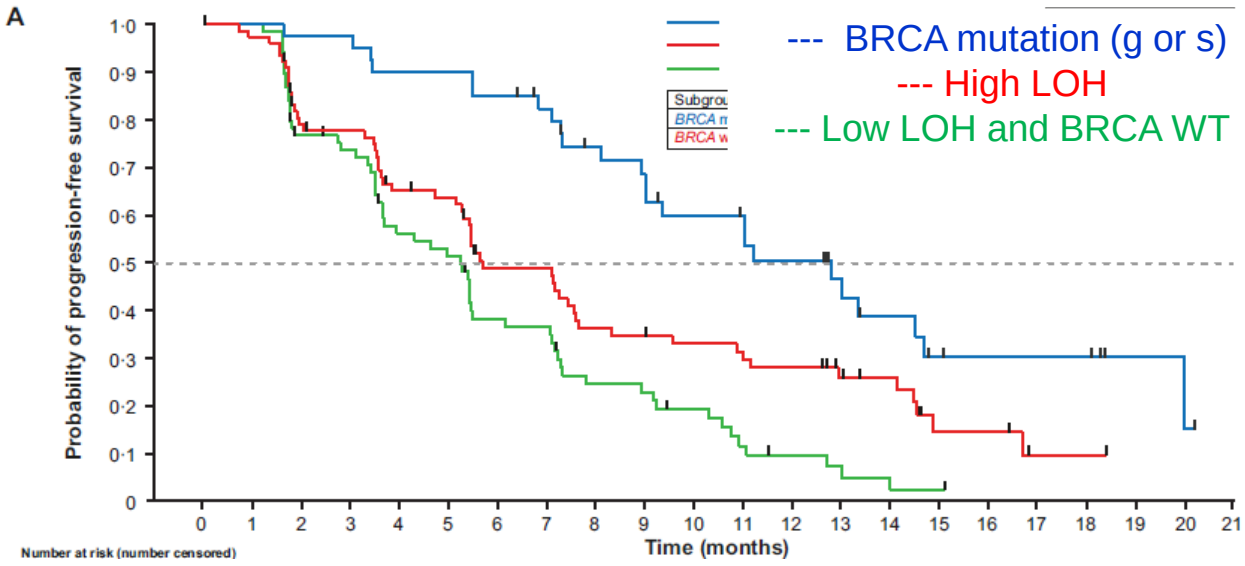
Lancet Oncol Jan 2017

DOES THE HRD SCAR OR LOH SCORE PREDICT BENEFIT FROM PARPI?

Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial

Elizabeth M Swisher, Kevin K Lin*, Amit M Oza, Clare L Scott, Heidi Giordano, James Sun, Gottfried E Konecny, Robert L Coleman, Anna V Tinker, David M O'Malley, Rebecca S Kristeleit, Ling Ma, Katherine M Bell-McGuinn, James D Brenton, Janiel M Cragun, Ana Oaknin, Isabelle Ray-Coquard, Maria I Harrell, Elaina Mann, Scott H Kaufmann, Anne Floquet, Alexandra Leary, Thomas C Harding, Sandra Goble, Lara Maloney, Jeff Isaacson, Andrew R Allen, Lindsey Rolfe, Roman Yelensky, Mitch Raponi, Iain A McNeish**

PFS

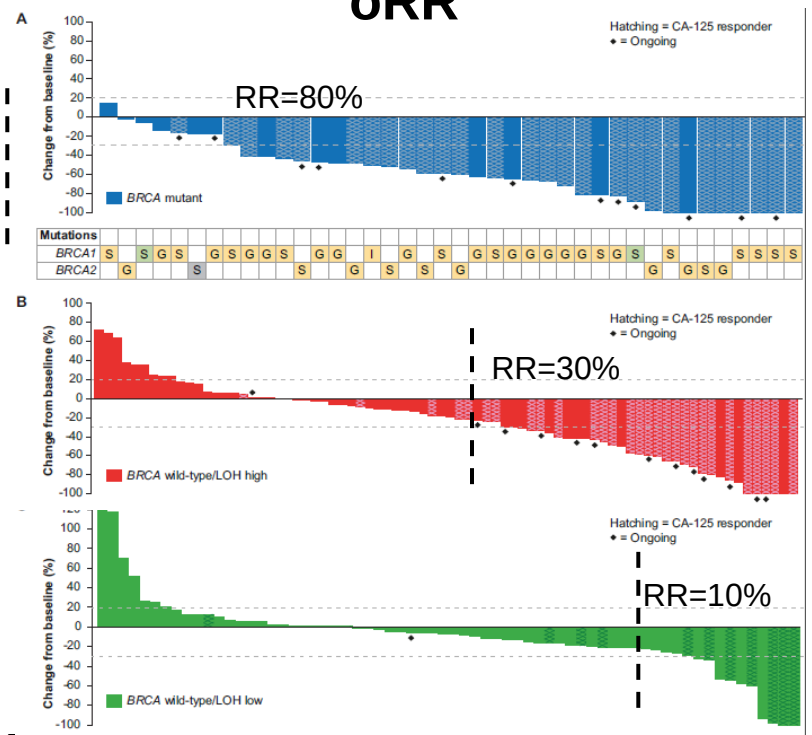


Non-BRCA mutated HRD tumors (high LOH) respond to PARPi

Although less so than BRCA mutated OC

Lancet Oncol Jan 2017

oRR



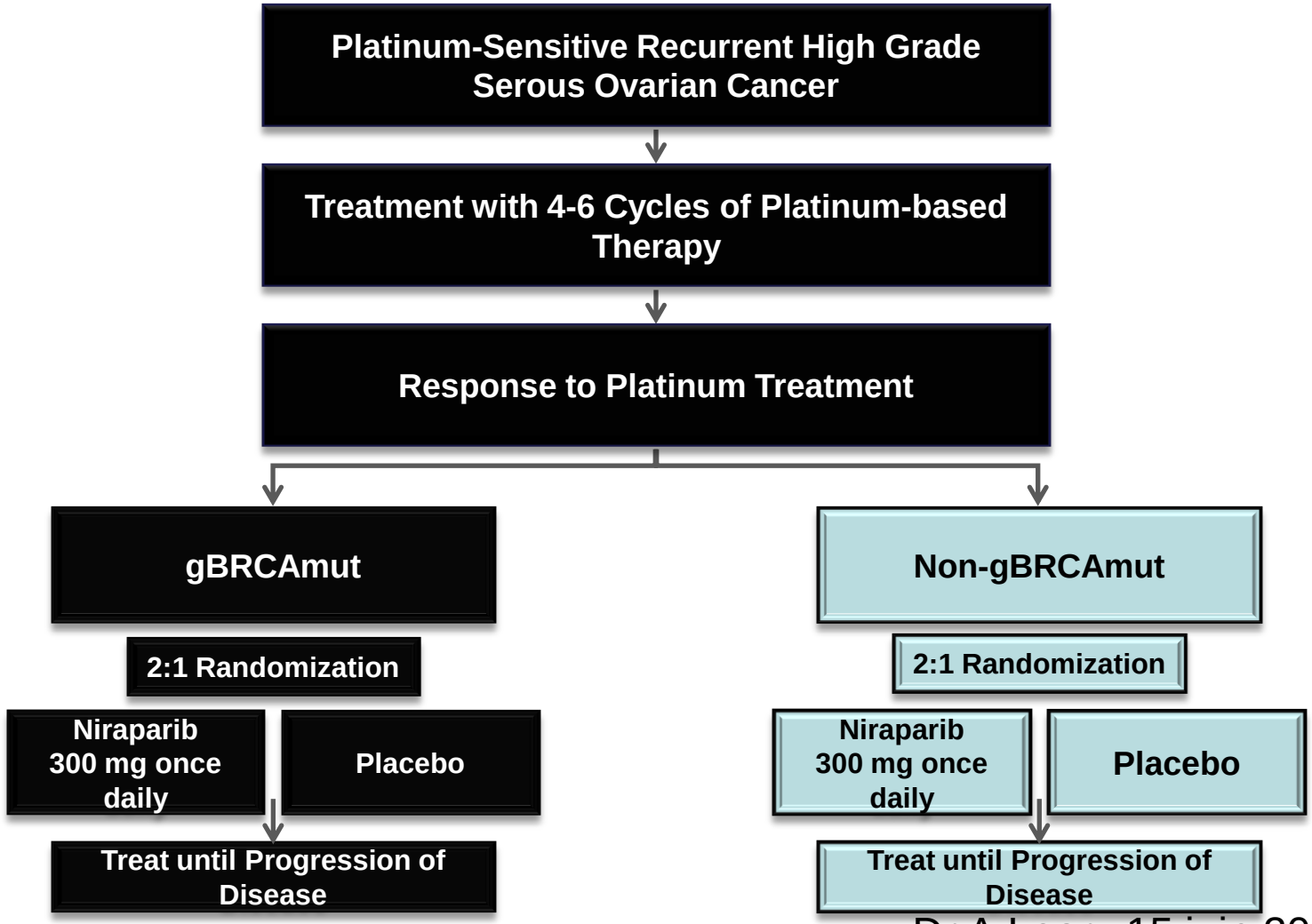
Dr.A.Leary 15 juin 2017 - Journée GFCO 2017

The NEW ENGLAND JOURNAL of MEDICINE

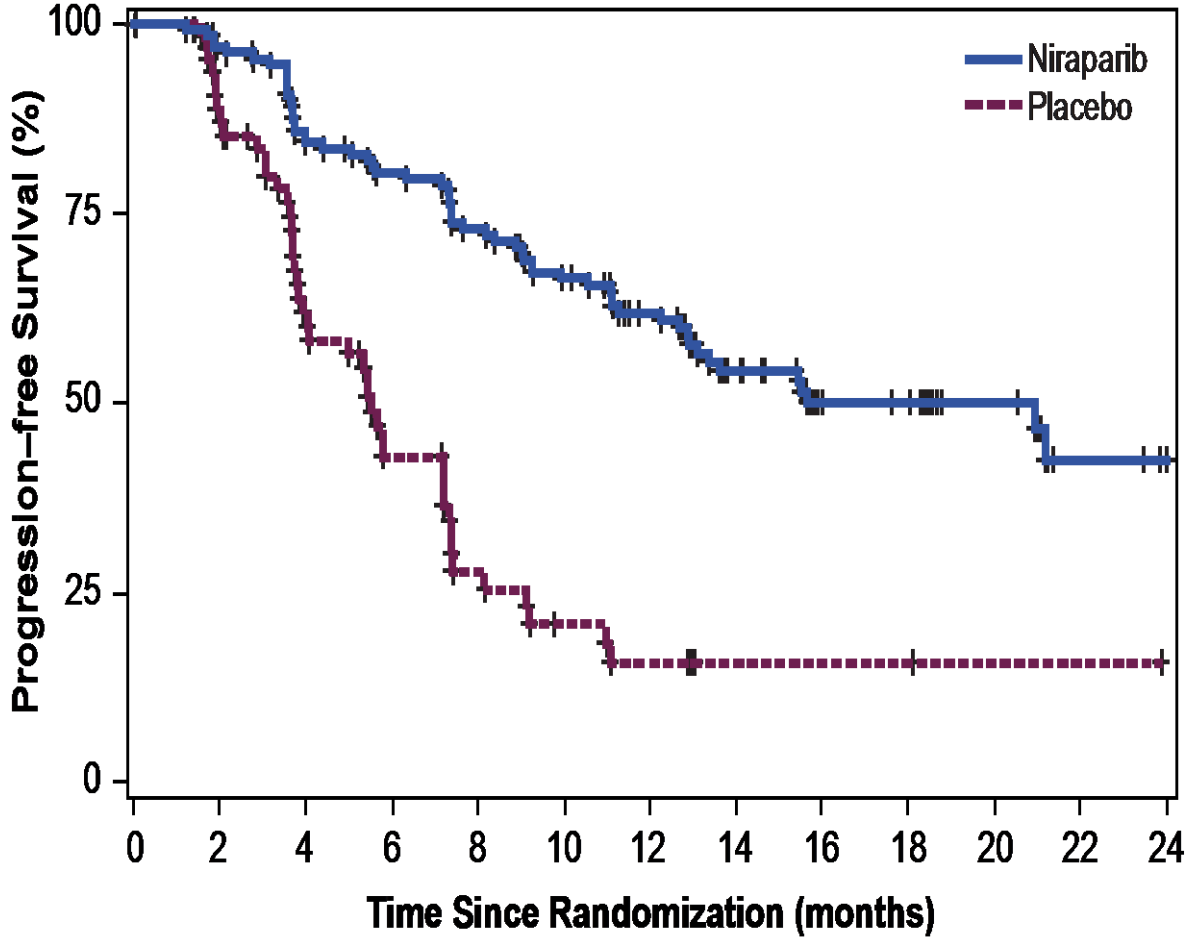
ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo,



Progression-free Survival: gBRCAmut

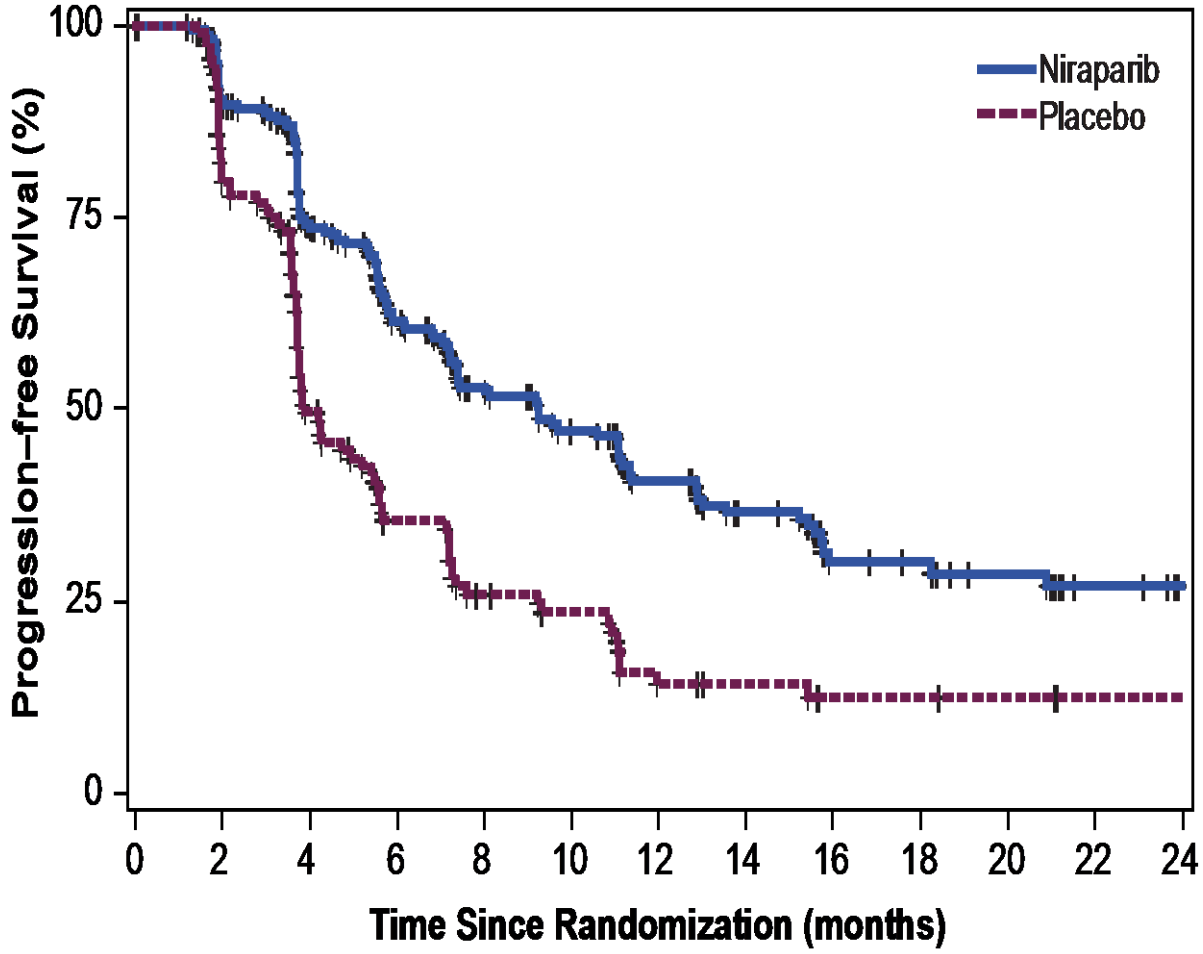


Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NR)	**0.27** (0.173, 0.410) p<0.0001	62%	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16%	16%

Bénéfice de > 15 mois

Mirza et al 2016

Progression-free Survival: non-gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001	41%	**30%**
Placebo (N=116)	**3.9** (3.7, 5.5)		14%	12%

Can we identify the subset of BRCA WT OC that benefits the most from PARPi?

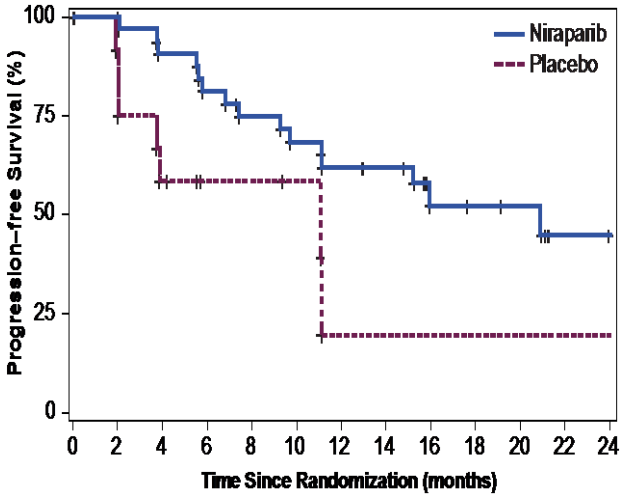
Mirza et al 2016

Exploratory Analysis: PFS in Subgroups of Non-gBRCAmut Cohort

HRD-positive

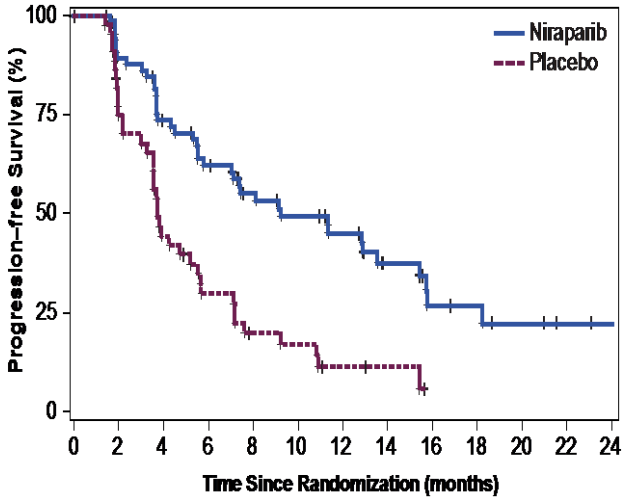
sBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=35)	**20.9** (9.7, NR)	**0.27** (0.081, 0.903) p=0.0248	62%	**52%**
Placebo (N=12)	**11.0** (2.0, NR)		19%	19%



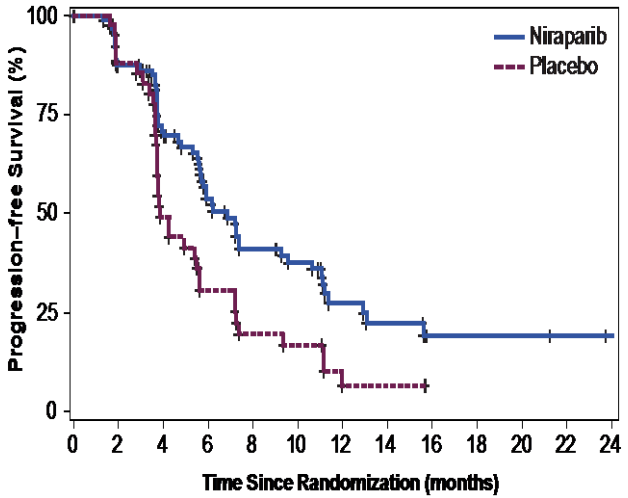
BRCAwt

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%



HRD-negative

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19%**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%



Mirza et al 2016

Authors Conclusions

- Niraparib significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer, regardless of *BRCA* mutation or HRD status
  - gBRCAmut: HR 0.27
  - Non-gBRCAmut: HR 0.45
  - Non-gBRCAmut HRD-positive: HR 0.38
  - Non-gBRCAmut HRD-negative (exploratory): HR 0.58

- These landmark results warrant niraparib maintenance therapy to whole study population

Perhaps expensive genomic characterization is not needed, platinum sensitivity is valid surrogate predictive marker for PARP inhibitor sensitivity?

Mirza et al 2016

Genomic profiling of HGSOC

Homologous recombination deficiency (HRD) in 50% of HGSOC:

→ First targeted therapy in HGSOC associated with a genomic biomarker – germline or somatic BRCA mutations (RR to PARPi=80%)

→ Can we identify the subset of BRCA WT patients that could benefit from PARP inhibitors?

- High LOH score?
- Mutations in non-BRCA HR genes?
- Platinum sensitivity?

Genomic profiling of HGSOC

Homologous recombination deficiency (HRD) in 50% of HGSOC:

→ First targeted therapy in HGSOC associated with a genomic biomarker – germline or somatic BRCA mutations (RR to PARPi=80%)

→ Can we identify the subset of BRCA WT patients that could benefit from PARP inhibitors?

- High LOH score?
- Mutations in non-BRCA HR genes?
- Platinum sensitivity?

When do we need information on BRCA mutations or HRD?

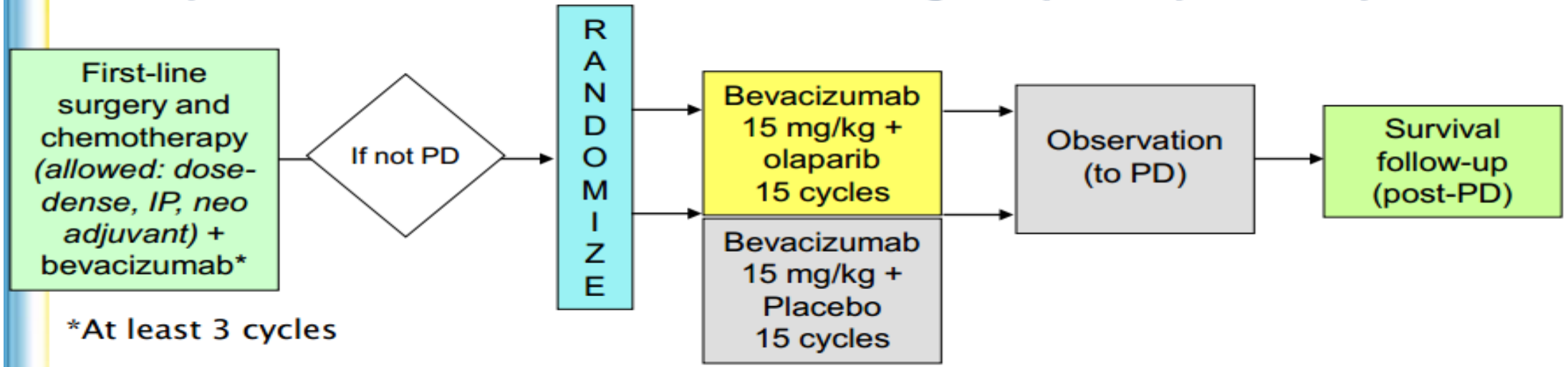
At relapse?

At diagnosis?

PAOLA1

Platine, **A**vastin and Olaparib in first line advanced high grade ovarian carcinoma patients

- **Phase III randomized, placebo–controlled, double–blind, multicenter**
- **Olaparib tablets administered at 300 mg daily for up to 15 cycles.**



RESISTANCE MUTATIONS TO PARP INHIBITORS?

Secondary Somatic Mutations Restoring *BRCA1/2* Predict Chemotherapy Resistance in Hereditary Ovarian Carcinomas

Barbara Norquist, Kaitlyn A. Wurz, Christopher C. Pennil, Rochelle Garcia, Jenny Gross, Wataru Sakai, Beth Y. Karlan, Toshiyasu Taniguchi, and Elizabeth M. Swisher

45 ptes BRCA mutated and relapse biopsied → To identify **reversion mutations restoring BRCA WT function**

45% of patients biopsied for a **platinum resistant** relapse showed **acquired reversion mutation** restoring BRCA wild-type function

Journal of Pathology
J Pathol 2013; **229:** 422–429
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/path.4140

ORIGINAL PAPER

Secondary mutations in *BRCA2* associated with clinical resistance to a PARP inhibitor

Louise J Barber,[1] Shahneen Sandhu,[2] Lina Chen,[1] James Campbell,[1] Iwanka Kozarewa,[1] Kerry Fenwick,[1] Ioannis Assiotis,[1] Daniel Nava Rodrigues,[1] Jorge S Reis Filho,[1] Victor Moreno,[2] Joaquin Mateo,[2] L Rhoda Molife,[2] Johann De Bono,[2] Stan Kaye,[2] Christopher J Lord[1] and Alan Ashworth[1]

Acquired reversion BRCA mutations associated with platinum and PARP inhibitor resistance

Whole-genome characterization of chemoresistant ovarian cancer

Ann-Marie Patch[1,2]*, Elizabeth L. Christie[3]*, Dariush Etemadmoghadam[3,4,5]*, Dale W. Garsed[3]*, Joshy George[6], S
Katia Nones[1,2], Prue Cowin[3], Kathryn Alsop[3], Peter J. Bailey[1,7], Karin S. Kassahn[1,8], Felicity Newell[1], Michael C. J.

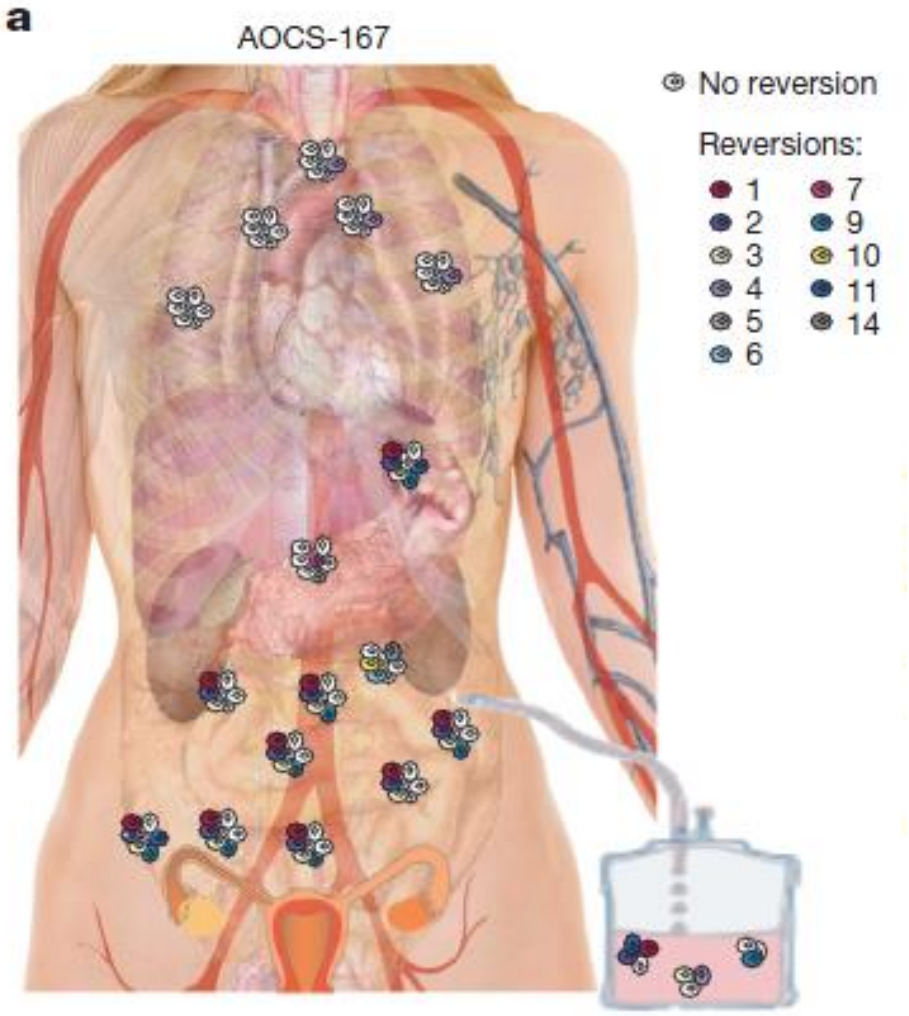
Matched analysis of primary tumor and relapse or post-mortem biopsy

5 BRCA mutated patients showed a reversion mutation restoring WT BRCA at relapse

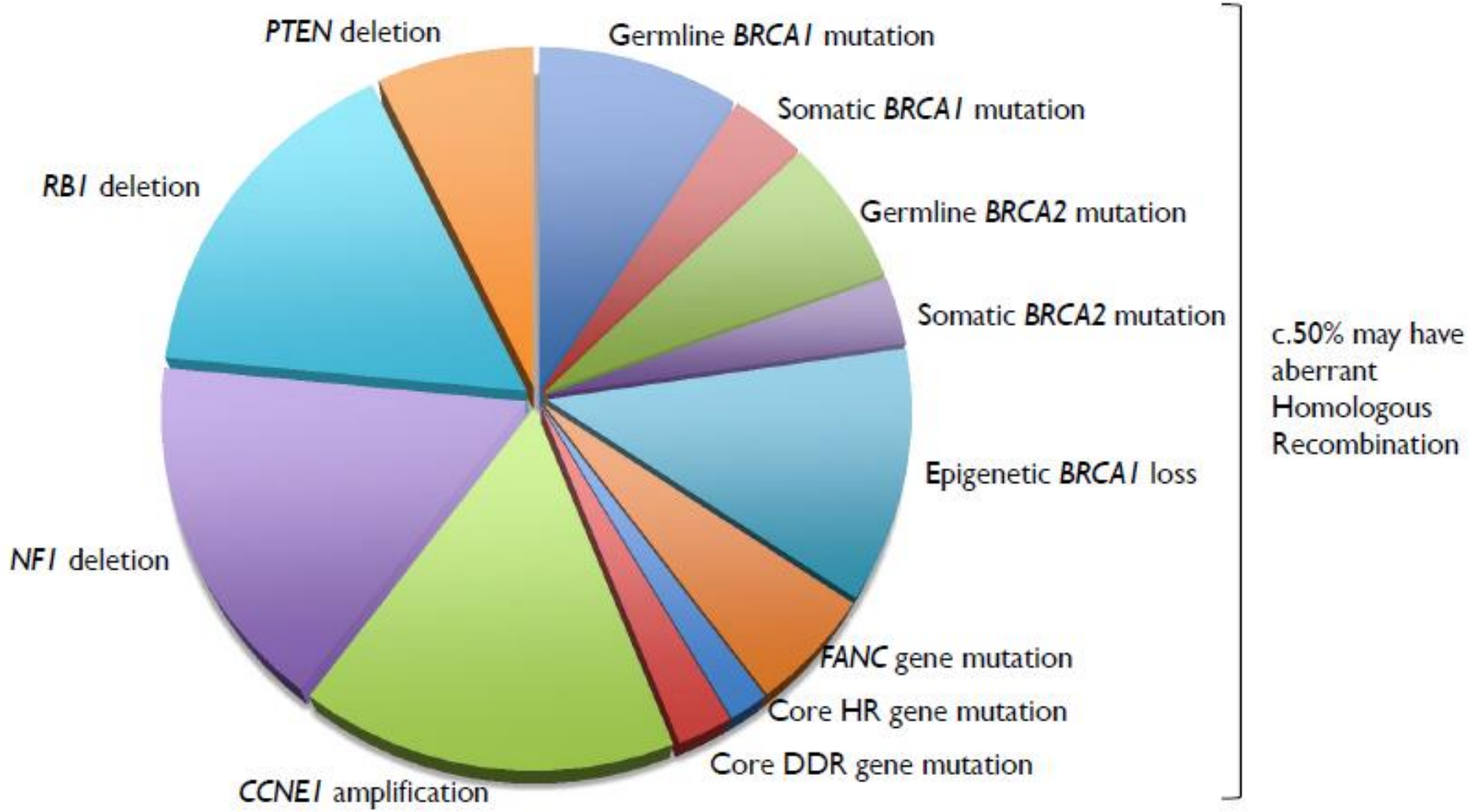
One post mortem analysis:

14 different reversion BRCA mutations!

Was resistant to platinum and PARP inhibitor

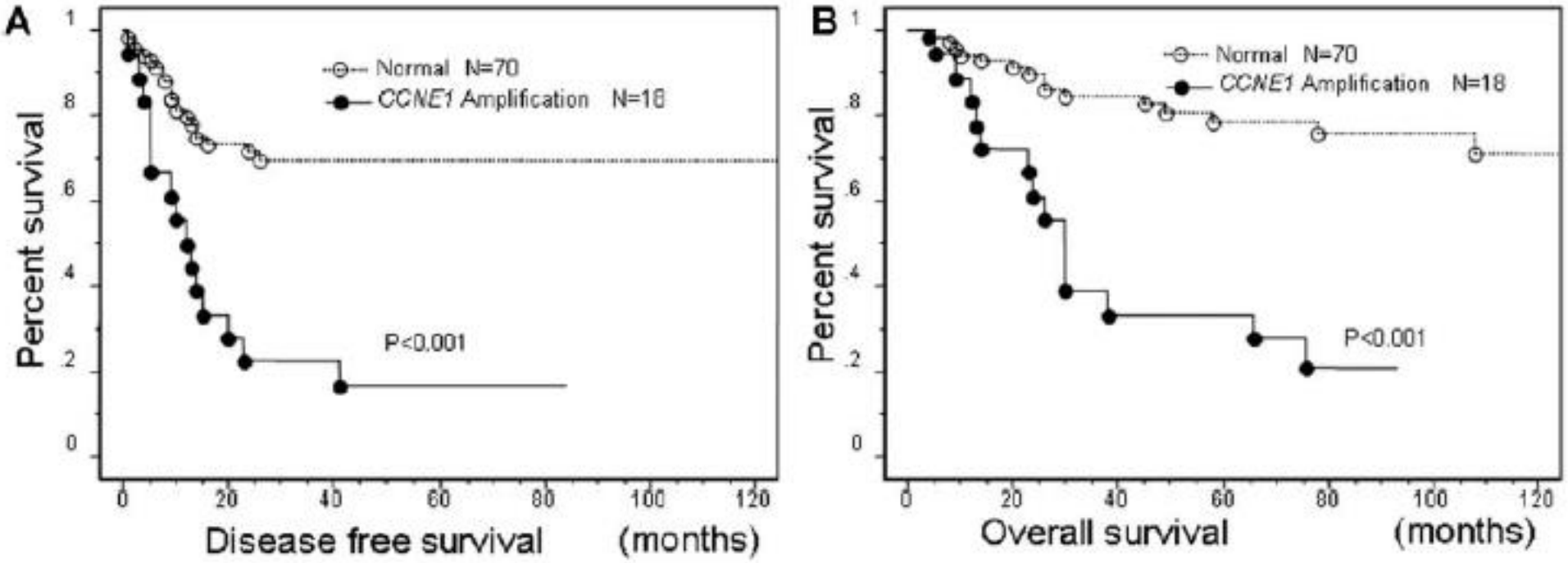


HGSOC: 50% genomic alterations associated with HRD, how about the other half?



TCGA, Nature (2011) 474:609; Martins et al Genome Biol. (2014) 15:526; ICGC – unpublished data; Etemadmoghadam, D et al CCR (2009) 15:1417;

CCNE1 amplification poor prognostic marker



- Mutually exclusive from HRD
- Associated with platinum resistance?

Nakayama et al Cancer (2010) 116:2

Genomic profiling of HGSOC

Homologous recombination deficiency (HRD) in 50% of HGSOC:

→ First targeted therapy in HGSOC associated with a genomic biomarker – germline or somatic BRCA mutations (RR to PARPi=80%)

→ Can we identify the subset of BRCA WT patients that could benefit from PARP inhibitors?

- High LOH score?
- Mutations in non-BRCA HR genes?
- Platinum sensitivity?

→ May soon need information regarding HRD status sooner, at diagnosis

→ Need to identify markers showing restoration of HR with resistance

→ Useful molecular markers in the non-HRD subset (50% of HGSOC)

Molecular subtypes of epithelial ovarian cancer

High grade serous ovarian cancer (75%)

- High Ki67
- Genomically unstable
- Chemosensitive but poor prognosis
- Universal TP53 mutation – few other mutations
- Associated with BRCA1/2 germline mutations (12-15%)
- Genomic homology with triple negative BC

Rare subtypes (25-30%)

- Histologic similarities with other primary tumors
- Chemotherapy resistance
- Frequent oncogenic mutations

Subtypes of rare OC

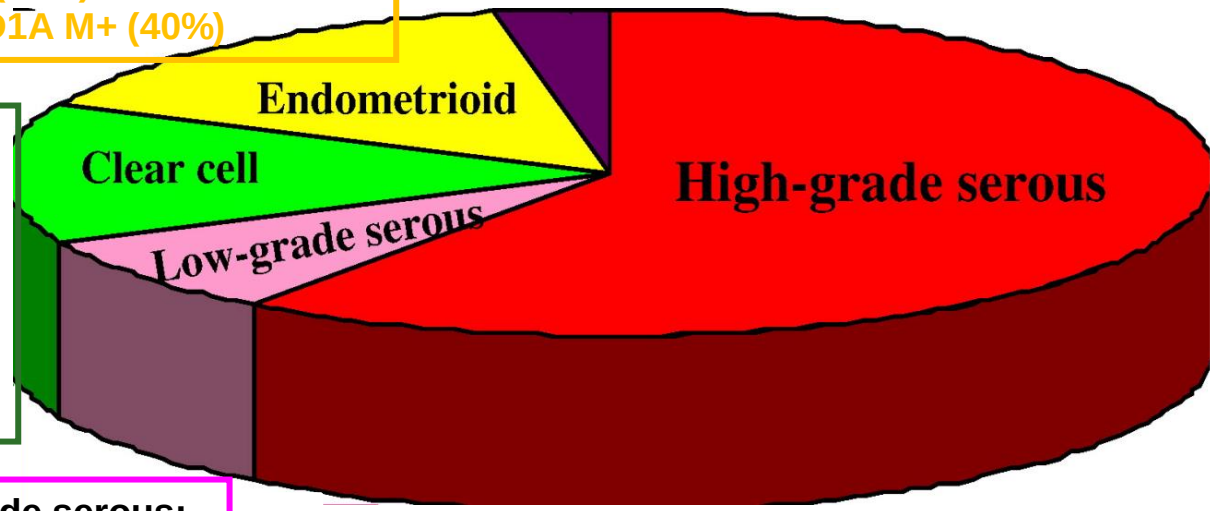
Invasive histology	Histological similarities
Low grade serous	
Mucinous	Colorectal cancer
Endometrioid	Endometrial cancer
Clear cell	Renal cell cancer
Transitional cell/Brenners	Urothelial tumors

Recurrent genomic alterations in rare subtypes of epithelial ovarian cancer

Endometrioid:
PTEN M+ or loss (40%)
PIK3CA M+ (20%)
MSI (19%)
ARID1A M+ (40%)

Mucinous:
KRAS M+ (40-60%)
HER2 Amp (18%)
MSI (17%)

M+: Mutation
Amp: amplification



Clear cell:
PTEN loss (20%)
Met Amp (12%)
HER2 Amp (15%)
PIK3CA M+ (30%)
ARIDIA (60%)
MSI (12%)

Low grade serous:
KRAS M+ 40%
BRAF M+ 5%

Among rare subtypes of epithelial OC:

- Genomic alterations are **histology-specific**,

and

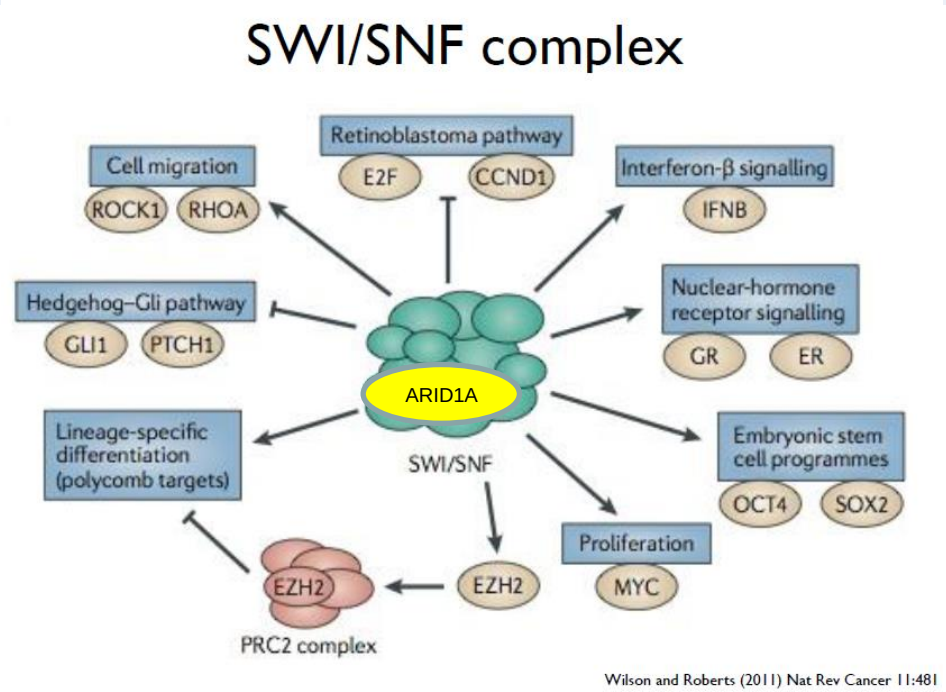
- Frequently actionable

ARID1A mutations common in Clear cell and endometrioid ovarian cancers

Table I. Tumors with *ARID1A* mutations (13-32).

Tumor	Rate (%)
Ovarian clear cell carcinoma	46-57
Ovarian endometrioid carcinoma	30
Low-grade endometrioid carcinoma	40
Renal clear cell carcinoma	34
Gastric carcinoma	8-27
Transitional cell carcinoma of the bladder	13
Esophageal adenocarcinoma	9.1-15
Hepatocellular carcinoma	10-13
Esophageal carcinoma	9
Pulmonary adenocarcinoma	8
Prostate carcinoma	8
Pancreatic carcinoma	2-8
Breast carcinoma	2-4
Burkitt lymphoma	14-17
Neuroblastoma	6
Medulloblastoma	2

Takeda, 2016



Wilson and Roberts (2011) Nat Rev Cancer 11:481

- Early event (found in precursor lesions)
- **ARID1A**= component of the SWI/SNF chromatin remodelling complex
- Tumor suppressor - regulation of
  - Lineage-specific differentiation,
  - Proliferation
  - Migration…

ARIDI1A mutation: Synthetic lethality with ATR inhibition

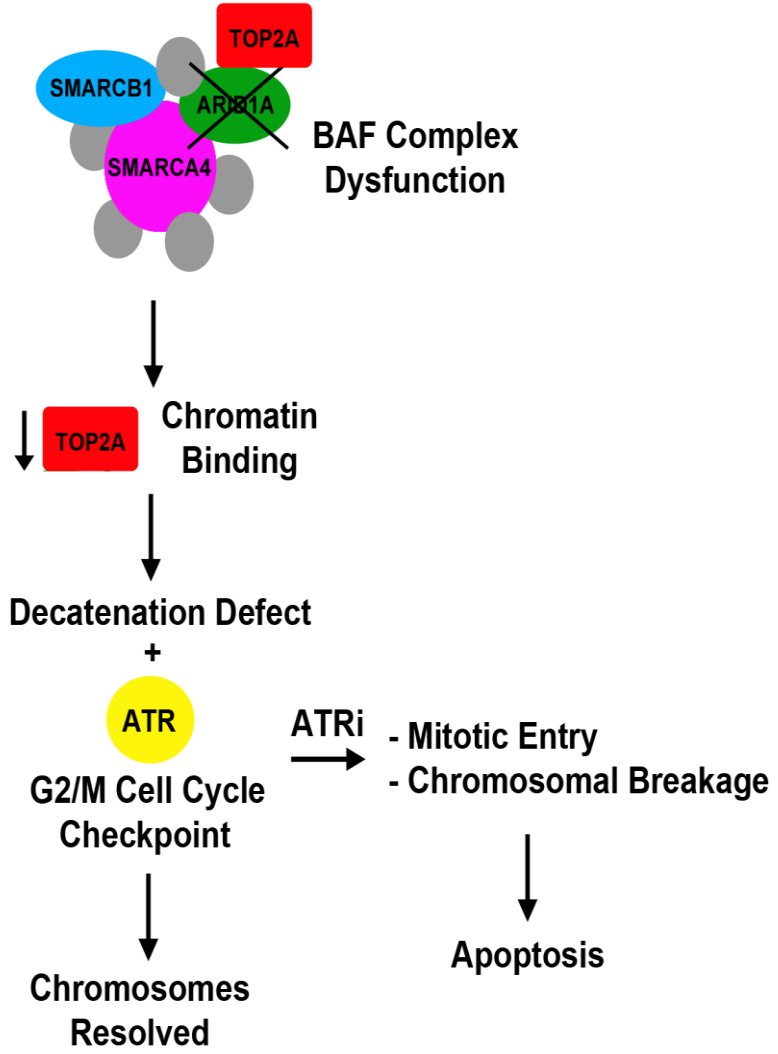
ARID1A required for localisation of TOP2A to DNA

TOP2A causes DSBs in DNA and facilitates transport of one double helix through another

ATR activity normally invoked when TOP2A defective

ARID1A defect = TOP2A defect = activation of ATR signaling cascade = delayed progression through S and G2

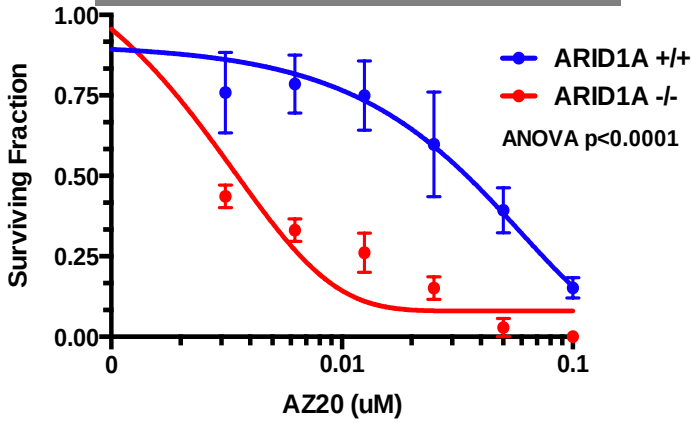
ARID1A defect plus ATRi = cells fail to adequately respond to TOP2A defect = premature cytokinesis in the face of unresolved DNA structures



Williamson ….Lord Nature Comm. Dec 2016

ARID1A mutant tumour cells are sensitive to small molecule ATR inhibitors, both *in vitro* and *in vivo*

ATR small molecule inhibitor *in vitro*



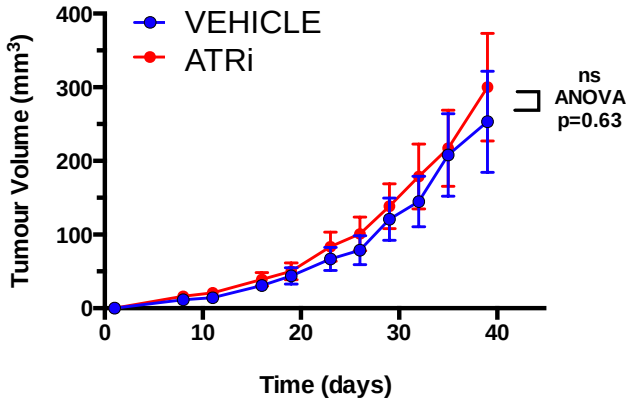
ARID1A mutations are frequent:

50% of clear cell ovarian cancers

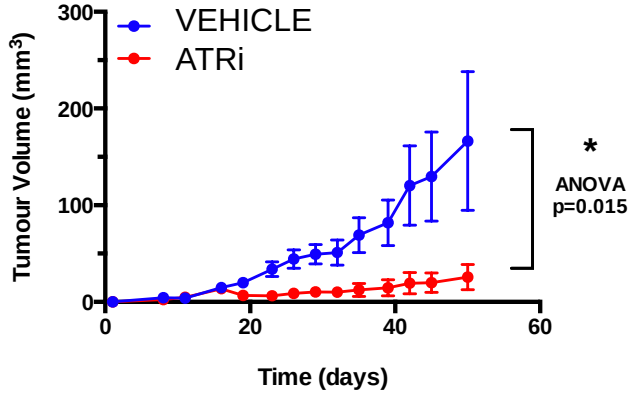
30%-40% of endometrioid ovarian cancers

May become useful predictive biomarker in the future

ATR small molecule inhibitor *in vivo* *ARID1A WT xenografts*



ATR small molecule inhibitor *in vivo* *ARID1A DEFICIENT xenografts*



Williamson ….Lord Nature Comm. Dec 2016

Microsatellite instability (MSI) frequent in non-serous ovarian cancer

MSI: - Mutations (or promoter hypermethylation) in mismatch repair (MMR) genes
- Initially described as germline (Lynch)
- Somatic MMR mutations also described
- leads to hypermutated tumor → sensitivity to immunotherapies

1234 OC cases in 22 studies

Histology	% MSI	N (tumours tested)
ALL epithelial OC	10%	Over 1000
Serous	8%	564
Endometrioid	19%	314
Clear cell	12%	117
Mucinous	17%	101

Murphy 2011

Useful predictive biomarker for
Immune therapies in MSI ovarian cancer?

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations
    - BRCA somatic mutations
    - Alterations in other HR genes
    - HRD score
    - Is platinum sensitivity enough

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations √
    - BRCA somatic mutations
    - Alterations in other HR genes
    - HRD score
    - Is platinum sensitivity enough

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations √
    - BRCA somatic mutations √
    - Alterations in other HR genes
    - HRD score
    - Is platinum sensitivity enough

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations √
    - BRCA somatic mutations √
    - Alterations in other HR genes **?**
    - HRD score
    - Is platinum sensitivity enough

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations √
    - BRCA somatic mutations √
    - Alterations in other HR genes ?
    - HRD score ?
    - Is platinum sensitivity enough

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Summary: Molecular biomarkers in epithelial ovarian cancer

- **In most frequent HGSOC:**
  - **Homologous recombination DNA repair deficiency**
  - What are the most useful molecular markers?
    - BRCA germline mutations √
    - BRCA somatic mutations √
    - Alterations in other HR genes **?**
    - HRD score **?**
    - Is platinum sensitivity enough **Perhaps….**

- **In non-serous epithelial OC:**
  - Actionable alterations frequent: ARID1A mutations, MSI, HER2 amplifications…
  - In the near future these genomic alterations may become relevant to offer 'personalized' treatment

Diagnostic value of genomic characterization of rare ovarian tumors?

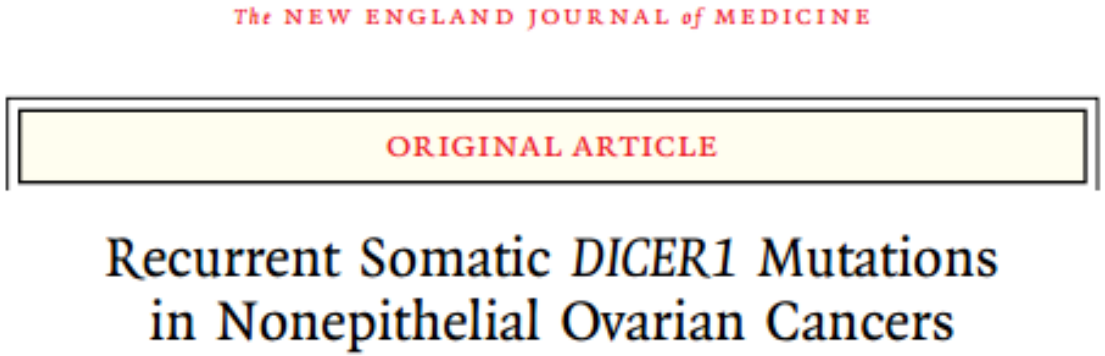
Molecular markers in non-epithelial ovarian cancer

- Germ cell ovarian cancer
- Sex-cord tumors of the ovary
  - Granulosa cell tumors
  - Sertoli-Leidig tumors
- Small cell cancer of the ovary, hypercalcemic type (SCCOHT)…

- Rare
- Diagnostic challenge
- Diagnostic value of genomic characterization

Molecular markers in non-epithelial ovarian cancer

>90% adult granulosa tumors



DICER1: endoribonuclease involved in microRNA processing
Mutated in 50% of Sertoli-Leidig tumors

Shah et al , 2009; Heravi-Moussavi et al, 2011

Molecular markers in non-epithelial ovarian cancer

>90% adult granulosa tumors

Screening for these genomic alterations has entered routine practice as **diagnostic** test

DICER1: endoribonuclease involved in microRNA processing
Mutated in 50% of Sertoli-Leidig tumors

Shah et al , 2009; Heravi-Moussavi et al, 2011

SCCOHT : Small Cell Carcinoma of the Hypercalcemic Type, OC

EXTREMELY RARE
< 1% of ovarian cancers

Highly aggressive form of ovarian cancer

- Mean age of diagnosis : **23 years**
- Poor Prognosis
- Frequently mis-diagnosed (confused with germ cell, round cell tumors, granulosa…)
- **Diagnostic challenge** : requires pathologist with expertise ‘rare ovarian tumors’
- Accurate **diagnosis urgency** needed because the right treatment needs to be started quickly

SMARCA4 mutation universal in SCCOHT

3 publications

in March 2014

Confirmed

***SMARCA4* mutations**

in SCCOHT

LETTERS

nature genetics

Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type

Leora Witkowski[1–3,26], Jian Carrot-Zhang[3,4,26], Steffen Albrecht[5], Somayyeh Fahiminiya[3,4], Nancy Hamel[1,6], Eva Tomiak[7], David Grynspan[8], Emmanouil Saloustros[9], Javad Nadaf[3,4], Barbara Rivera[1,3], Catherine Gilpin[7], Ester Castellsagué[1,3], Rachel Silva-Smith[1,2], François Plourde[1,2], Mona Wu[1,3], Avi Saskin[3], Madeleine Arseneault[3,4], Rouzan G Karabakhtsian[10,25], Elizabeth A Reilly[10], Frederick R Ueland[10], Anna Margiolaki[9], Kitty Pavlakis[11], Sharon M Castellino[12], Janez Lamovec[13], Helen J Mackay[14], Lawrence M Roth[15], Thomas M Ulbright[15], Tracey A Bender[15], Vassilis Georgoulias[9], Michel Longy[16], Andrew Berchuck[17], Marc Tischkowitz[18], Inga Nagel[19], Reiner Siebert[19], Colin J R Stewart[20], Jocelyne Arseneau[21], W Glenn McCluggage[22], Blaise A Clarke[23], Yasser Riazalhosseini[3,4], Martin Hasselblatt[24], Jacek Majewski[3,4] & William D Foulkes[1–3,6]

Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*

Pilar Ramos[1,14], Anthony N Karnezis[2,3,14], David W Craig[1], Aleksandar Sekulic[1,4], Megan L Russell[1], William P D Hendricks[1], Jason J Corneveaux[1], Michael T Barrett[1], Karey Shumansky[5], Yidong Yang[5], Sohrab P Shah[2,5], Leah M Prentice[3], Marco A Marra[6], Jeffrey Kiefer[1], Victoria L Zismann[1], Troy A McEachron[1], Bodour Salhia[1], Jaime Prat[7], Emanuela D'Angelo[7], Blaise A Clarke[8], Joseph G Pressey[9], John H Farley[10], Stephen P Anthony[11], Richard B S Roden[12], Heather E Cunliffe[1,13], David G Huntsman[2,3,15] & Jeffrey M Trent[1,15]

Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary

Petar Jelinic[1,5], Jennifer J Mueller[1,5], Narciso Olvera[1], Fanny Dao[1], Sasinya N Scott[2], Ronak Shah[2], Jianjiong Gao[3], Nikolaus Schultz[3], Mithat Gonen[4], Robert A Soslow[2], Michael F Berger[2] & Douglas A Levine[1]

Nature, march 23rd 2014

SMARCA4 mutations are ubiquitous in SCCOHT (>90%)

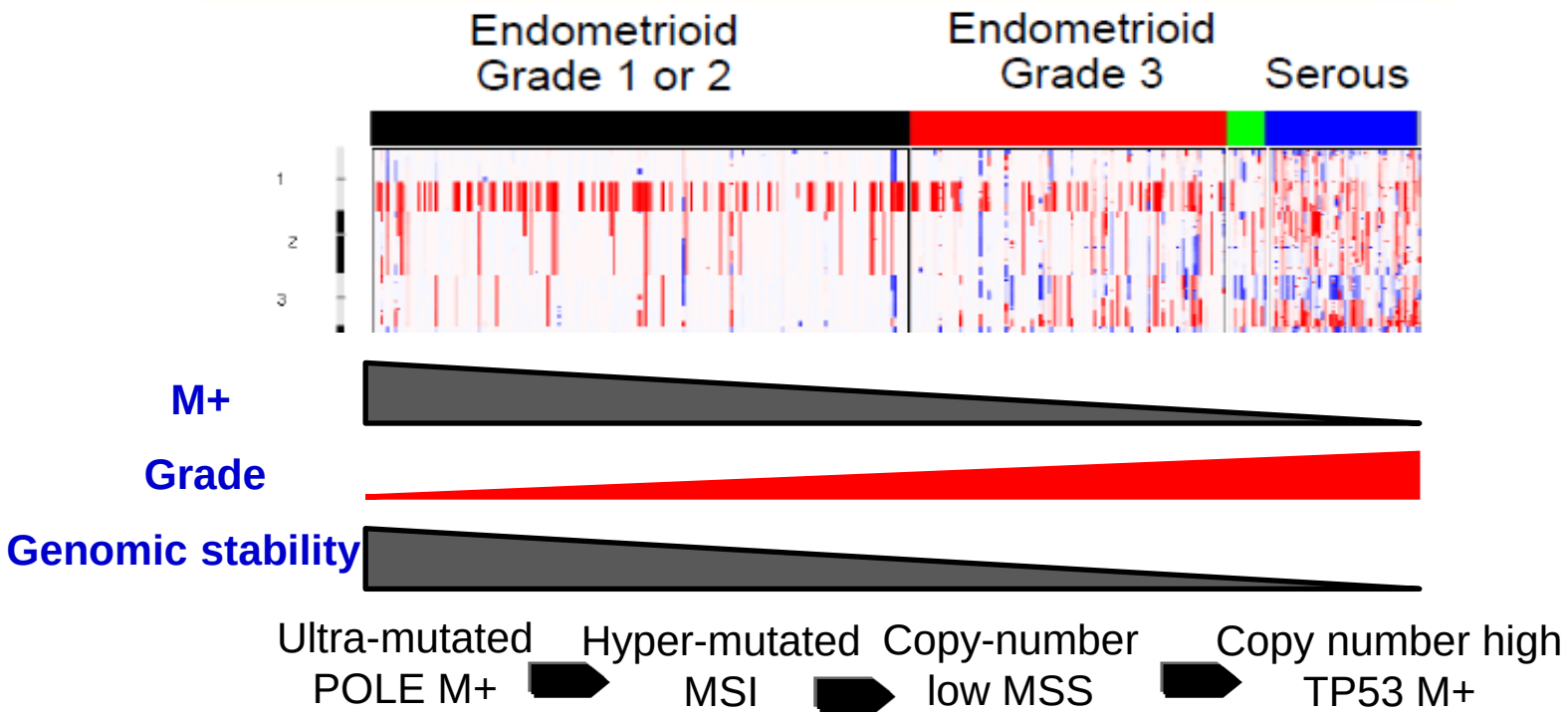
Screening for SMARCA4 mutation now routine **<u>diagnostic</u>** test in difficult to caracterize aggressive tumor in a young woman

Summary: Molecular/genomic markers in rare non-epithelial ovarian cancer

- Genomic profiling of rare ovarian tumors has provided a new useful diagnostic tool
- FOXL2 mutations for granulosa tumors
- DICER1 mutations for sertoli leidig tumors
- SMARCA4 mutations for small cell cancer of the ovaray of the hypercalcemic type

Genomic profiling of endometrial cancer

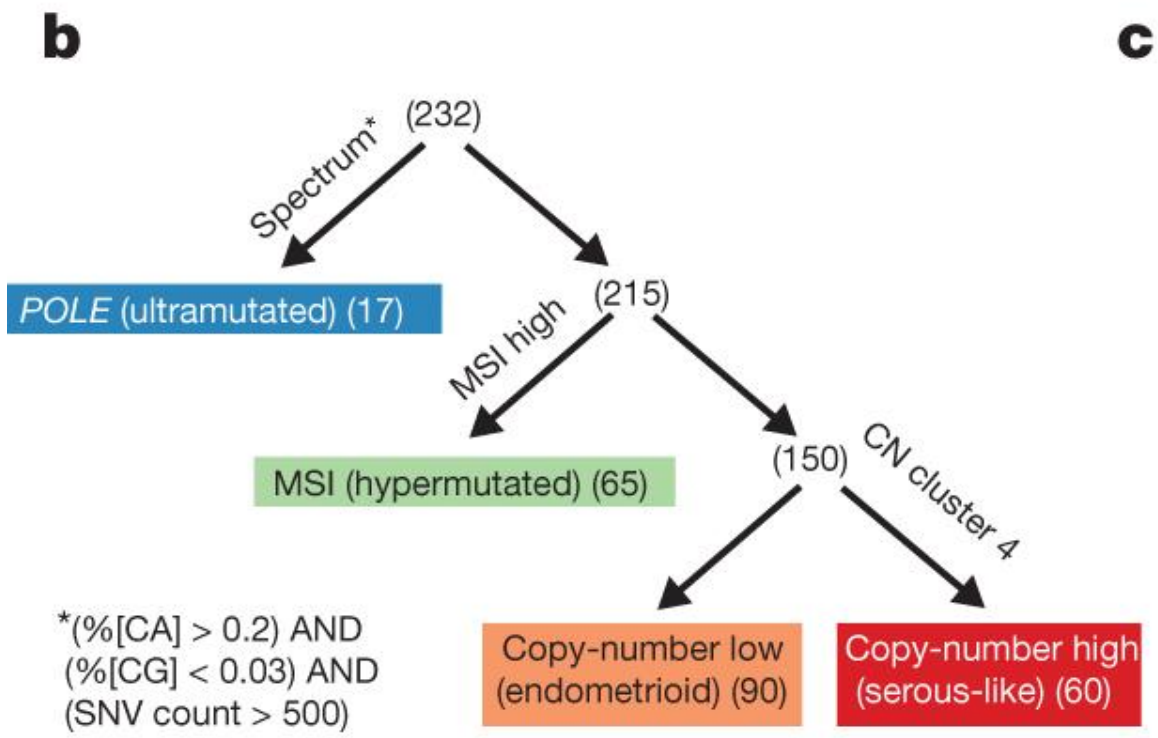
Not all Endometrial Cancers are the same…

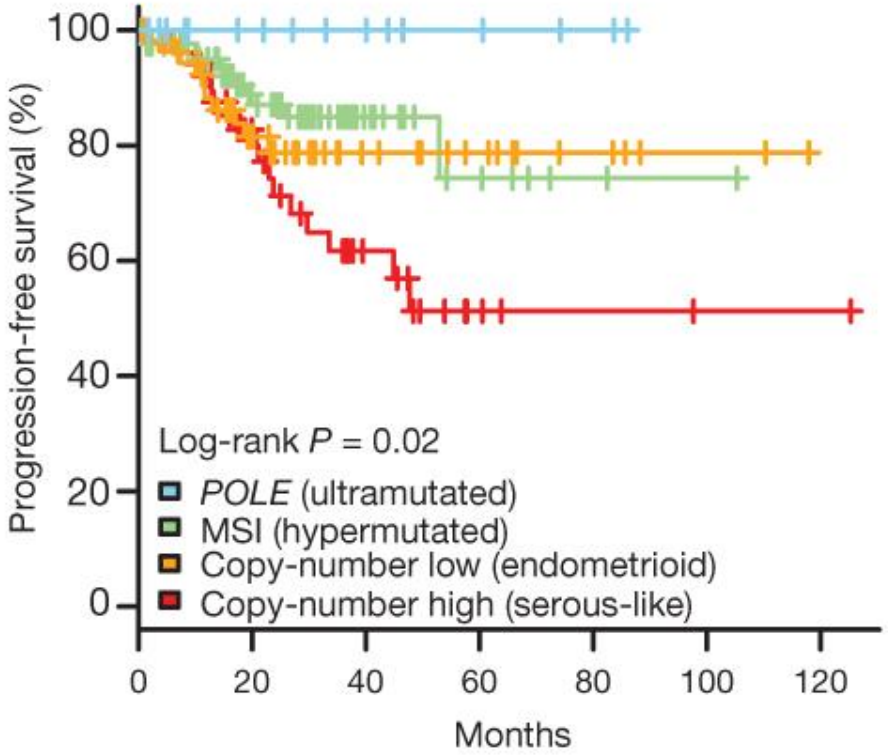


TCGA identified 4 classes of endometrial cancer
Classified according to mutation load and copy number

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Not all Endometrial Cancers are the same…





Genomic classification provides prognostic information:

- POLE mutated: best survival (could be spared toxic adjuvant treatment)
- TP53 mutated: worst. Need adjuvant chemotherapy?

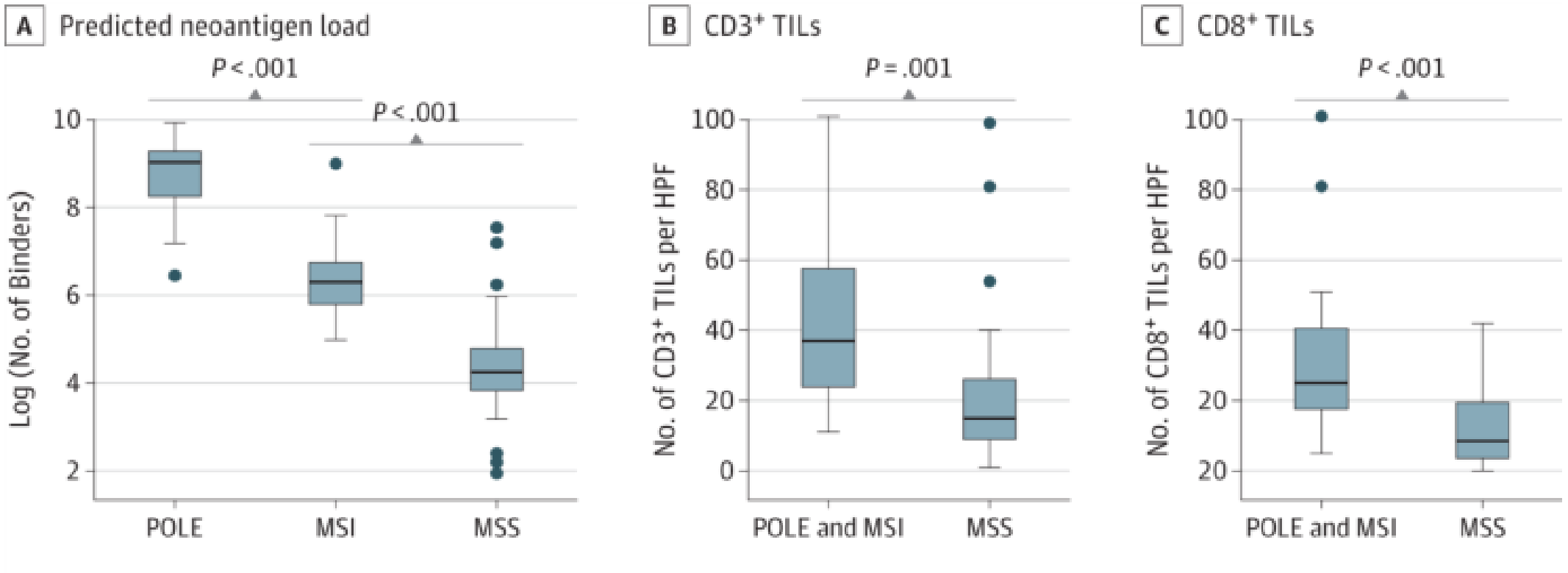
G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Does genomic profiling of endometrial cancer provide predictive information?

POLE mutated and MSI endometrial cancers: High mutation load and high TILs

The JAMA Network

From: **Association of Polymerase e–Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1**



POLE/MSI tumors

High mutation load

More neo-antigens

Increased TILS CD3+/CD8+

Increased PD1/PDL1+ expression

Response to PD1/PDL1 inhibitors?

Response to PD1 inhibitor in MSI vs MSS tumors

	MSS CRC N=18	MSI CRC N=10	MSI tumors N=7
RR	0	40%	70%

Le D NEJM 2015

RR= 70% in MSI non colorectal cancers (including endometrial cancer)

POLE/MSI tumors

High mutation load

More neo-antigens

Increased TILS CD3+/CD8+

MAY 2017

FDA Approves Pembrolizumab for Microsatellite Instability-High and Mismatch Repair Deficient Cancers

PD1/PDL1 inhibitors?

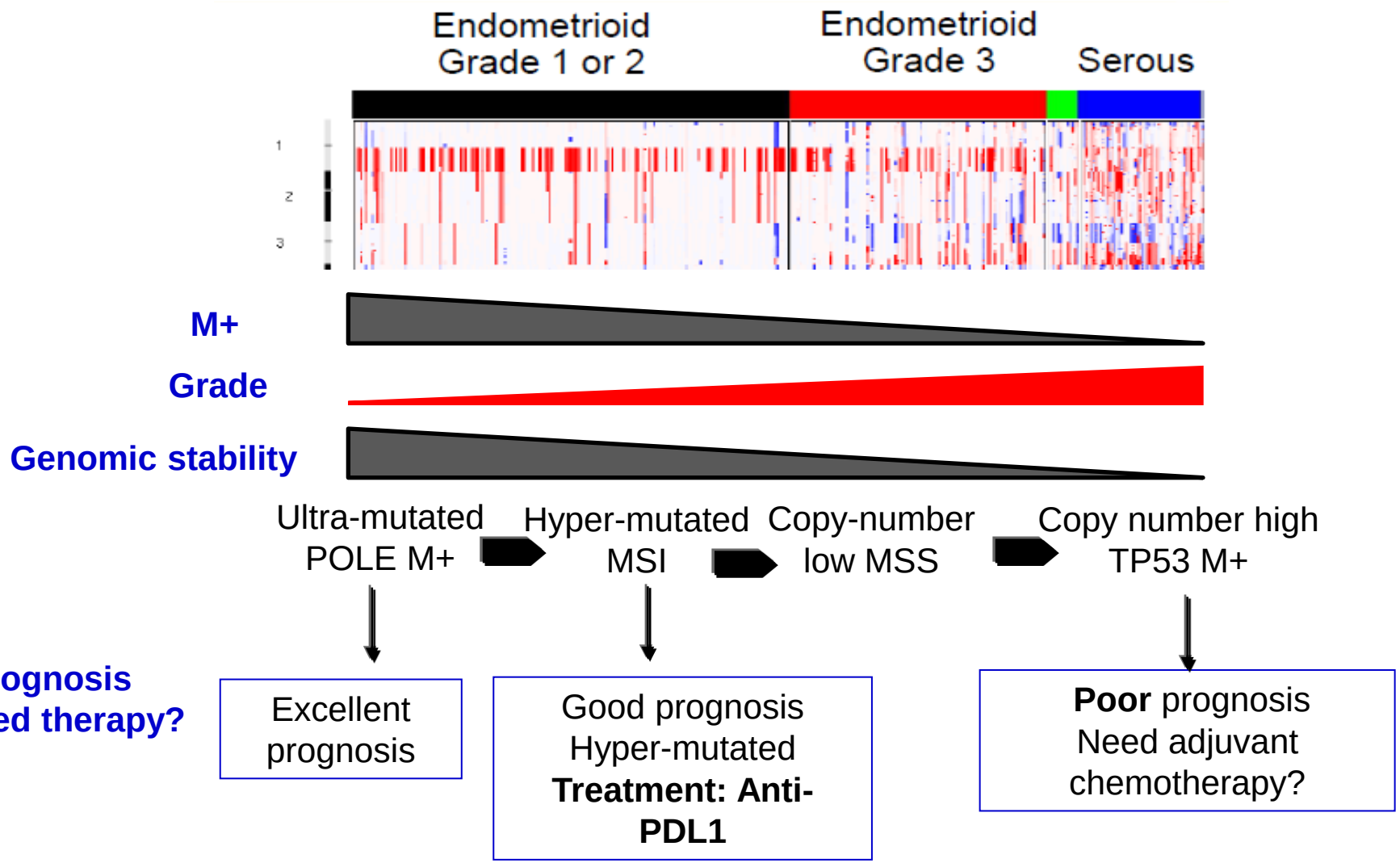
Response to PD1 inhibitor in MSI vs MSS tumors

	MSS CRC N=18	MSI CRC N=10	MSI tumors N=7
RR	0	40%	70%

Le D NEJM 2015

RR= 70% in MSI non colorectal cancers (including endometrial cancer)

Genomic biomarkers in Endometrial Cancer



Conclusions: Value of genomic profiling in endometrial cancers

Most EC are cured by local treatment alone

Greatest value of genomic profiling in refining prognostic groups:

- **POLE: Excellent prognosis**
- **TP53: Poorest prognosis**

Actionable alterations?

- MSI yes!
- TP53 mutations: need post-operative chemotherapy?

Biomarkers in gynecological tumors: Conclusion

In HGSOC: PARP inhibitors: 1st targeted therapy associated with a genomic biomarker – g or s BRCA mutations

→ Can we identify the subset of BRCA WT with HR deficiency?

- High LOH score?
- Mutations in non-BRCA HR genes?
- Platinum sensitivity?

→ Will need this information earlier – At diagnosis

→ Other biomarkers? Reversion BRCA mutations, caracterizing the 'non-HRD'

In non-serous epithelial OC: Number of candidate predictive biomarkers (ARID1A mutations, MSI, HER2 amplifications…)

In non-epithelial OC: Useful diagnostic tool: FOXL2 mutations, SMARCA4 mutations

In endometrial cancers: Prognostic (POLE or TP53 mutations) and predictive (MSI)