Rethinking “Ovarian” Cancer...

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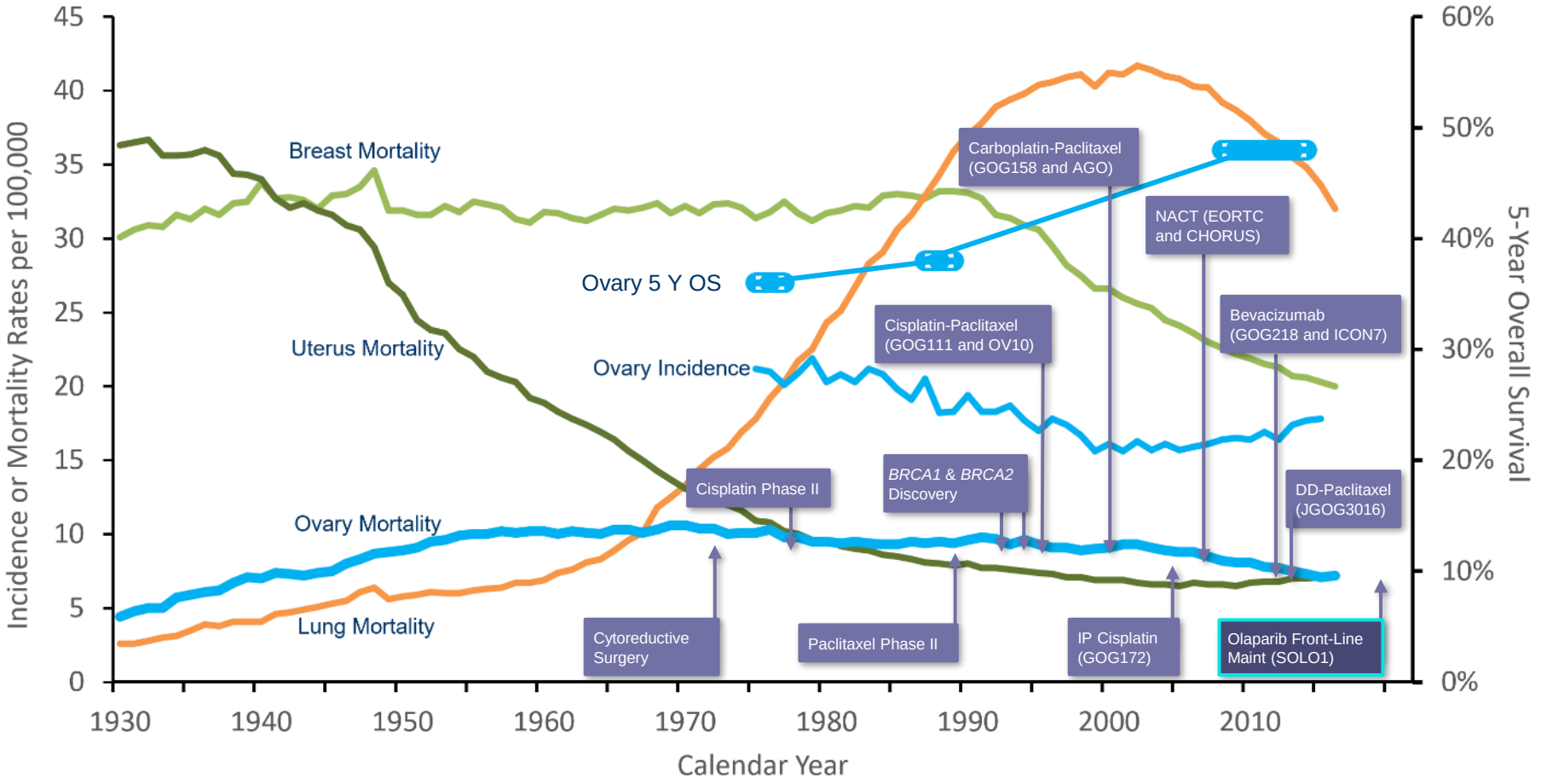
Long Term Outcomes (US: Women)

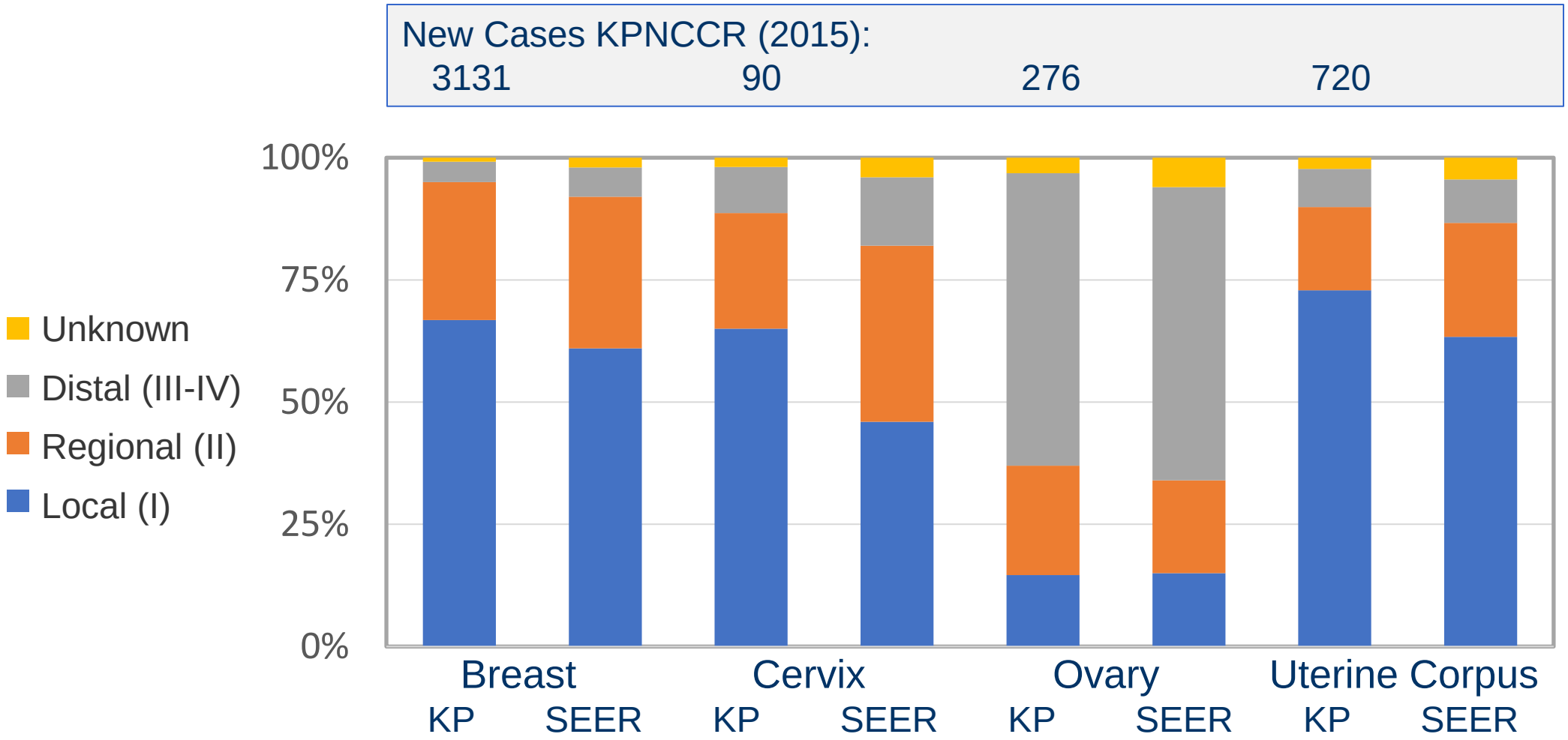


- Improvements in median PFS, OS, and QoL
- Benefits of chemotherapy and cytoreductive surgery appear maximized
- Modest reduction in incidence and mortality from 2005 (Possibly related to ↑RR-BSO and ↓HRT)
- No impact on overall case-fatality ratio (or cure)
- Impact of PARPi pending

American Cancer Society® Cancer Statistics Center

Gourley C and Bookman MA. *J Clin Oncol* 2019; 37:2386-97

Stage at Diagnosis (NCAL and National)



KPNCCR 2006 - 2012

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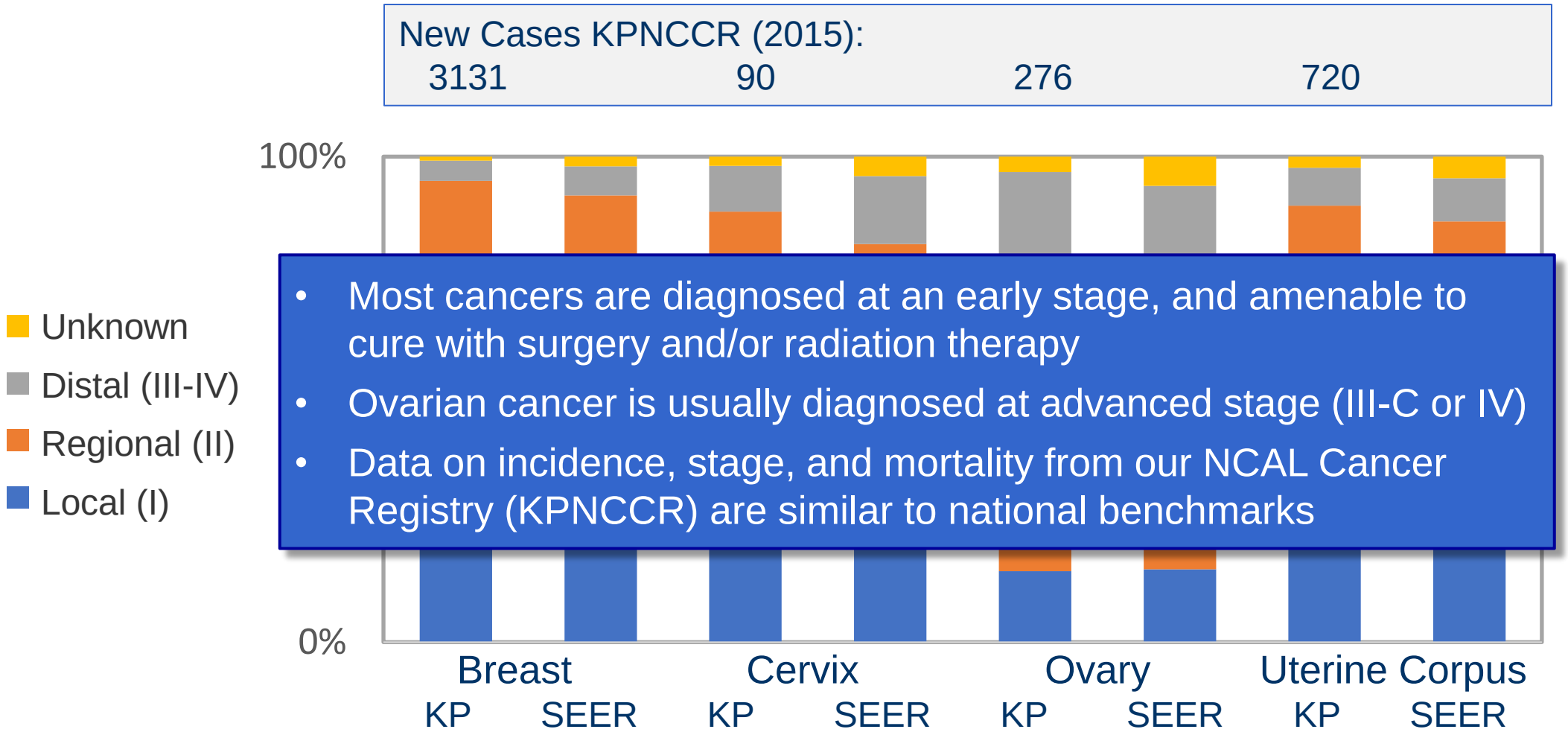
Stage at Diagnosis (NCAL and National)



- Most cancers are diagnosed at an early stage, and amenable to cure with surgery and/or radiation therapy
- Ovarian cancer is usually diagnosed at advanced stage (III-C or IV)
- Data on incidence, stage, and mortality from our NCAL Cancer Registry (KPNCCR) are similar to national benchmarks

KPNCCR 2006 - 2012

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Epithelial Cancers Involving the Ovary

	HGSC	CCC	EC	MC	LGSC	CS
Distribution: FIGO III-IV	75%	4%*	12%	2%	4%	3%
Genetic Risk	BRCA1/2 HR	HNPCC	HNPCC	None known	None known	BRCA1/2 (minor)
Other Risks	↓ Risk with OC, pregnancy	None known	↓ Risk with OC, ↑ Risk with HRT	None known	None known	None known
Precursors	STIC	Endometriosis	Endometriosis	MBT	SBT	HGSC HGEC
Chemotherapy	Sensitive, then resistant	Resistant	Sensitive	Resistant	Resistant	Resistant
Molecular Genetics	TP53(P53) BRCA1/2 PI3K HRD	PI3K ARID1A MMR-MSI	PTEN CTNNB1 POLE MMR-MSI FGFR	KRAS cErbB2(HER2)	BRAF KRAS NRAS	TP53(P53) cErbB2(HER2)
Targets	PARP, Angiogenesis	Angiogenesis, Immune CPI	ER, PR, mTOR, Immune CPI	HER2	RAS/RAF-MEK Hormonal	HER2

* CCC 30% in Asia

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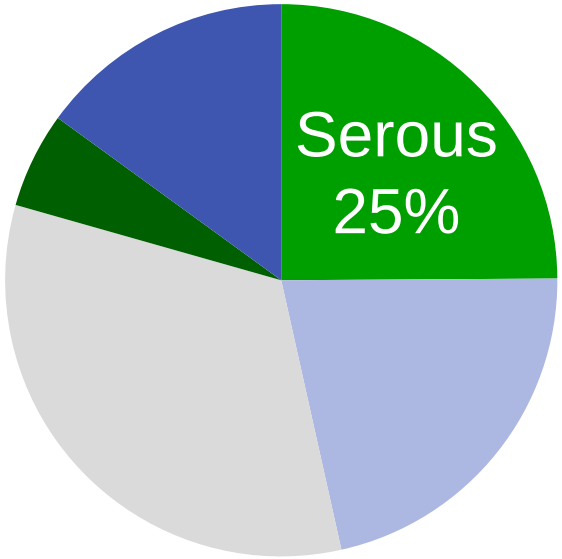
Other Risks	↓ R p					own
Precursors						C C
Chemotherapy	Ser					ant
Molecular Genetics	T BR					53) ER2)
Targets	PARP, Angiogenesis	Angiogenesis, Immune CPI	ER, PR, mTOR, Immune CPI	HER2	RAS/RAF-MEK Hormonal	HER2

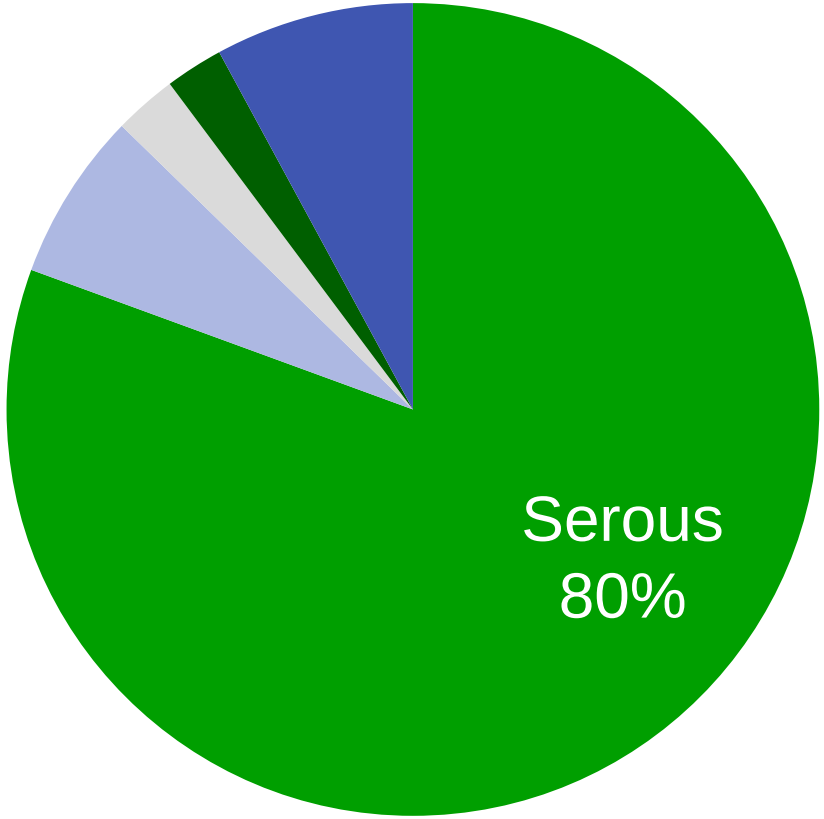
- Distinct cancer subtypes defined by clinical, genetic, and molecular features, as well as site of origin and precursor lesions
- Stage at diagnosis remains the single most important prognostic factor across all tumor types
- Individualized management decisions should be based on pathology, stage, and biology (may avoid over-treatment)
- Platinum compounds remain the most active agents developed to date, limited by the near-universal emergence of platinum resistance
- Resistance to Natural Products and other agents is distinct from platinum resistance, with an impact on treatment planning

* CCC 30% in Asia

Ovarian Histology by Stage

GOG 0157
Stage I-II





GOG 0182
Stage III-IV

Serous Endometrioid Clear Cell Mucinous Mixed

Bell JG. *Gynecol Oncol* 2006;102:432-9

Bookman MA, et al. *J Clin Oncol* 2009;27:1419-25

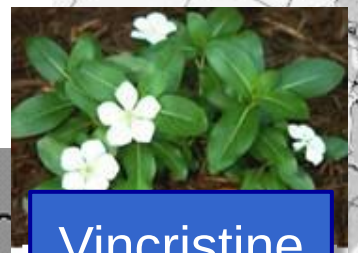
Ovarian Cancer: True, False, or…

- Screening with Pap smears, CA125, pelvic exams, and endovaginal ultrasound will detect early-stage ovarian tumors and reduce mortality
- Women who use oral contraceptives experience a life-long reduction in risk of 40%
- Post-menopausal hormone replacement does not have an impact on risk
- Nulliparity (with or without infertility) is associated with an increased risk of ovarian cancer
- The majority of ovarian cancers are associated with inherited mutations in genes such as BRCA1/2

Ovarian Cancer: True, False, or…

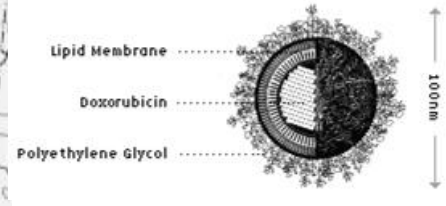
The “Non-Platinums”: All Natural Ingredients…

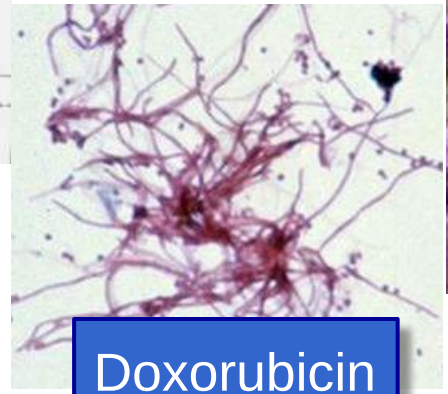
Etoposide



Vincristine
Vinblastine

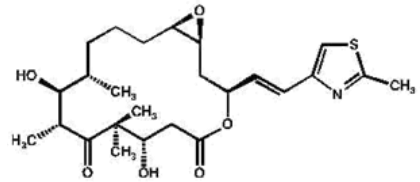
Paclitaxel
Docetaxel





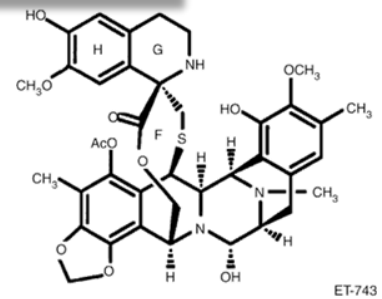
Doxorubicin

Epothilone-B
Ixebepilone



Topotecan
Irinotecan

Trabectedin



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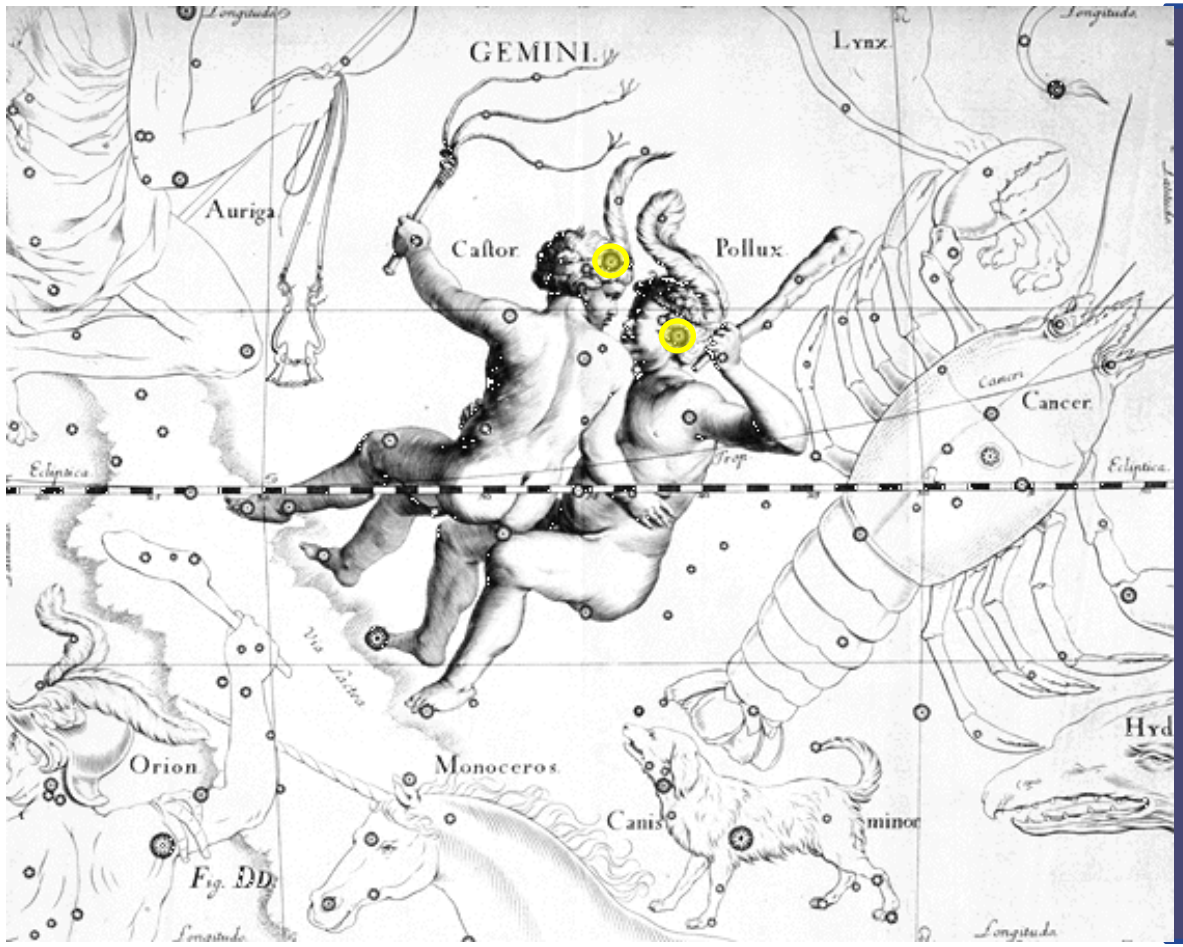
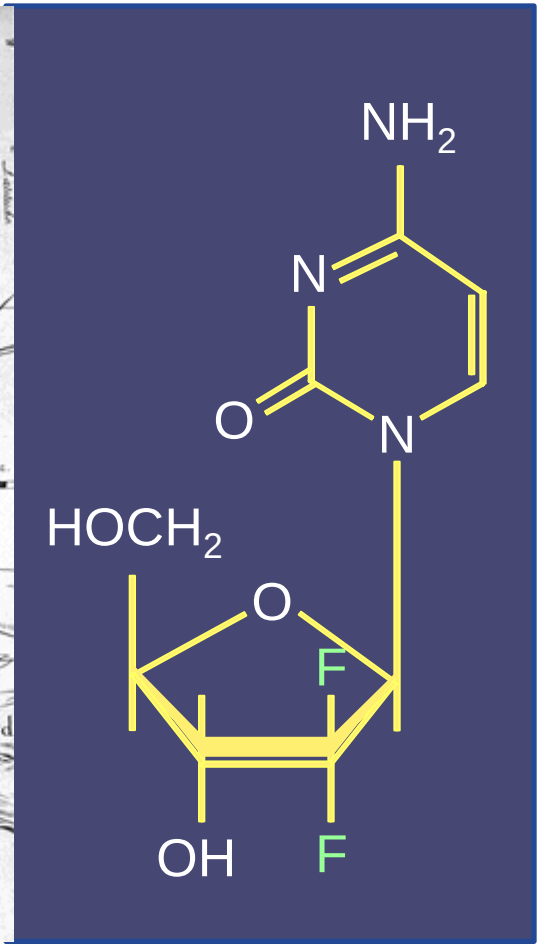
Imitating Nature (with a Twist)…

Gemcitabine (2′2′-difluorodeoxycytidine)





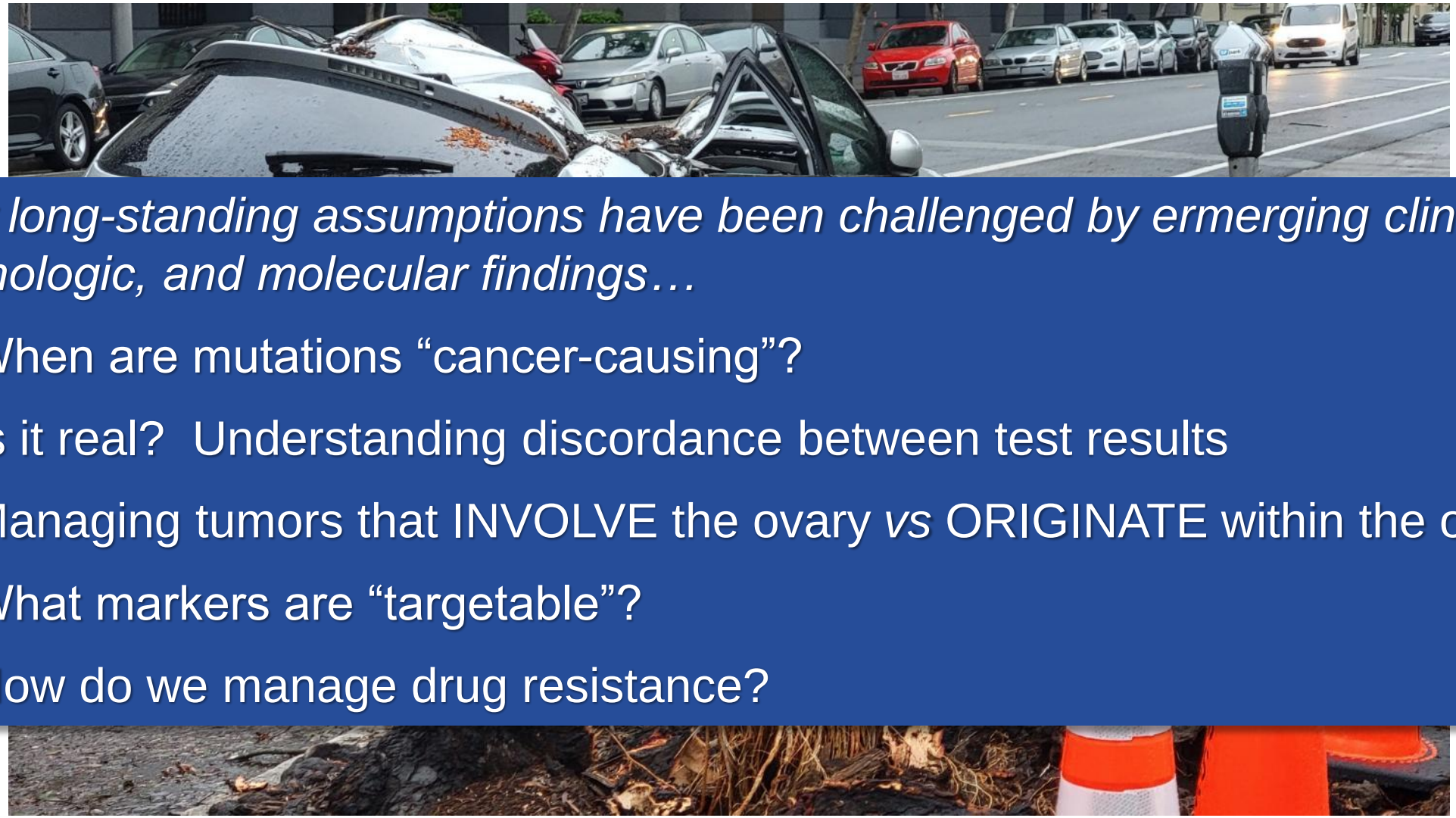
Targets Ribonucleotide Reductase (RR), Thymidylate Synthase (TS), and DNA Nucleotide pools, with incorporation of dFdCTP into DNA

Results in masked chain termination during DNA synthesis.

Uptake dependent on rate-saturable phosphorylation.

Mechanisms of resistance are largely specific to gemcitabine.

Reconstructing Cause and Effect…



Our long-standing assumptions have been challenged by ermerging clinical, pathologic, and molecular findings…

- When are mutations “cancer-causing”?
- Is it real? Understanding discordance between test results
- Managing tumors that INVOLVE the ovary *vs* ORIGINATE within the ovary
- What markers are “targetable”?
- How do we manage drug resistance?

First Endometrial Cancer Consensus Conference on Clinical Research

Incheon, South Korea NOV2023

KGOG Korean Gynecologic Oncology Group

GCIG GYNECOLOGIC CANCER INTERGROUP

21st Annual Cancer Conference 15NOV2024

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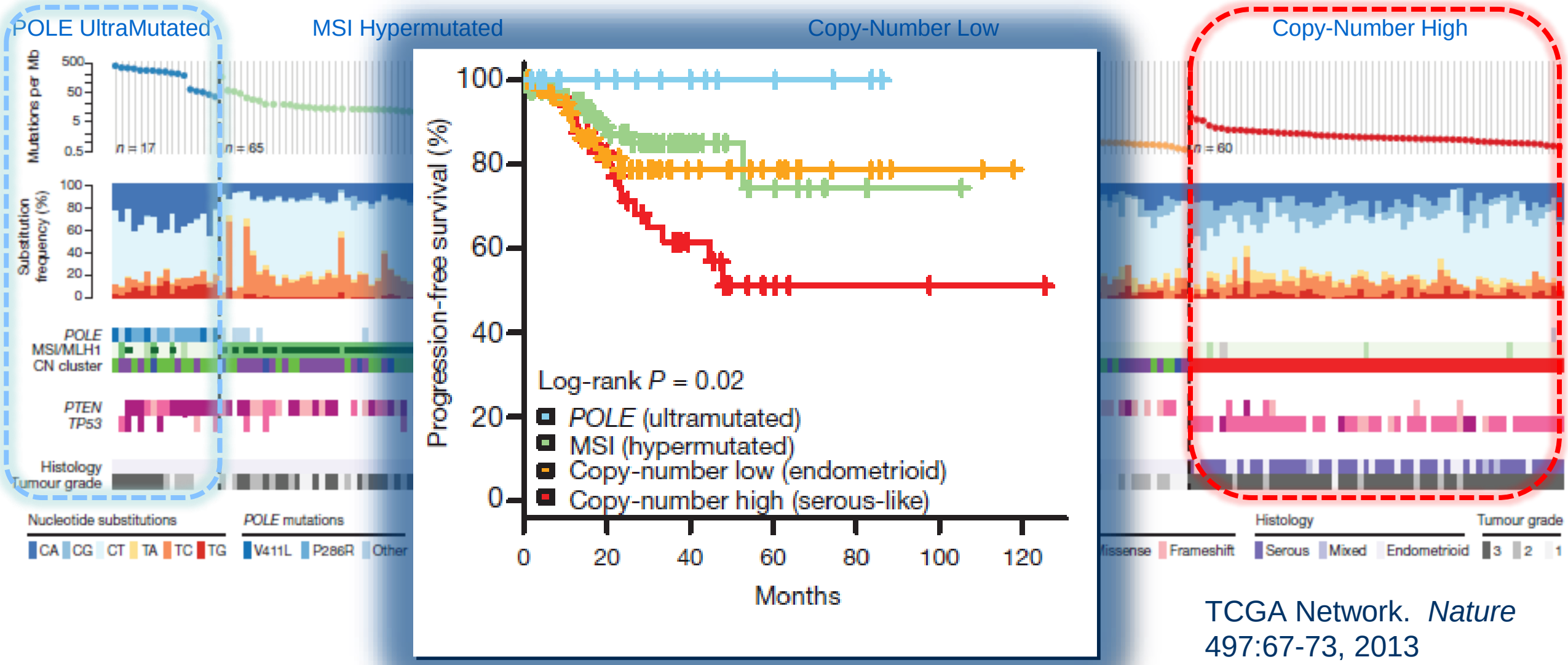
Targeting Endometrial Cancer: TCGA



TCGA Network. *Nature* 497:67-73, 2013

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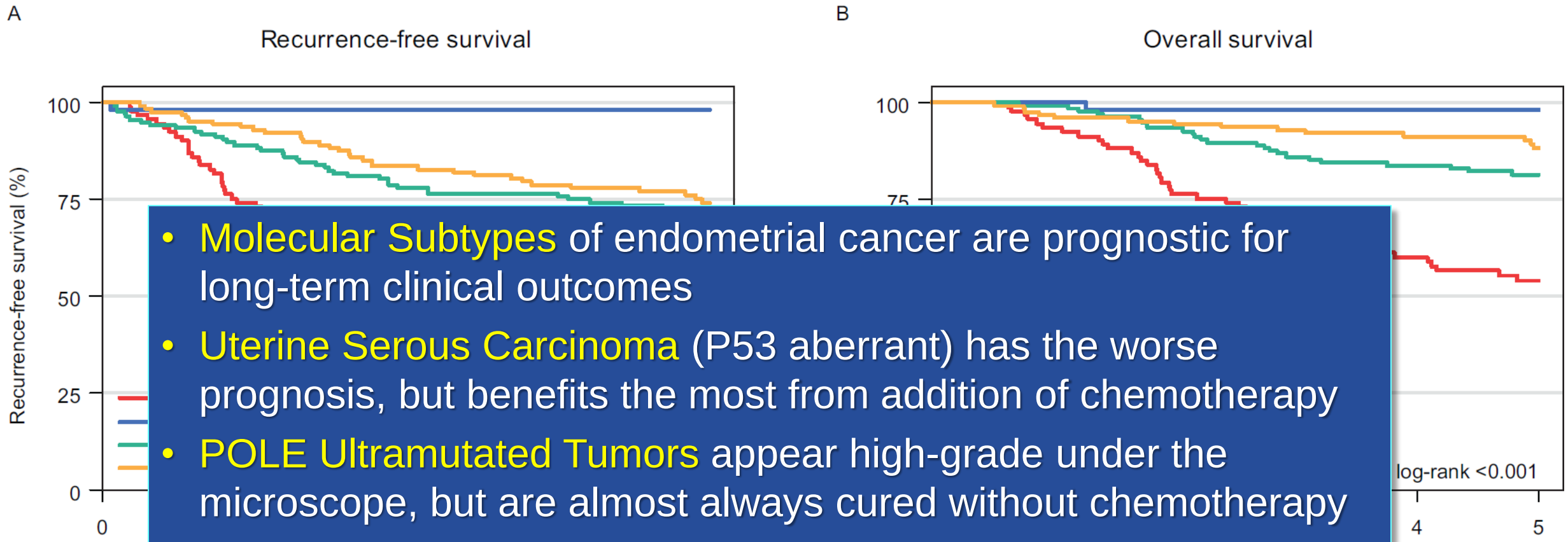
PORTEC3: Molecular Subtypes



- Molecular Subtypes of endometrial cancer are prognostic for long-term clinical outcomes
- Uterine Serous Carcinoma (P53 aberrant) has the worse prognosis, but benefits the most from addition of chemotherapy
- POLE Ultramutated Tumors appear high-grade under the microscope, but are almost always cured without chemotherapy
- Clinical Management should be individualized in accordance with molecular findings

León-Castillo A, et al. PORTEC3 *J Clin Oncol*. 2020;38:3388-3397

Dual Molecular Classifiers: Lynch Syndrome and P53

69 Y old woman, abnormal bleeding

- CT: Widened endometrial stripe (1.7 cm) with peripheral enhancement
- Endometrial Bx: High-Grade Serous Carcinoma (P53 aberrant), loss of MSH6 on IHC (MMRd)
- Staging: Laparoscopic TAH-BSO, Omentectomy, PLND. Endometrioid adenocarcinoma, FIGO Grade 2 (P53 aberrant), Atypia without definitive serous histology, pT1a pN0 (FIGO IA), 45% MMI, focal LVSI

Tumor content	80% (molecularly informed)	Cancer Type	Endometrial Cancer
Surface area	30 mm²	Subtype	Uterine Endometrioid Carcinoma

FBXW7 p.R465C
NM_033632.3:c.1393C>T
Estimated variant allele frequency: 55%

FGFR1 amplification
Estimated copy number: 6
Confidence interval: 5.4 - 7.4

MSH6 p.V717Afs*18
NM_000179.2:c.2150_2153del
Estimated variant allele frequency: 51%

PIK3CA p.R88Q
NM_006218.2:c.263G>A
Estimated variant allele frequency: 41%

PIK3R1 p.S565R
NM_181523.2:c.1695C>A
Estimated variant allele frequency: 40%

PPP2R1A p.R182W
NM_014225.5:c.544C>T
Estimated variant allele frequency: 43%

PTEN p.G282*
NM_000314.4:c.844G>T
Estimated variant allele frequency: 36%

PTEN p.R233*
NM_000314.4:c.697C>T
Estimated variant allele frequency: 44%

RB1 p.R358*
NM_000321.2:c.1072C>T
Estimated variant allele frequency: 72%

SMARCA4 p.R381*
NM_001128849.1:c.1141C>T
Estimated variant allele frequency: 19%

TP53 p.R273H
NM_000546.5:c.818G>A
Estimated variant allele frequency: 74%

Endometrioid Oncogenic Driver

Tumor Suppressor

Uterine Serous Ca

dMMR, Lynch

Biomarker Findings

MSS
Microsatellite Stable

Dual Molecular Classifiers: Lynch Syndrome and P53

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Germline Risk Panel Testing (62 Genes)

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
MSH6	c.2150_2153del (p.Val717Alafs*18)	heterozygous	PATHOGENIC
MSH2	c.48G>C (p.Glu16Asp)	heterozygous	Uncertain Significance

VUS

MSH2
p.E16D
NM_000251.2
c.48G>C
43% VAF

Lynch Syndrome (HNPCC)

MSH6 p.V717Afs*18
NM_000179.2:c.2150_2153del
Estimated variant allele frequency: 51%

Dual Molecular Classifiers: Lynch Syndrome and P53

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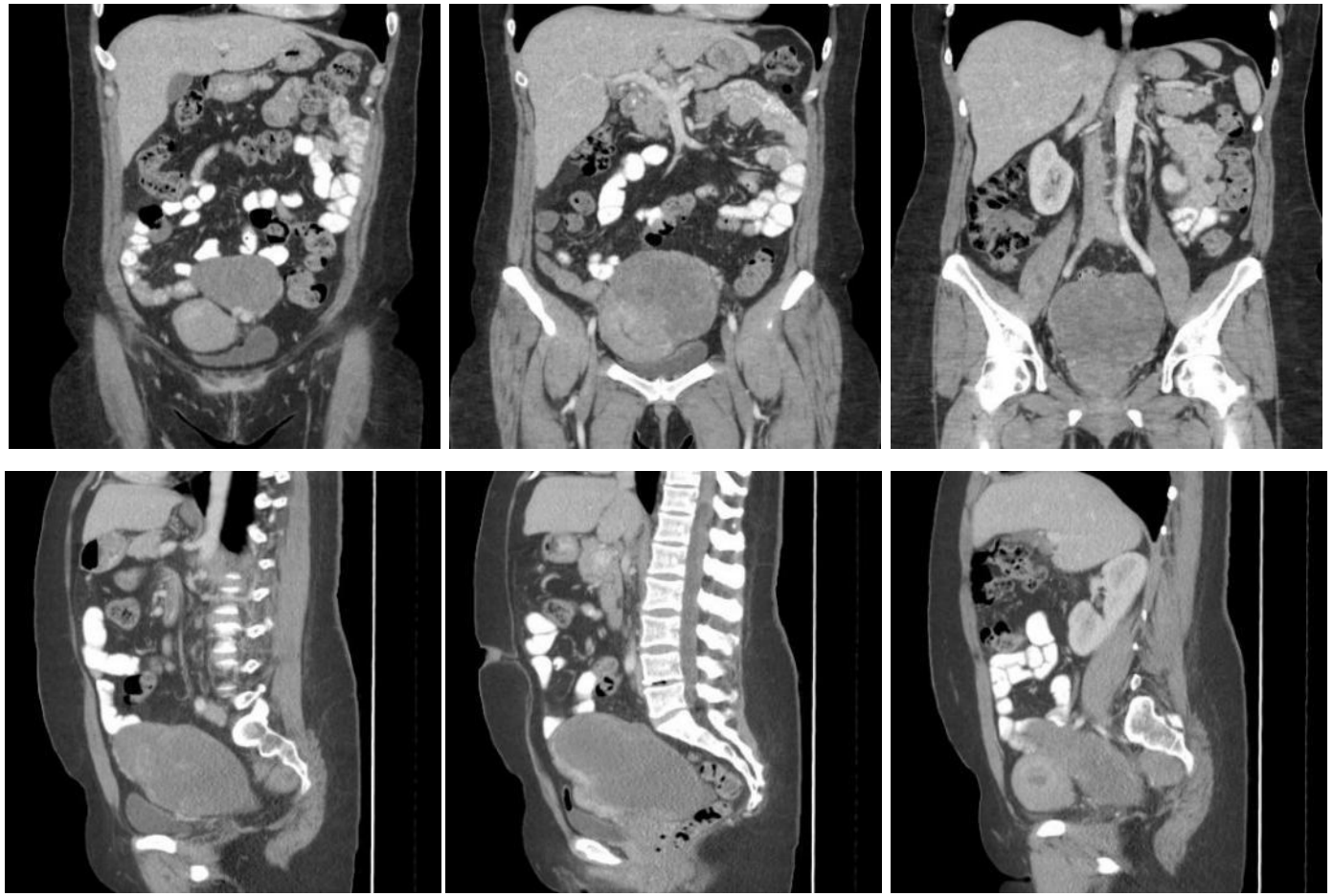
Your Recommendation Post-Surgery:

A. Observation/Surveillance without additional therapy
B. Chemotherapy
C. Immunotherapy
D. Radiation Therapy (HDR-VBT)

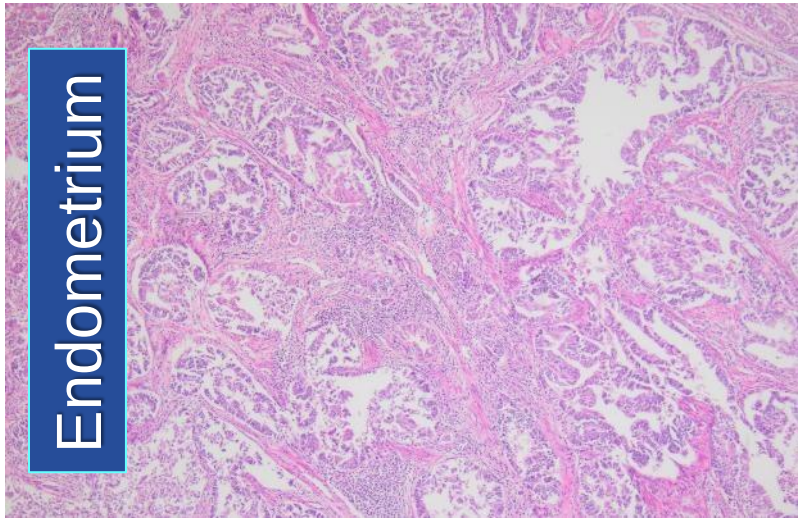
- Lynch Syndrome (HNPCC, inherited↑cancer risk)
- Tumor MMRd, but without MSI (second intact copy of *MSH6*)
- *TP53*mut appears to be the dominant molecular finding within this cancer
- Received HDR-VBT and chemotherapy without recurrence

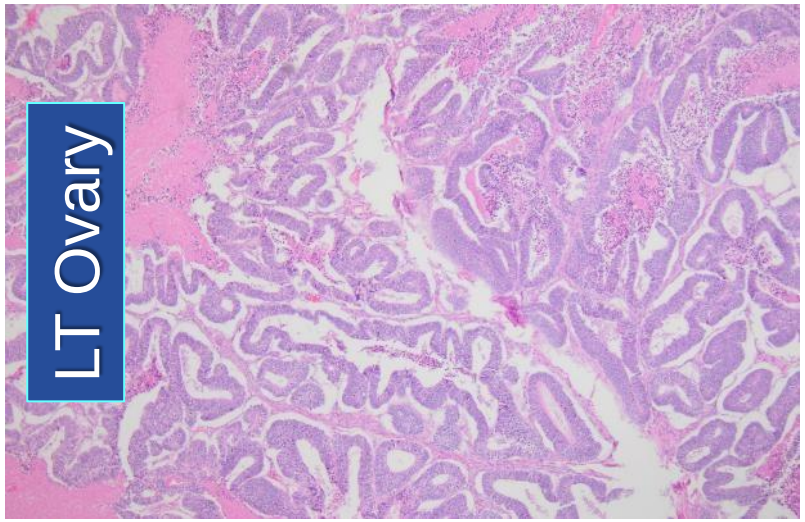
One Primary *vs* Synchronous Primaries

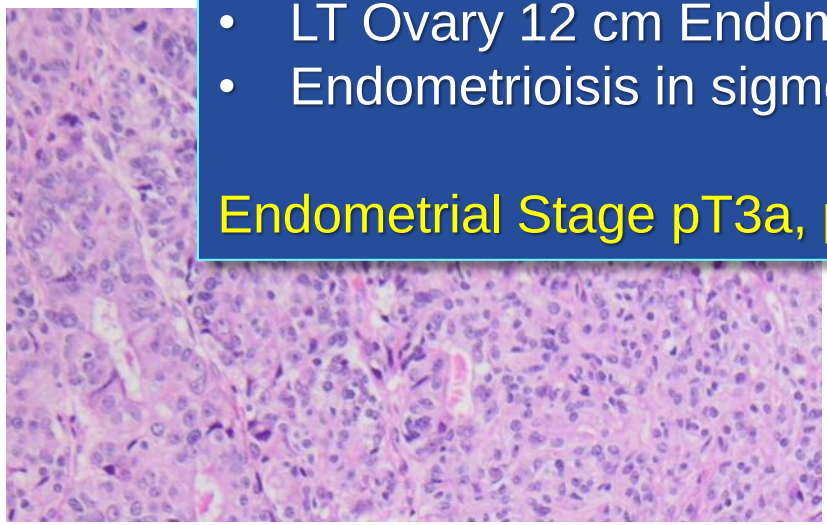
- 42 year-old with abnormal menstrual bleeding. Endometrial Bx with EIN, complex hyperplasia, and atypia
- No improvement with megestrol
- CT and Pelvic US with complex 12 cm LT adnexal mass and irregular endometrial thickening. CA125 = 502
- Hysteroscopy: Endometrioid AdenoCa, with secretory, mucinous, and squamous metaplasia, FIGO Grade 1-2, LVSI+, ER+, P53wt, MMRp.



One Primary *vs* Synchronous Primaries







Laparoscopic TAH-BSO, Omentectomy, Biopsies. No macroscopic residual.

- 5 cm uterine mass, Endometrioid AdenoCa, Grade 2, squamous metaplasia, 70% MMI, LVSI+
- LT Ovary 12 cm Endometrioid AdenoCa
- Endometrioisis in sigmoid nodule

Endometrial Stage pT3a, pNx/cN0, cM0 (FIGO III-A)

Photomicrographs:
Maria Serrano KP-SFO

One Primary *vs* Synchronous Primaries

NGS LT Ovary (Tumor Content 90%)

ATM p.R1618*
NM_000051.3:c.4852C>T
Estimated variant allele frequency: 44%

ATM p.R250*
NM_000051.3:c.748C>T
Estimated variant allele frequency: 45%

BRCA1 p.M1?
NM_007294.3:c.3G>T
Estimated variant allele frequency: 49%

BRCA2 p.E2129*
NM_000059.3:c.6385G>T
Estimated variant allele frequency: 43%

MSH6 p.E544*
NM_000179.2:c.1630G>T
Estimated variant allele frequency: 43%

PIK3CA p.E110del
NM_006218.2:c.328_330del
Estimated variant allele frequency: 30%

POLE p.P286R
NM_006231.3:c.857C>G
Estimated variant allele frequency: 47%

PTEN p.R130Q
NM_000314.4:c.389G>A
Estimated variant allele frequency: 89%

TP53 p.F113L
NM_000546.5:c.339C>A
Estimated variant allele frequency: 46%

TP53 p.R213*
NM_000546.5:c.637C>T
Estimated variant allele frequency: 46%

Biomarker Findings

MSS — MS Stable
Microsatellite Stable

TMB High
TMB - High
Mutations per MB: 147
Confidence interval: 126 - 171

PD-L1 - Low
RNA expression score: 0

Additional Mutations Identified from TMB Analysis

ADGRB3 p.D717Y	ADGRB3 p.R1400I	ADGRB3 p.T942S	AKAP9 p.L283V	APC p.R1096*	ARID1A p.D1785E
ARID1A p.R1989*	ATM p.I1035L	BCL10 p.L24V	BLM p.S778F	BRIP1 p.K1232N	BUB1B p.E507*
CDH11 p.D672Y	CDH2 p.L855P	CRKL p.Y105*	CSMD3 p.D3250E	CYP2C19 p.S23N	DCC p.E1159*
DCC p.T610A	DPYD p.S500Y	DST p.E778*	DST p.P4283H	DST p.R1269*	EPHA3 p.R241K
FN1 p.I1994M	FOXO1 p.S345F	GUCY1A2 p.R700M	HLF p.S258L	HSP90AB1 p.E372D	JAK1 p.E913A
JAK1 p.F575S	JAK1 p.L891P	JAK2 p.K217N	KAT6A p.R688C	KDR p.G95*	KMT2A p.R1716W
LRP1B p.D1741E	LRP1B p.E4584*	LTK p.T757I	MAGI1 p.R1138*	MCL1 p.S285R	MSH2 p.M485I
MSH6 p.S256G	MTOR p.E804K	MYH11 p.D619N	MYH11 p.E1109V	MYH11 p.E512*	NFKB1 p.F412C
NSD1 p.L812F	NTRK3 p.E276D	NUMA1 p.E294*	PIK3CG p.E1073K	PKHD1 p.E567K	PKHD1 p.F955L
PKHD1 p.G1679*	PKHD1 p.S3017P	POT1 p.H437N	PPARG p.L421I	PPARG p.N440S	PRDM1 p.L760M
PRKDC p.S1667*	PTEN p.R130Q	PTPRD p.F14L	PTPRD p.I562L	RET p.F31L	RNF213 p.K399T
	ROS1 p.E738D	SAMD9 p.E1356*	SEPT9 p.D503G	SETD2 p.S2327I	SMARCA4 p.E780G
	TAF1L p.E547D	TAF1L p.K1358T	TET2 p.L552I	TGM7 p.K207N	TIMP3 p.K49N
	TP53 p.F113L	TRIM24 p.S422F	TSHR p.R109W	WRN p.E379*	WRN p.E399K

- Overall findings consistent with POLE ultramutated tumor
- TMB High (point mutations across entire genome)
- MMRp (MS Stable)
- BRCA1/2 “bystander” mutations (non-pathogenic)

One Primary *vs* Synchronous Primaries

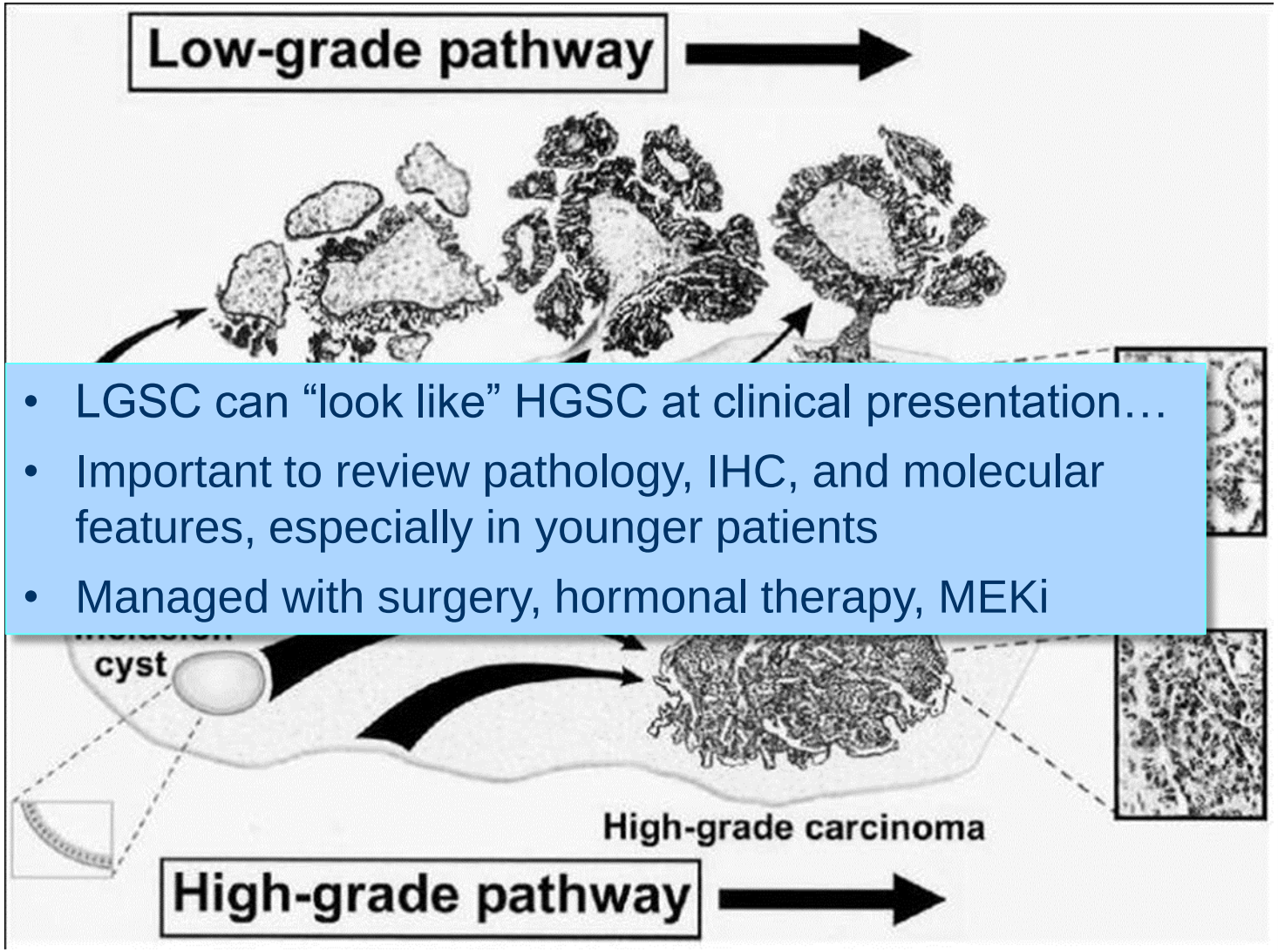
42 year-old, CT and Pelvic US with complex 12 cm LT adnexal mass and irregular endometrial thickening. CA125 = 502. Endometrioid adenocarcinoma with secretory, mucinous, and squamous metaplasia FIGO Grade 1-2, EIN, 70% MMI, LVSI+. IHC ER+, P53wt, pMMR. Stage pT3a, pNx/cN0, cM0 (FIGO III-A) POLE Hypermutated (MS Stable, TMB High)

Your Recommendation Post-Surgery:

A. Observation/Surveillance without additional therapy
B. Chemotherapy
C. Immunotherapy
D. Radiation Therapy (HDR-VBT)
E. Radiation Therapy (Pelvic EBRT)
F. Chemotherapy followed by Radiation Therapy (Pelvic EBRT)

- Endometrial cancer involving LT ovary, not “Synchronous Primaries”
- *POLE*mut ultramutated state, with excellent prognosis (based on PORTEC3)
- Received HDR-VBT without chemotherapy, NED after 5 years

LGSC vs HGSC: Molecular and Clinical Biology



- LGSC can “look like” HGSC at clinical presentation…
- Important to review pathology, IHC, and molecular features, especially in younger patients
- Managed with surgery, hormonal therapy, MEKi

- Mutations in BRAF, KRAS, NRAF
- Downstream MEK activation
- Not Associated with High-Risk Families
- Younger age at diagnosis (pre-MP)
- ER+/PR+, low mitotic rate
- Intact p53 and DNA Repair
- Genomic Stability with Low TMB
- Low-Elevated or Normal CA125
- 80% early-stage (FIGO I-II)

- Uniform aberrant p53 (TP53mut)
- Frequent loss 17q21 (BRCA1), 13q12 (BRCA2), 13q14 (RB1)
- Associated with High-Risk Families
- Older age at diagnosis (post-MP)
- Defective DNA Repair (HRD)
- Genomic Instability but with Low TMB
- ↑CA125
- 80% advanced-stage (FIGO III-IV)

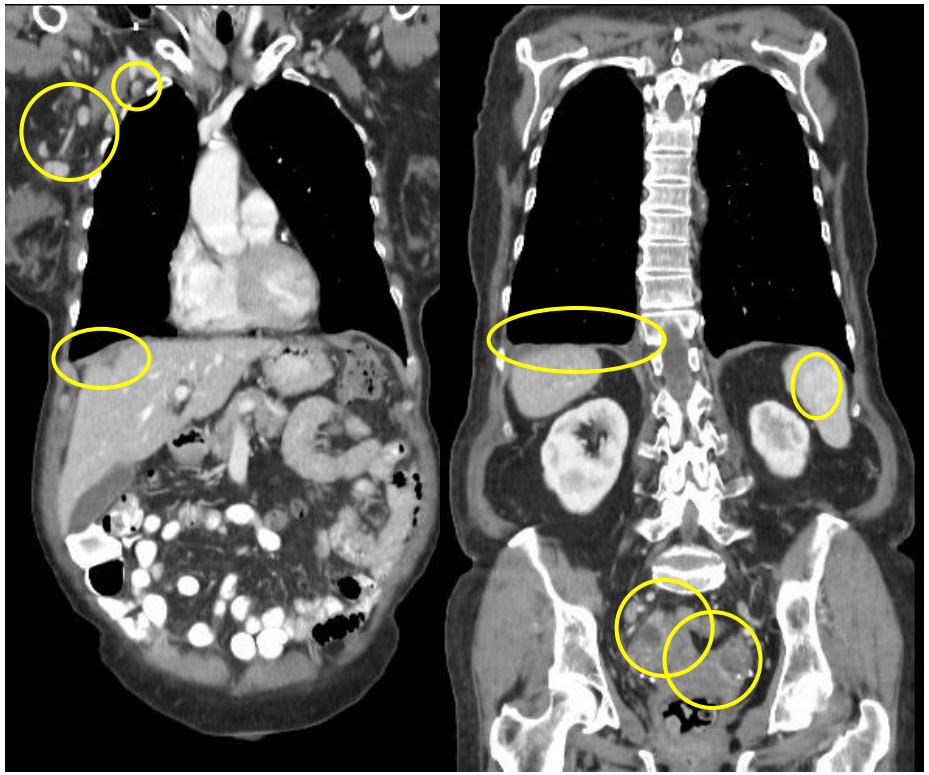
Modified from: Singer et al., *Am J Surg Pathol* 29:218-24, 2005

Platinum-Refractory High-Grade Serous Cancer

75 yo with new onset AFib. CT: Bilateral complex adnexal masses, perihepatic implants, splenic lesion, RT pleural effusion, RT Ax LN, LT breast mass. CA125 = 1,698.

Breast and Ax LN Bx: HGSC, IHC P53 aberrant (diffuse expression), IHC+ for PAX-8, WT-1, ER. FIGO IVB

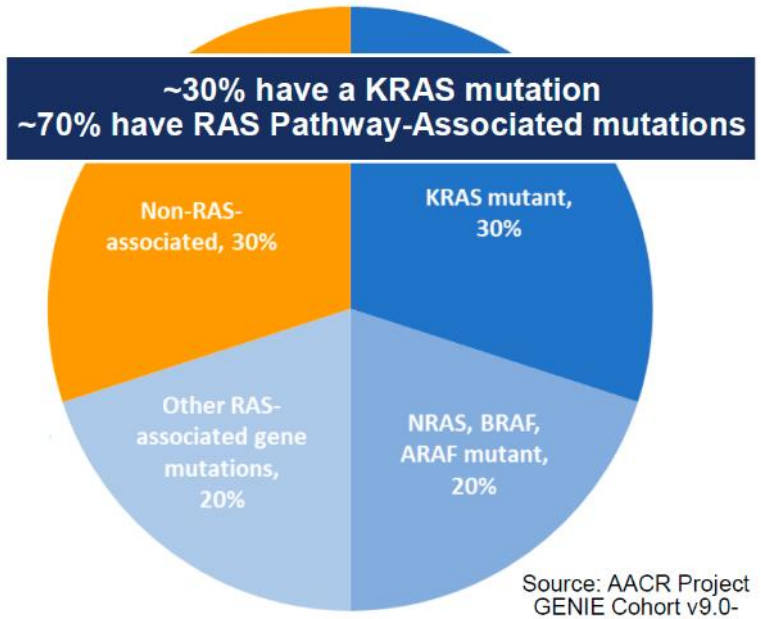
Germline Risk Panel: No pathogenic alterations

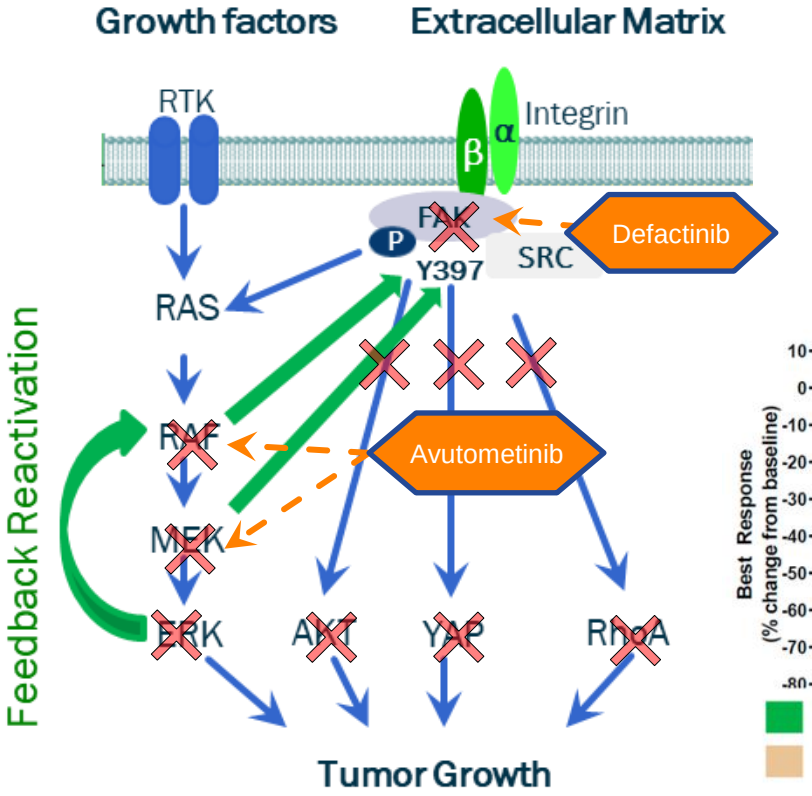


- NACT with Carboplatin and Paclitaxel x3 cycles
- No change in CA125, stable disease on CT imaging
- Molecular Profile: *KRAS*mut p.G12D, *TP53*wt, MS Stable

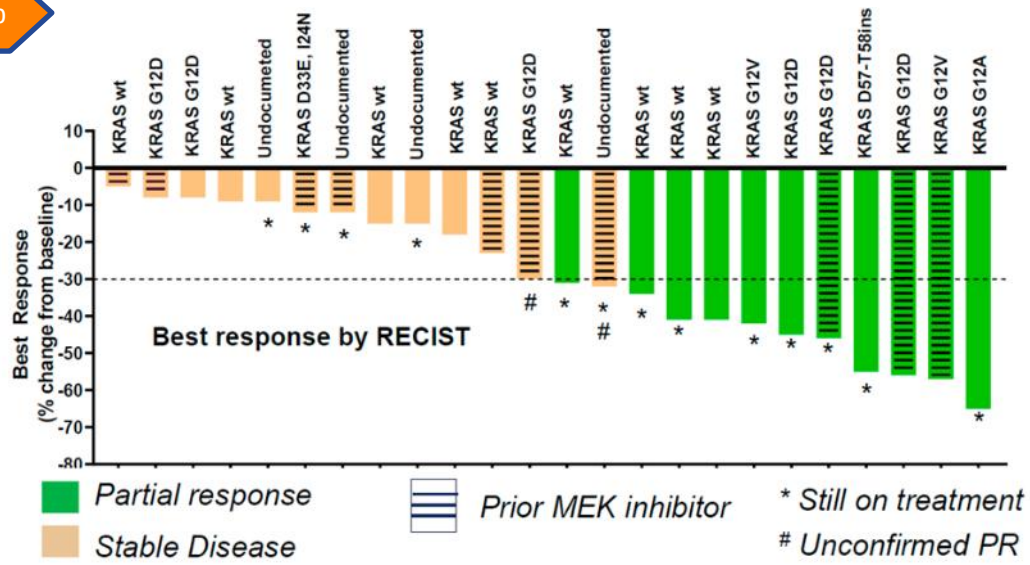
- Review of Breast and Ax LN Bx: mild-moderate atypia, low mitotic rate, P16 (-), P53 wild-type (original P53 overstained)
- **Diagnosis changed from HGSC to LGSC**
- Switched to hormonal therapy after cytoreductive surgery
- Residual metastatic disease stable for 3+ years on letrozole

Ovarian LGSC: Combined RAF/MEKi and FAKi





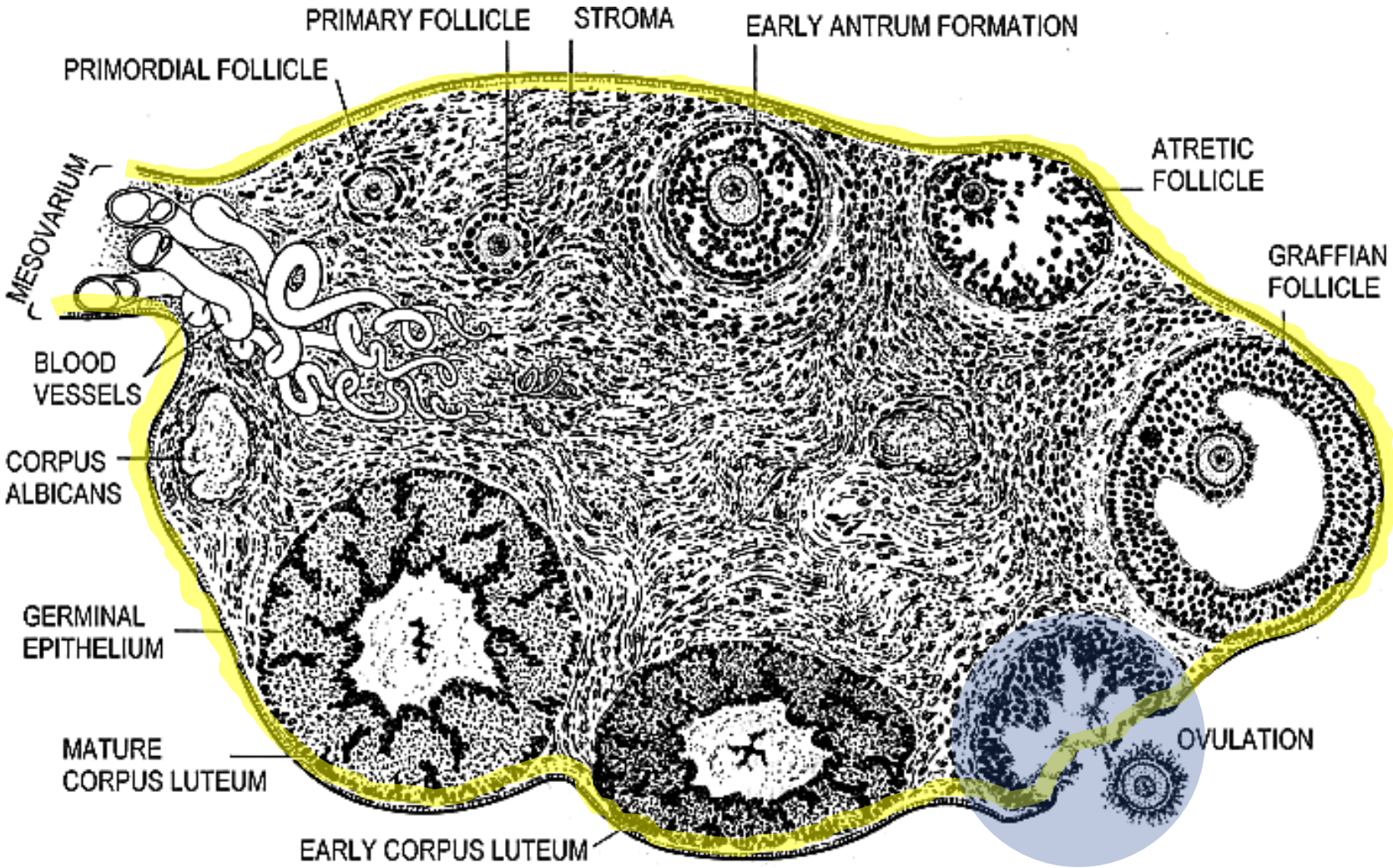
Avutometinib 3.2mg twice/week
Defactinib 200mg bid (21/28 days)



- The RAS/RAF→MEK/ERK intracellular signaling pathway is the dominant driver in LGSC
- Coordinated targeting (RAF/MEK and FAK) delays emergence of resistance
- Validation in RAMP 201 (GOG 3052, ENGOT-ov60, VS-6766-201) Avutometinib +/- Defactinib

Banerjee S, et al. ESMO 2021 Abstract 799

Ovarian Biology



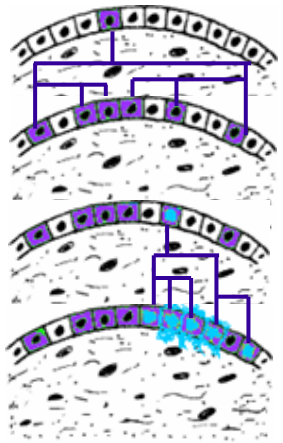
Modified from Yen and Jaffe, Reproductive Endocrinology, 1986

Carcinomas frequently involve the ovarian surface (Müllerian) epithelium

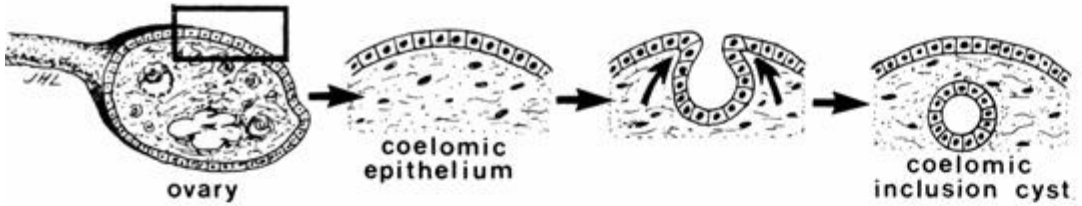
Ovulation facilitates implantation, cyst formation and transformation (cytokines, angiogenesis, wound healing)

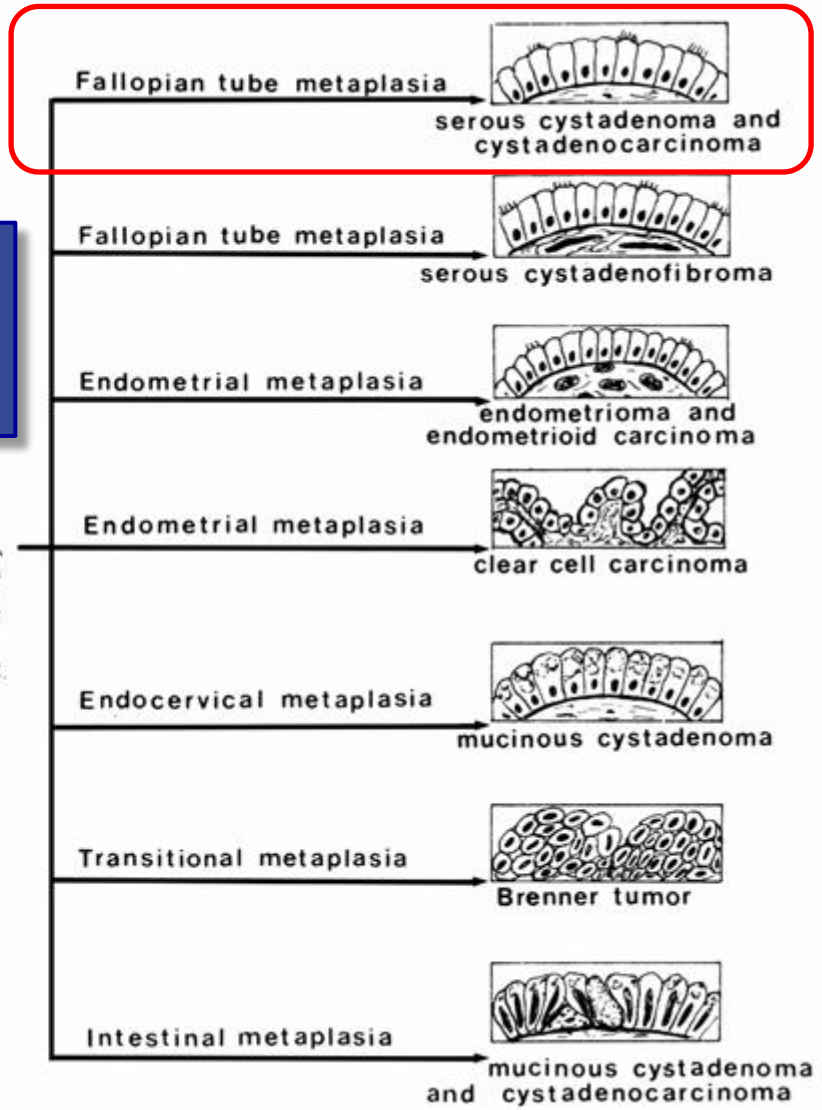
The ovary represents a “favored site” for tumor growth

Historical Perspective: Ovarian Surface Epithelium



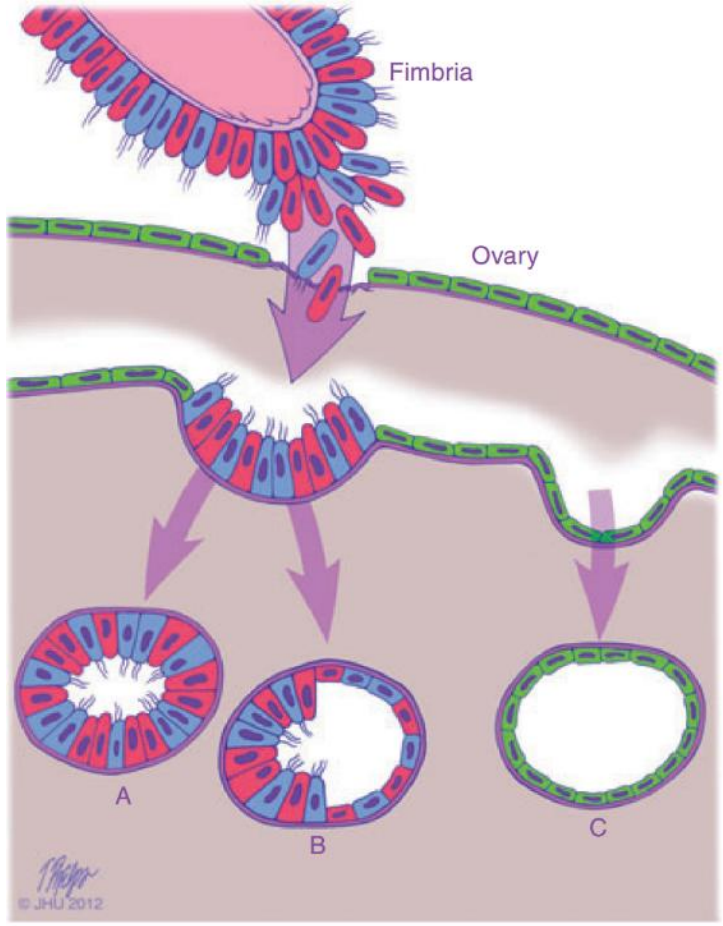
Prior emphasis on “metaplasia” within inclusion cysts to explain serous, endometrioid, clear cell, and mucinous histologies



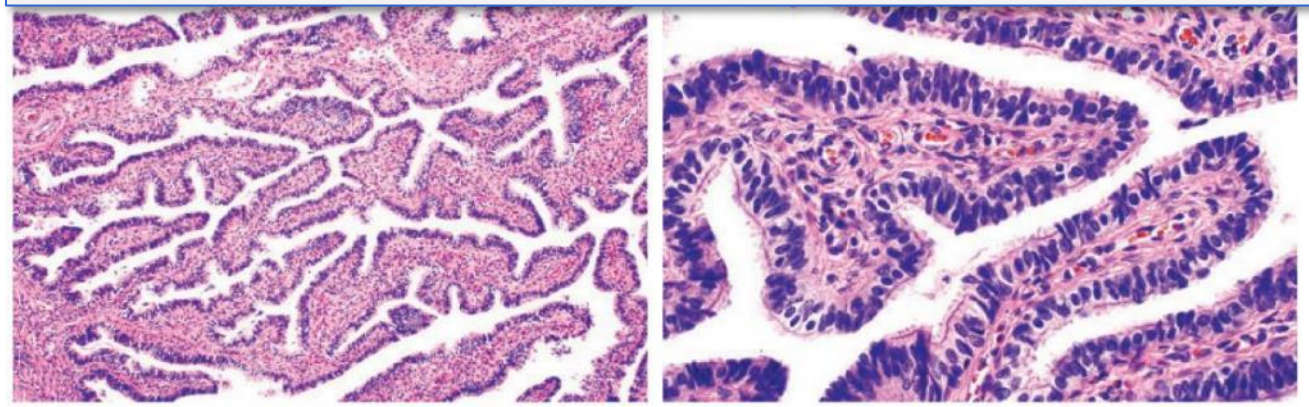


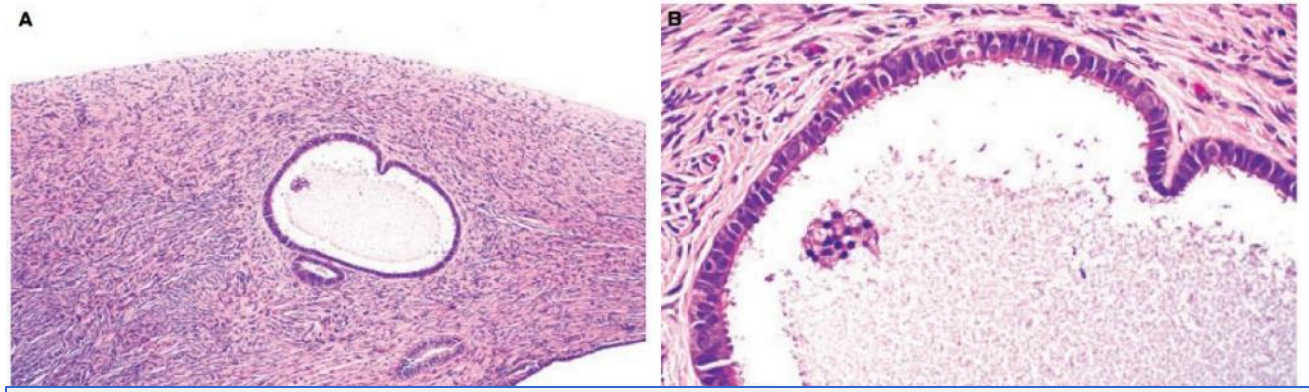
- The OSE is maintained life-long (germinal), without programmed maturation or senescence
- Mutations are retained and passed along to daughter cells
- Interruption of ovulation (OCPs, pregnancy) associated with decreased risk, possibly related to OSE involution

Recognizing the Diverse Origins of “Ovarian” Cancer



Normal Fallopian Tube with Ciliated and Secretory Cells

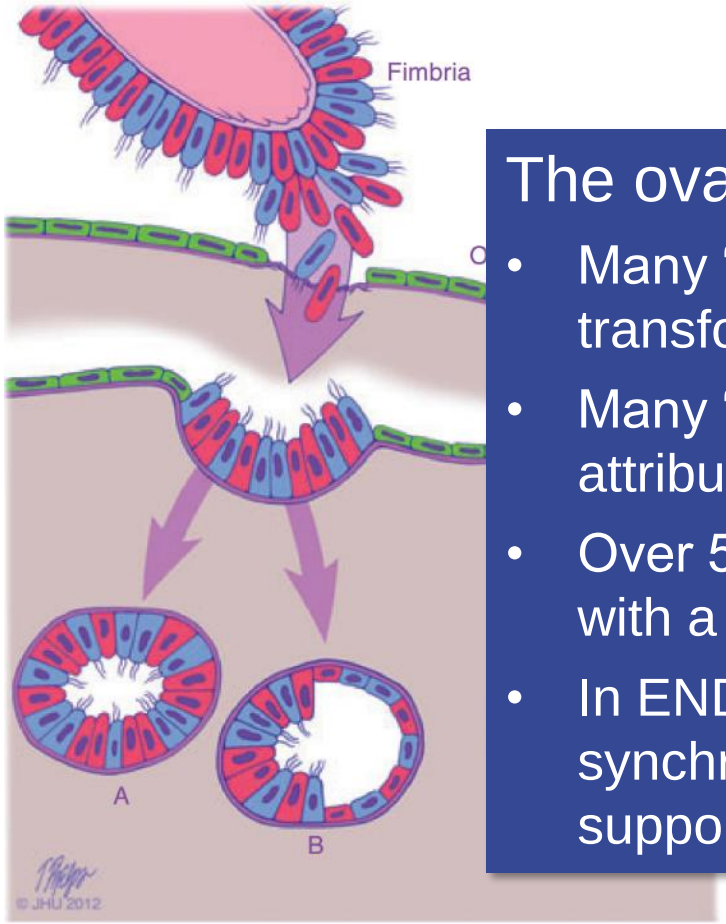




Normal Ovary with a “Fallopian” Inclusion Cyst

Vang R, Shih I-M, Kurman RJ. *Histopathology* 2013; 62:44-58

Recognizing the Diverse Origins of “Ovarian” Cancer



Normal Fallopian Tube with Ciliated and Secretory Cells

The ovary is a favored site of tumor implantation and growth

- Many “Ovarian” SEROUS tumors can be attributed to implantation of transformed fallopian tubal epithelium
- Many “Ovarian” ENDOMETRIOID and CLEAR CELL tumors can be attributed to endometriosis and/or endometrial cancer
- Over 50% of “Ovarian” metastatic MUCINOUS tumors are associated with a gastrointestinal primary lesion
- In ENDOMETRIAL CANCER, the presence of an isolated synchronous OVARIAN lesion does not adversely impact prognosis, supporting de-escalation of post-operative therapy

Normal Ovary with a “Fallopian” Inclusion Cyst

Vang R, Shih I-M, Kurman RJ. *Histopathology* 2013; 62:44-58

Endometrioid Ovarian Cancer

51 yo with abdominal discomfort. CT: 15 cm complex cystic mass, small LT PA and AortoCaval LN. No ascites, effusion, hydronephrosis or bowel obstruction. CA125 = 30

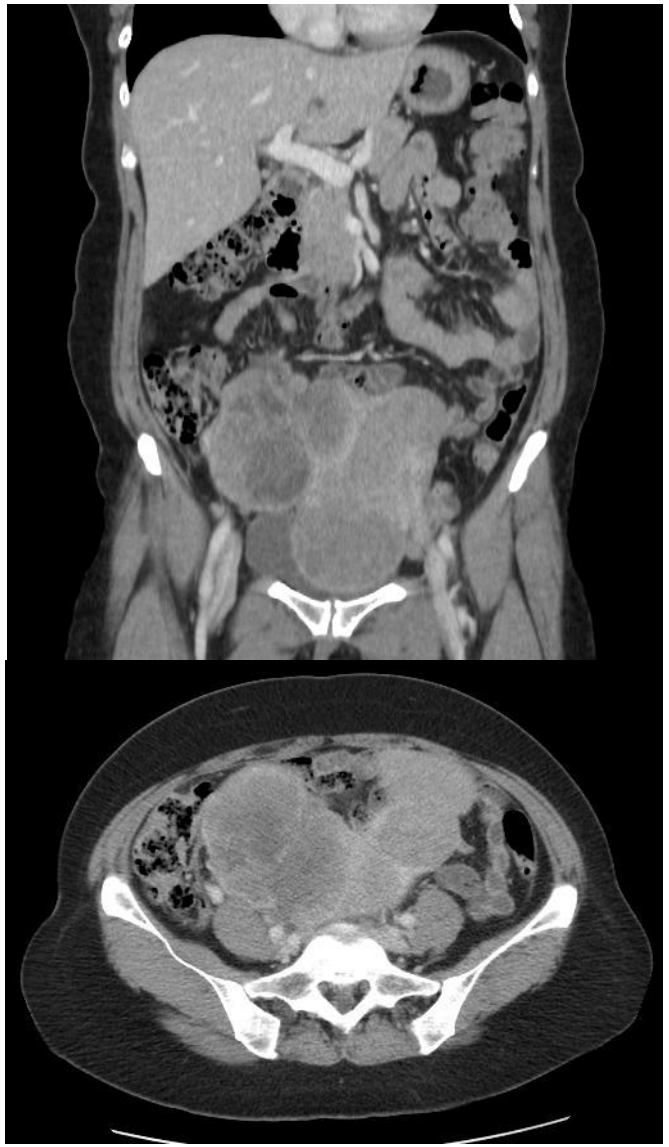
Surgery: Primary TAH-BSO, P-PA-LND, Omentectomy. Enlarged fibroid uterus and LT ovarian mass with matted pelvic LN. No gross residual.

Pathology: RT ovary 10.2 cm Grade 3 Endometrioid AdenoCa surface (+), Uterine serosa (+) with myometrial invasion. LT ovarian endometriosis. Omentum and LN (-). Mesothelial inflammation-endometriosis.

IHC P53wt, ER+ (focal), PAX8+, Stage pT2a, pN0 (FIGO IIA)

Your Recommendation:

A. Observation
B. Carboplatin and Paclitaxel x3 cycles
C. Carboplatin and Paclitaxel x6 cycles
D. Whole pelvic EBRT
E. Carboplatin and paclitaxel followed by whole pelvic EBRT



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IHC P53wt, ER+ (focal), PAX8+, Stage pT2a, pN0 (FIGO IIA)

- Carboplatin and Paclitaxel x6 cycles → clinical CR
- Germline cancer risk panel (34 genes) without pathogenic alterations

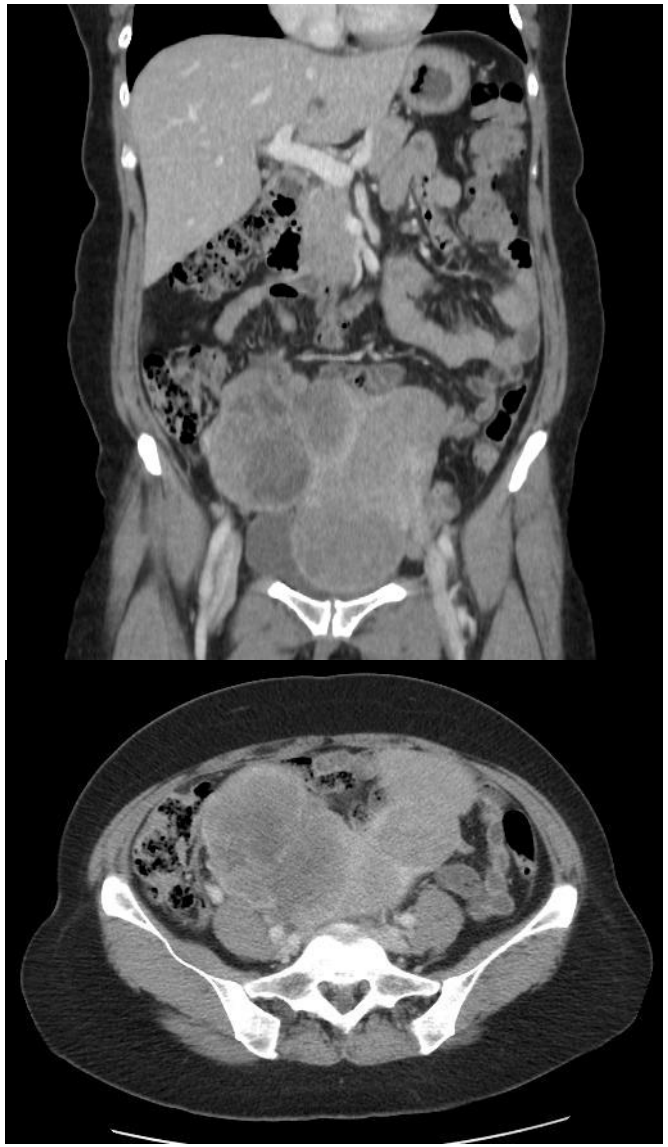
Your Recommendation Post-Chemotherapy:

A. Observation/Surveillance without additional therapy

B. Maintenance PARPi if HRD(+)

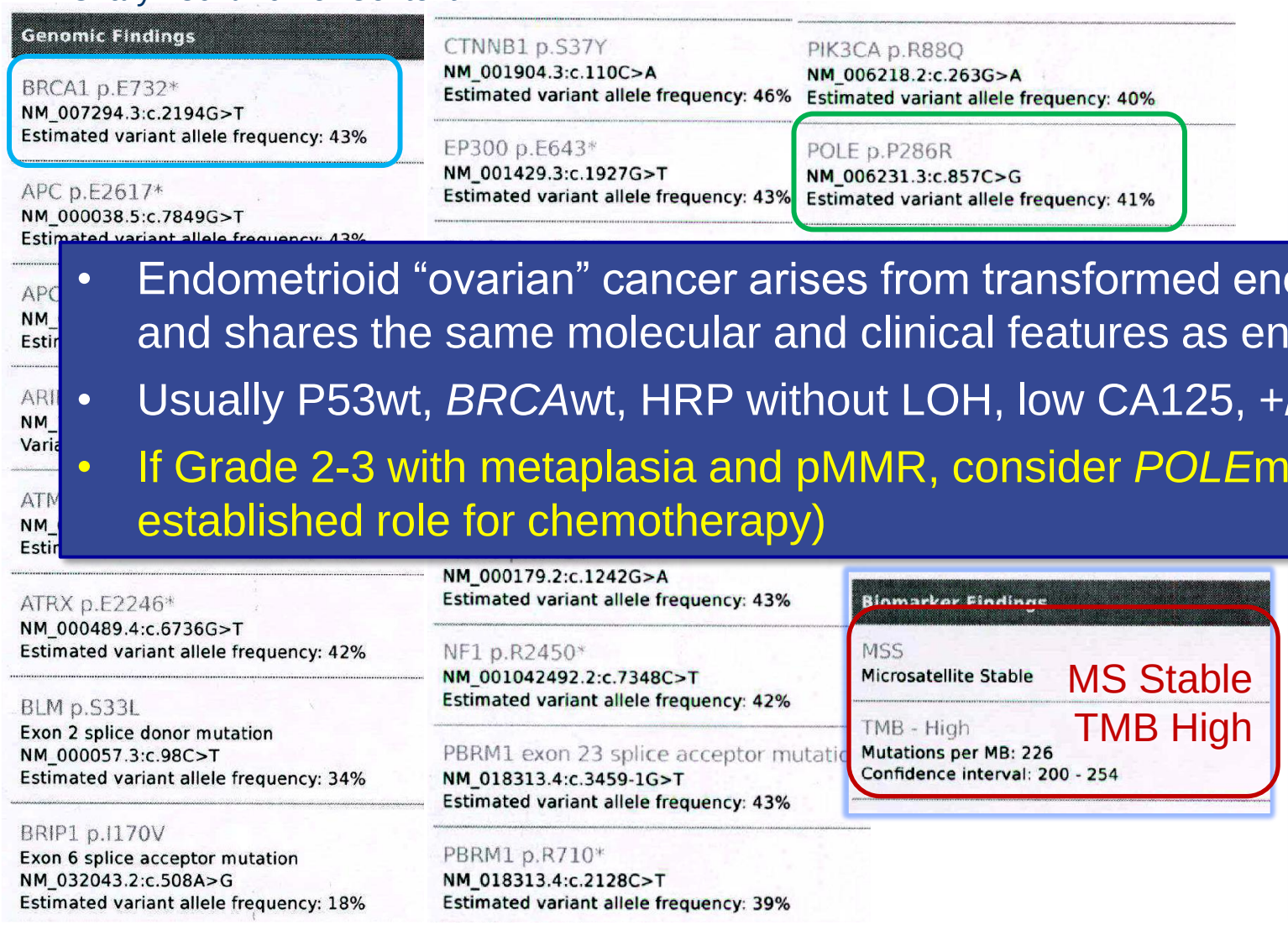
C. Maintenance PARPi regardless of testing

D. Tumor molecular profile (NGS, MSI, TMB)



Endometrioid Ovarian Cancer: Molecular Profile

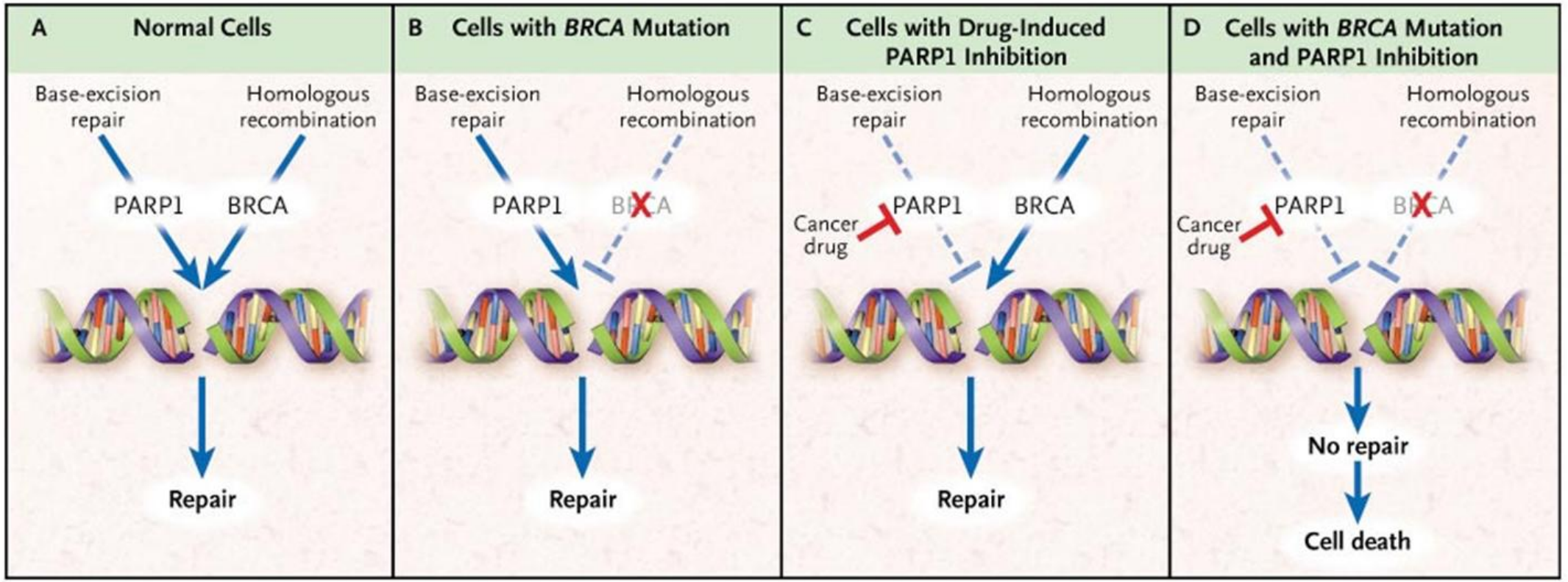
RT Ovary 80% Tumor Content



- Endometrioid "ovarian" cancer arises from transformed endometrium (or endometriosis), and shares the same molecular and clinical features as endometrial cancer
- Usually P53wt, *BRCA*wt, HRP without LOH, low CA125, +/- MMRd-MSI
- If Grade 2-3 with metaplasia and pMMR, consider *POLE*mut (OS near 100%, no established role for chemotherapy)

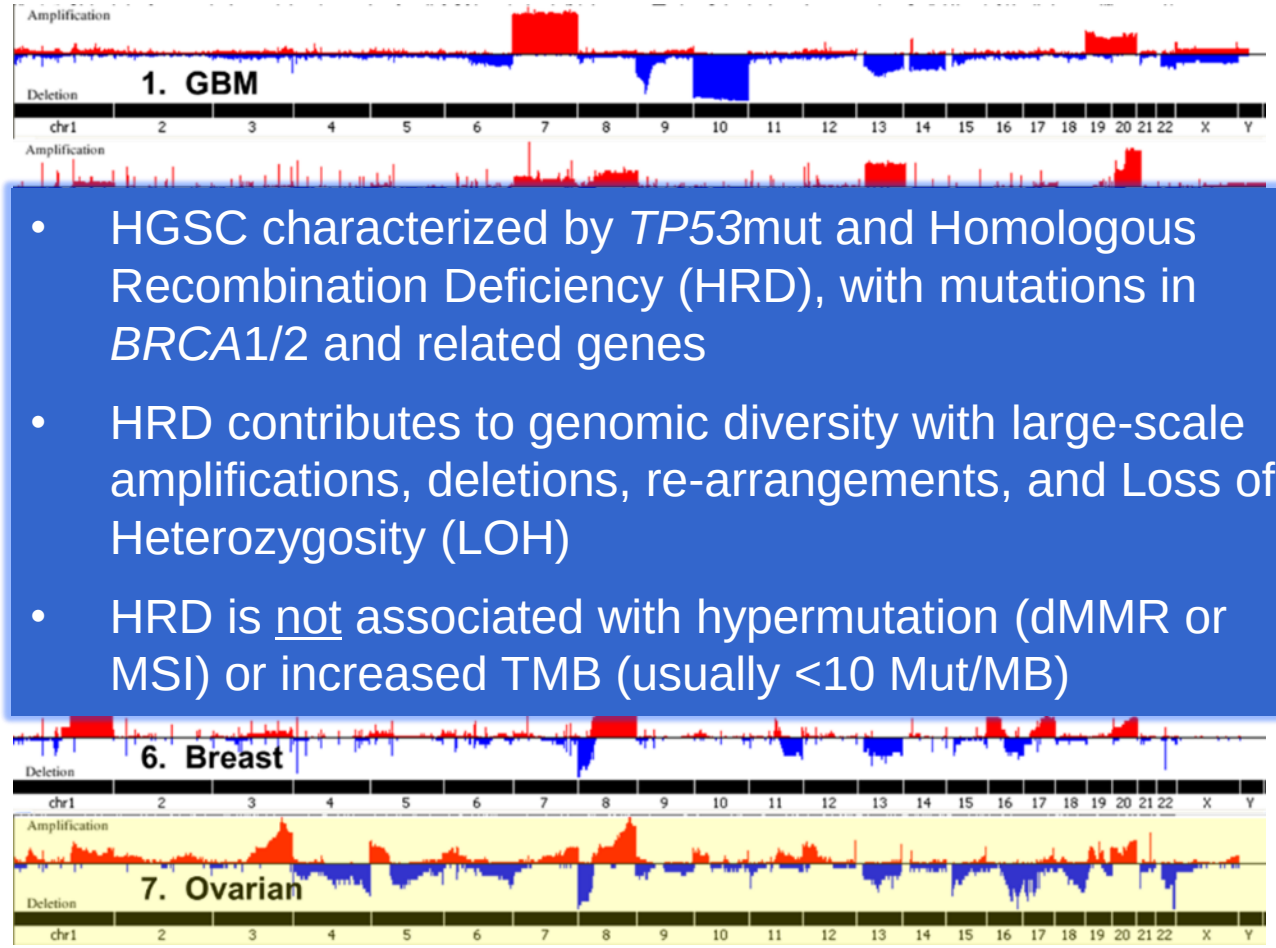
PARP Inhibition, HRD, Synthetic Lethality

Mechanism of Cell Death from Synthetic Lethality, as Induced by Inhibition of Poly(Adenosine Diphosphate [ADP]–Ribose) Polymerase 1 (PARP1).

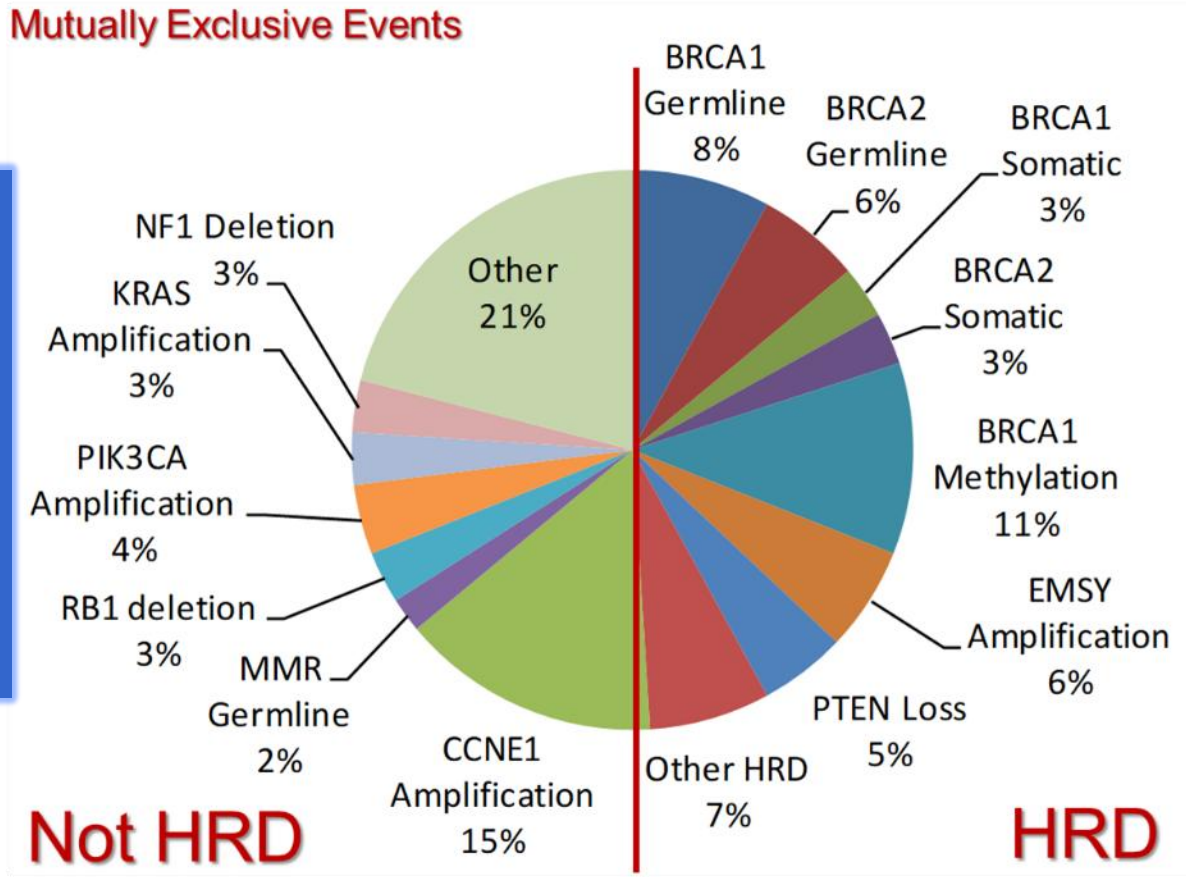


Iglehart JD, Silver DP. *N Engl J Med* 2009; 361:189-91

Large-Scale Genomic Diversity



- HGSC characterized by *TP53*mut and Homologous Recombination Deficiency (HRD), with mutations in *BRCA1/2* and related genes
- HRD contributes to genomic diversity with large-scale amplifications, deletions, re-arrangements, and Loss of Heterozygosity (LOH)
- HRD is <u>not</u> associated with hypermutation (dMMR or MSI) or increased TMB (usually <10 Mut/MB)



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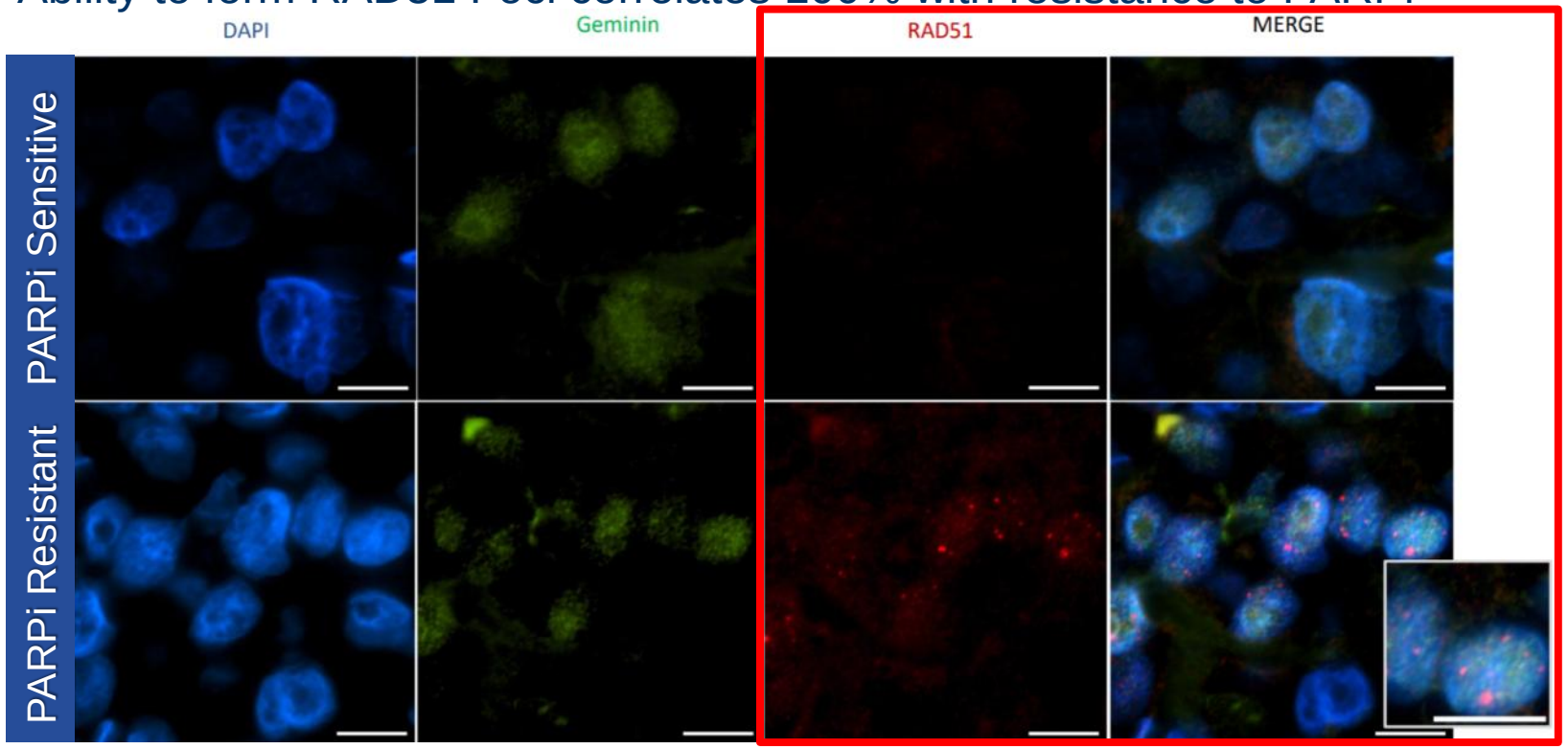
Measurement of HRD: LOH, Mutations, and RAD51C

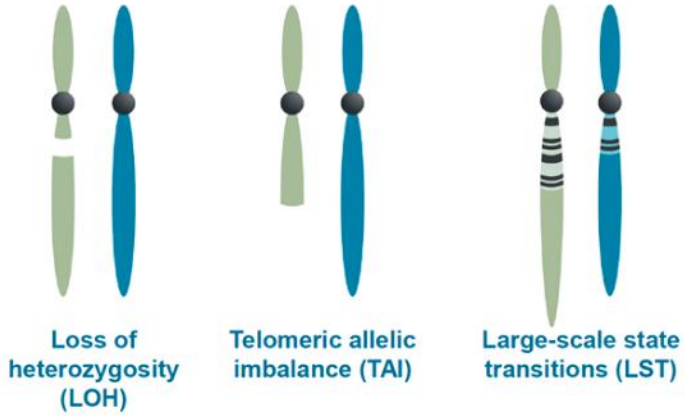
- Current assays identify deleterious mutations and/or provide an overall HR “score”
- Assays rely on fixed genomic changes, not real-time functional HR capacity
- No correlation of HR Score with development of PARPi resistance

RAD51 Focus-Forming Assay using human PDX exposed to PARPi *in vivo*
Ability to form RAD51 Foci correlates 100% with resistance to PARPi



Current HR Assays

Mutations in HR-FA Genes: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51C, RAD51D*

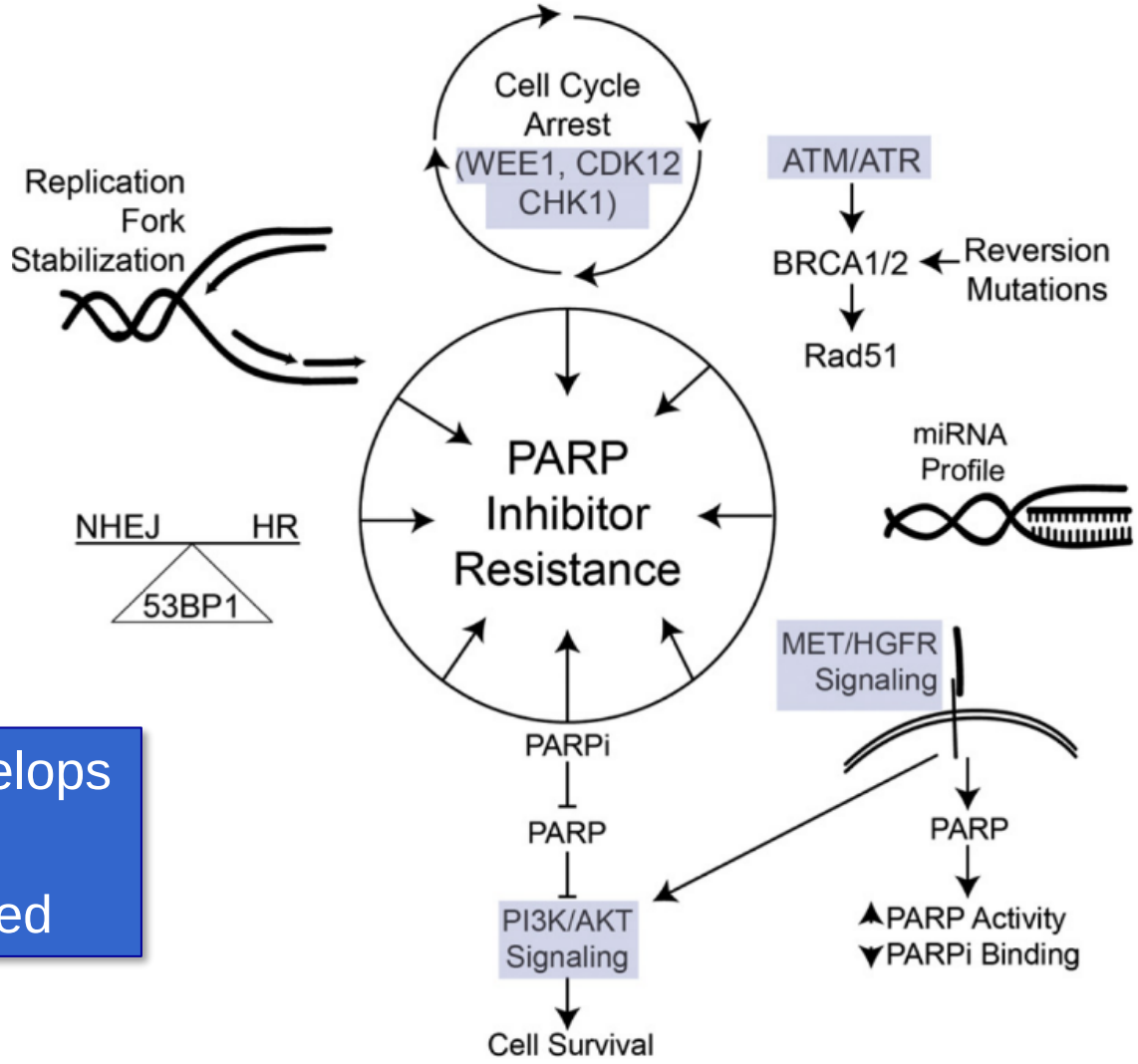


Castroviejo-Bermejo M, et al. *EMBO Mol Med* 2018; 10:e9172

PARPi Resistance: An Emerging Problem

- Restoration of BRCA1/2 function and HR via reversion mutations, leading to platinum and PARP resistance
- Clonal selection without LOH
- ↑HR and ↓NHEJ (error-prone DNA repair) by loss of 53BP1
- Stabilized replication forks with ↑DNA repair
- ↑Damage detection and cell cycle checkpoint activity, allowing for DNA repair
- ↑Drug efflux via p-glycoproteins
- Phosphorylation of PARP1 via MET
- Compensatory up-regulation of pro-survival pathways, such as PI3K/AKT
- miRNA mediated decrease in NHEJ

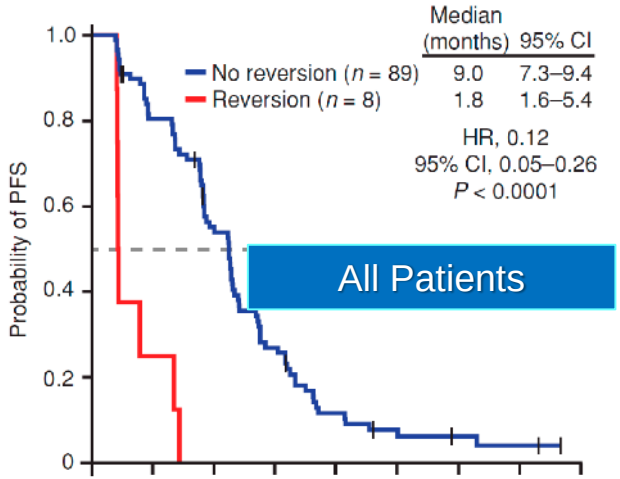
- In the majority of responding patients, resistance develops within one year, including tumors with *BRCA*mut
- The ability to overcome established resistance is limited

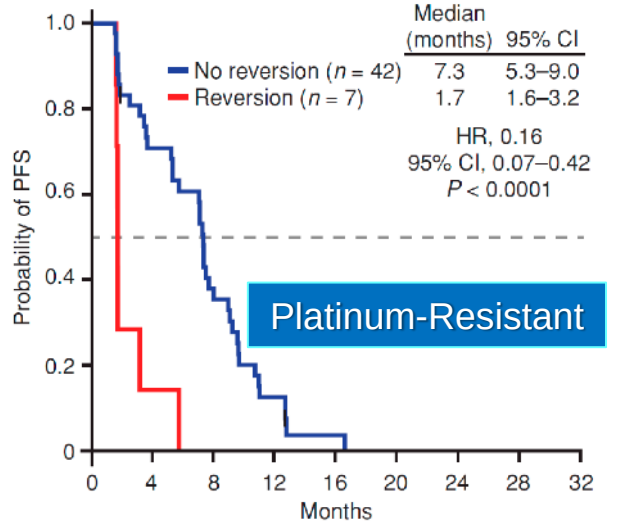


Bitler BG, et al. *Gynecol Oncol* 2017; 147:695-704

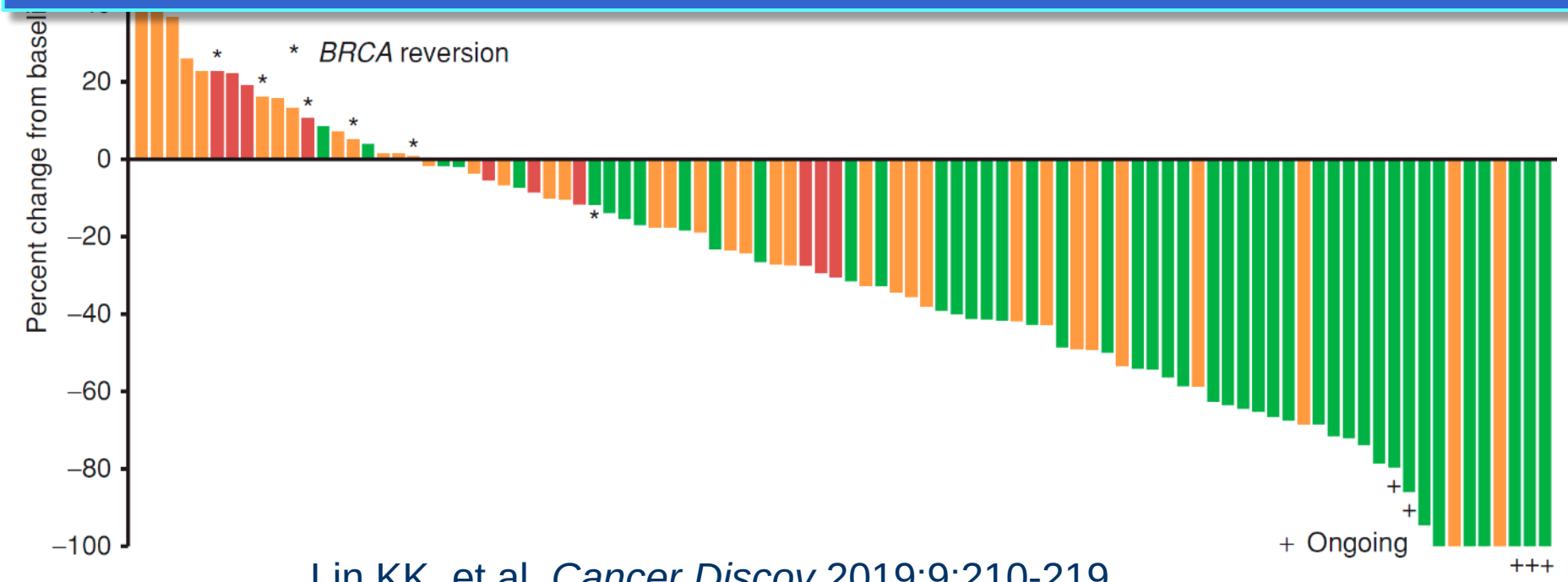
ARIEL2: *BRCA* Reversion Mutations

Open-label single-agent Rucaparib in patients with recurrent ovarian cancer





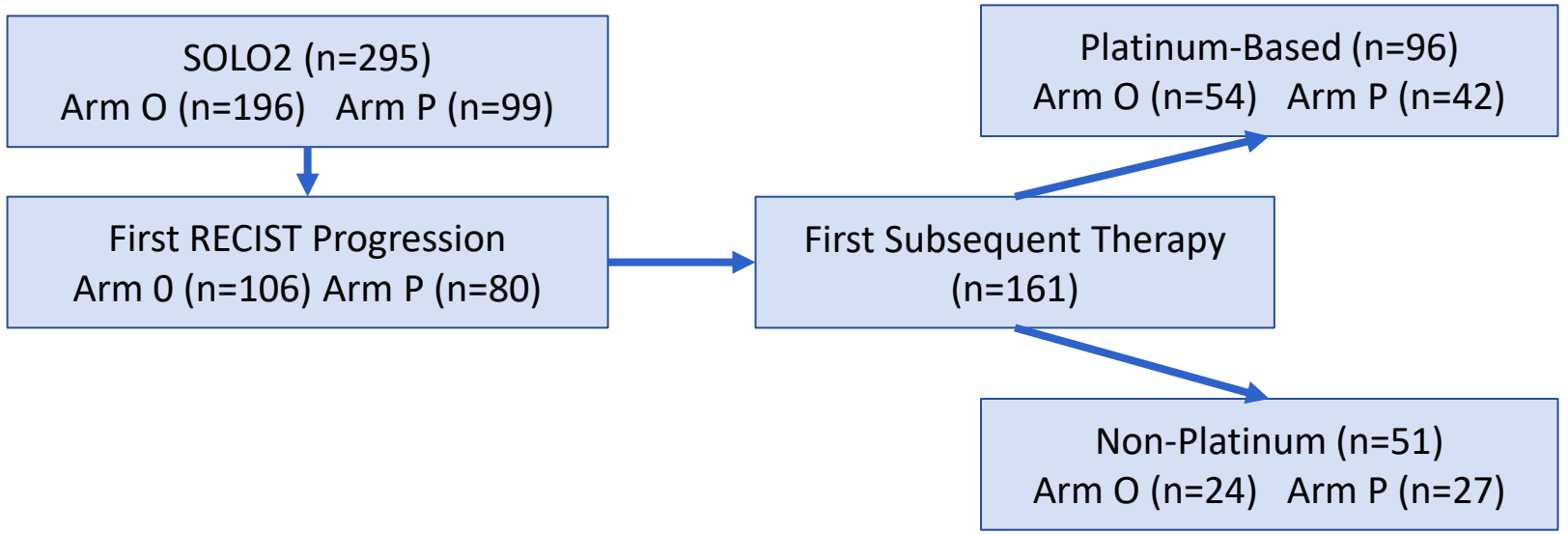
- Pretreatment cfDNA BRCA reversions in 14% of platinum-resistant cancers *vs* 2% (1/48) of platinum-sensitive cancers (P = 0.049)
- Patients without pretreatment reversions had ↑PFS *vs* those with reversions
- Postprogression cfDNA identified 8/78 patients not found pretreatment

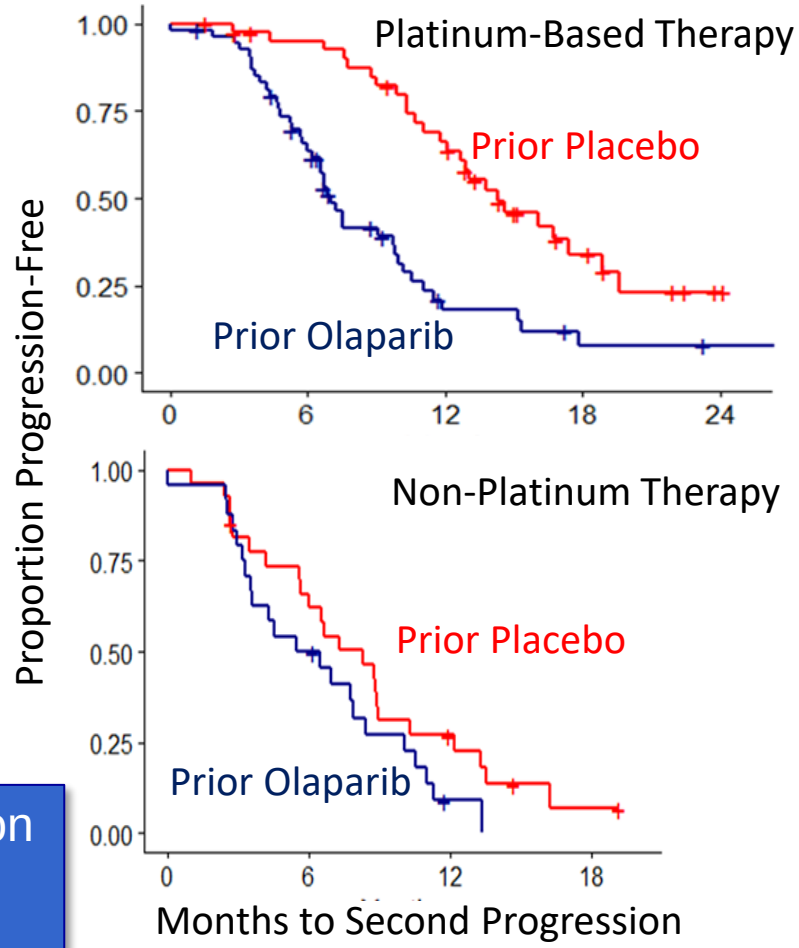


Lin KK, et al. *Cancer Discov* 2019;9:210-219

PARPi Resistance and Platinum Resistance…

Efficacy of subsequent chemotherapy in *BRCA*mut platinum-sensitive recurrent ovarian cancer following progression on olaparib *vs* placebo
Post-hoc analyses SOLO2/ENGOT Ov-21





- Platinum-based chemotherapy associated with ↓PFS after PARPi progression
- Potential interacton between PARPi resistance and platinum resistance
- Complex exploratory analysis of PFS2, but raises important questions

Frennel JS, et al. ESMO 2020

LG Endometrioid Ovarian Cancer with g*BRCA1*mut

47 yo with endometriosis and a 6.2 cm exophytic LT ovarian mass extending into the cul-de-sac with characteristic frond-like enhancing papillary projections suggestive of borderline tumor. CA125 = 24

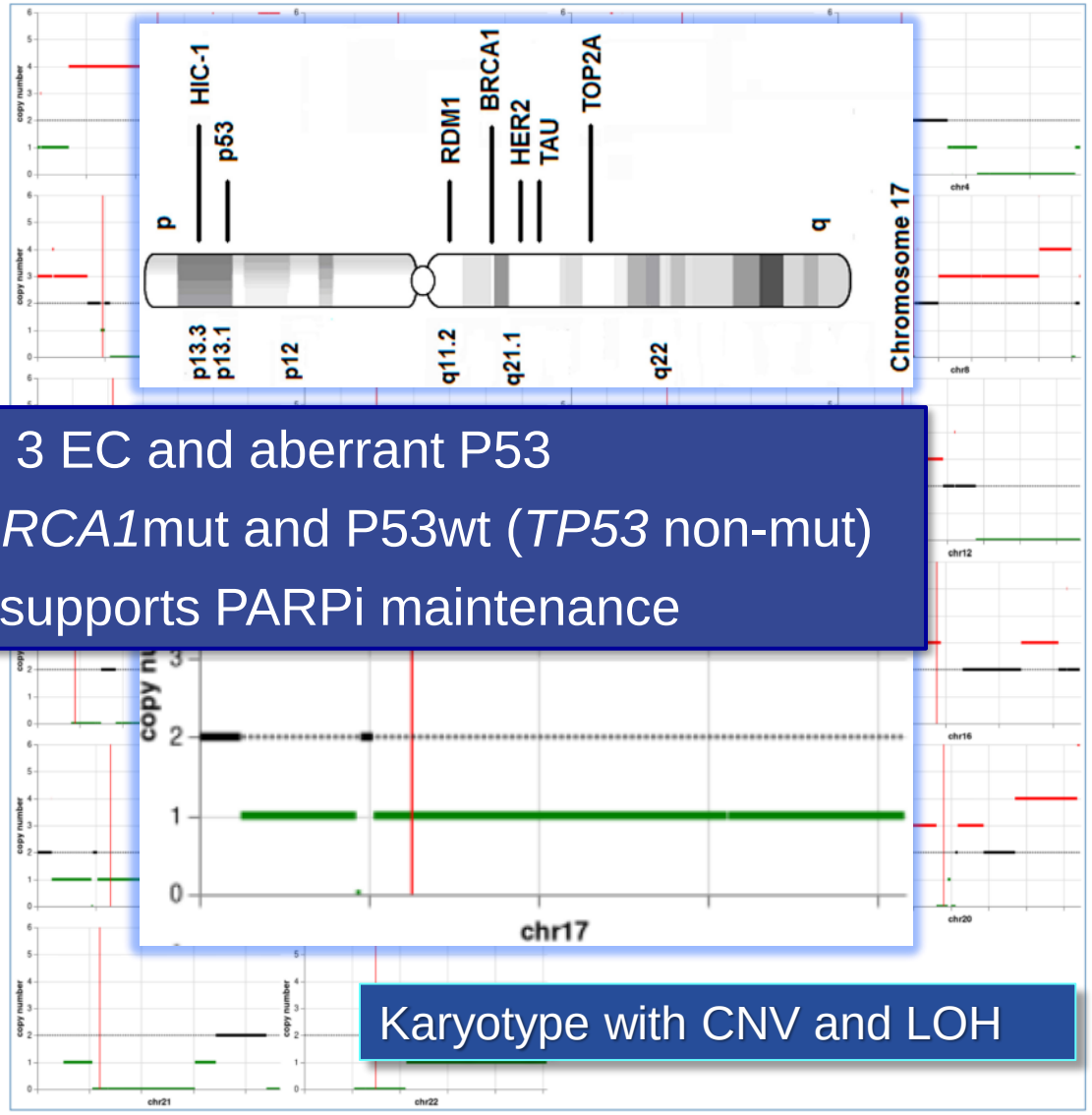
Primary Surgery: FIGO Grade I endometrioid cancer, bilateral ovarian surfaces, cul-de-sac, appendix serosa (pT3b, FIGO IIIB), MMRp, P53wt, P16+, ER+

TP53 or *KRAS*: MS Stable, TMB Low (4 Mut/MB), LOH High (48%).

- *BRCA1*mut usually associated with HGSC or Grade 3 EC and aberrant P53
- Example of a low-grade tumor with a pathogenic g*BRCA1*mut and P53wt (*TP53* non-mut)
- Presence of LOH (including single copy of *BRCA1*) supports PARPi maintenance

Your Recommendation:

A. PARPi maintenance
B. Hormonal Therapy (AI)
C. Observation



Karyotype with CNV and LOH

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HGSC with g*BRCA1*mut (without HRD-LOH)

59 yo with HGSC of ovarian or uterine origin involving descending colon, omentum, and mesentery without ascites. P53 equivocal (suspected null). CA125 = 52. Referred for NACT.

NGS: TP53 p.E224= (VAF 25%). MS Stable, TMB Low (3 Mut/MB), HRD-LOH Low (32% with threshold 46%).

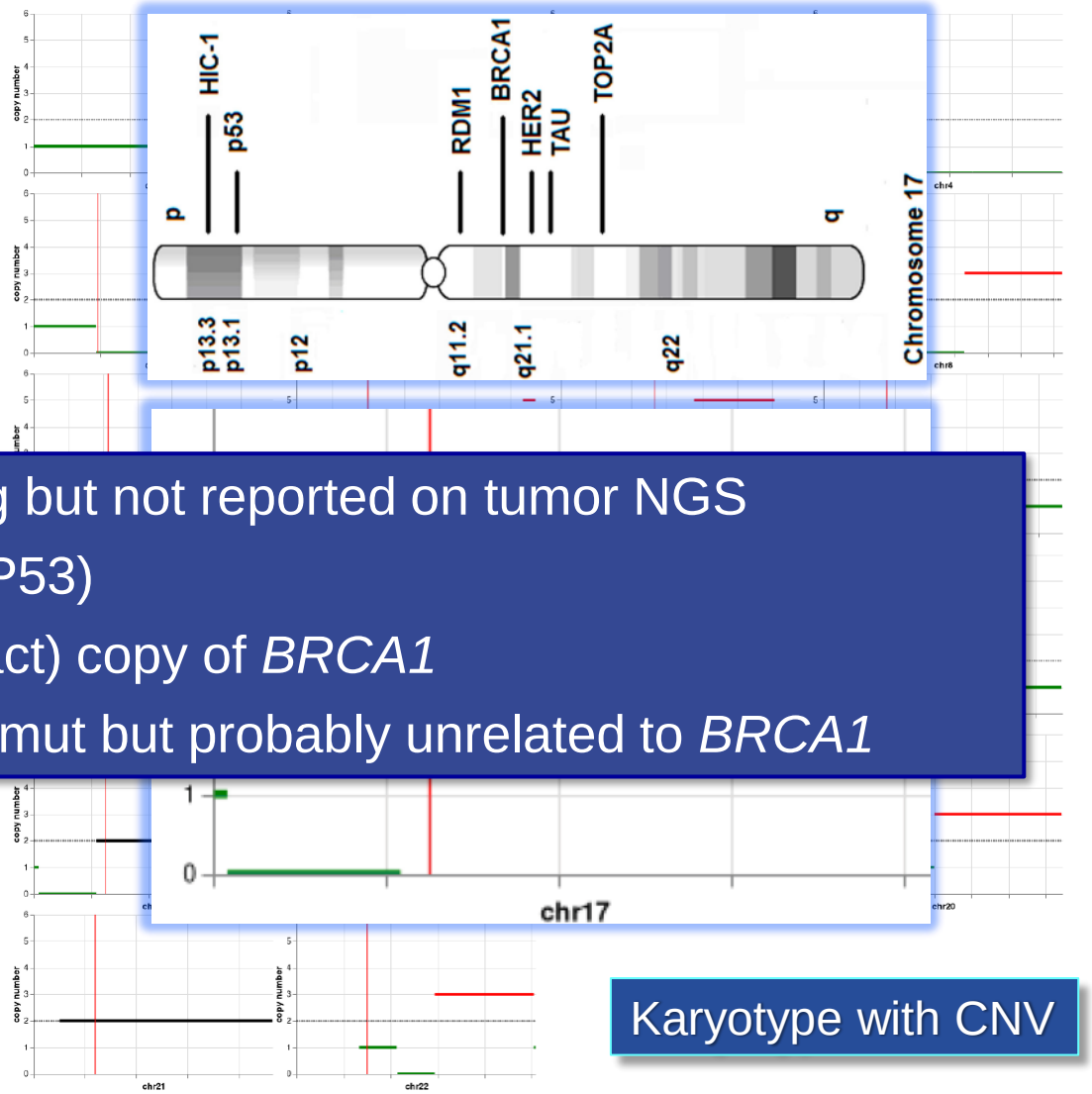
Germline: Pathogenic variant *BRCA1*, del exons 1-2 (not

- Pathogenic g*BRCA1*mut detected on germline testing but not reported on tumor NGS
- Karyotype with deletion at *TP53* locus (aberrant null P53)
- Absence of HRD-LOH most likely due to second (intact) copy of *BRCA1*
- Example of HGSC arising in the setting of a g*BRCA1*mut but probably unrelated to *BRCA1*

Your Recommendation:

A. NACT+ICS → PARPi maintenance

B. NACT+ICS without maintenance



Karyotype with CNV

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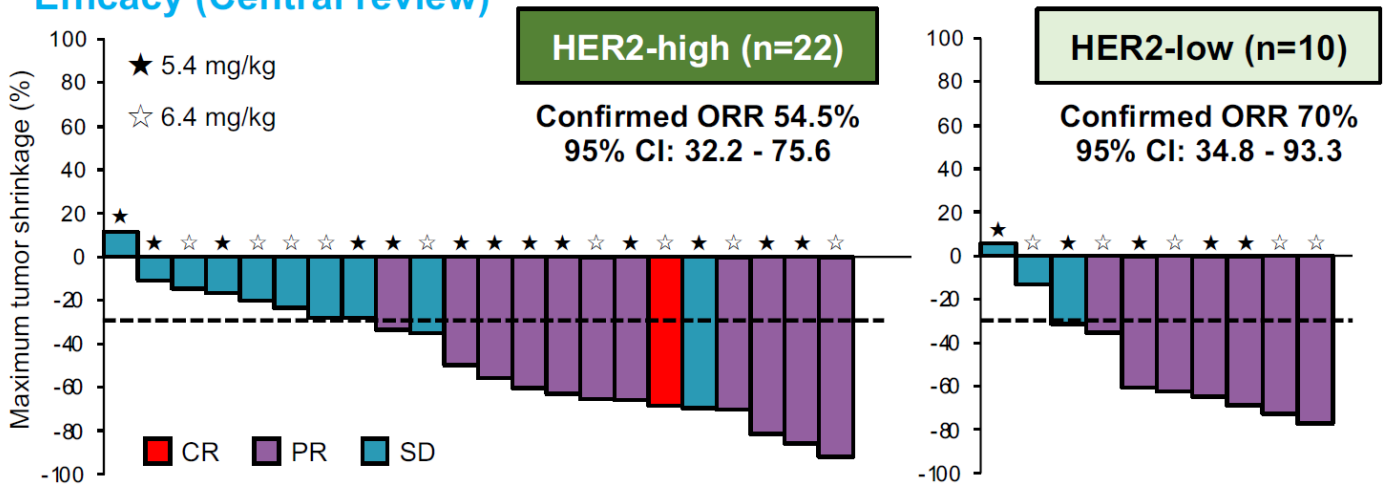
Uterine Carcinosarcoma: Trastuzumab Deruxtecan

Efficacy and safety of trastuzumab deruxtecan in HER2-expressing uterine carcinosarcoma (STATICE TRIAL, NCCH1615): A MULTICENTER, PHASE 2 CLINICAL TRIAL

Background:
- *ErbB2* (HER2) amplification in 14–20% of UCS
- HER2 IHC score 3+ ranges from 20 to 50%
- Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody-drug conjugate with potent topoisomerase I inhibitor payload

Eligibility:
- Unresectable UCS, progression post-chemotherapy
- HER2-positive IHC score ≥ 1+
- ECOG PS 0,1 and RECIST measurable

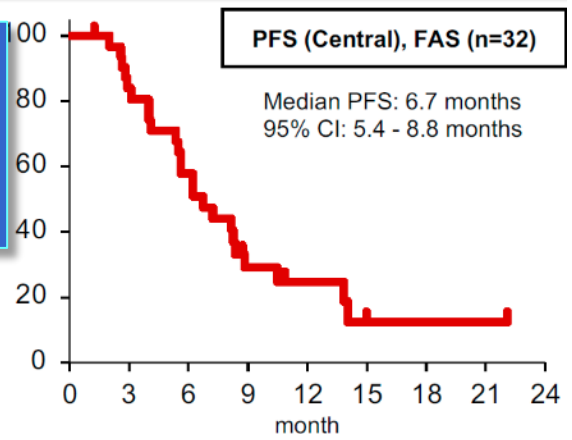
Efficacy (Central review)



- Phase II ORR and PFS with T-DXd exceeds historical data with all other agents
- ErbB2 gene amplification or high-level IHC not required for clinical activity
- Attention to the risk of pneumonitis from T-DXd

		(n=32)	(%)
Prior regimens	1	17	(53.1)
	2	9	(28.1)
	≥ 3	6	(18.8)

Fatigue	3 - 4	2	(6.1)
Pneumonitis	1	4	(12.1)
	2	4	(12.1)
	3	1	(3.0)



Hasegawa K, et al. ESMO 2021 Abstract 813P

Progressive Platinum-Resistant HGSC

58 yo with RT ovarian HGSC FIGO IVB, 20 cm adnexal mass, ascites, RT pleural effusion. cardiopulmonary adenopathy. CA125 = 1295

Primary optimal MACROscopic cytoreduction

Carboplatin-Paclitaxel x6 → PR (residual disease)

NGS: Ovary (70% tumor content), *TP53* p.C176W (VAF 70%), MS Stable, TMB Low, LOH+ (HRD)

PARPi + Bevacizumab maintenance x4 months → PD

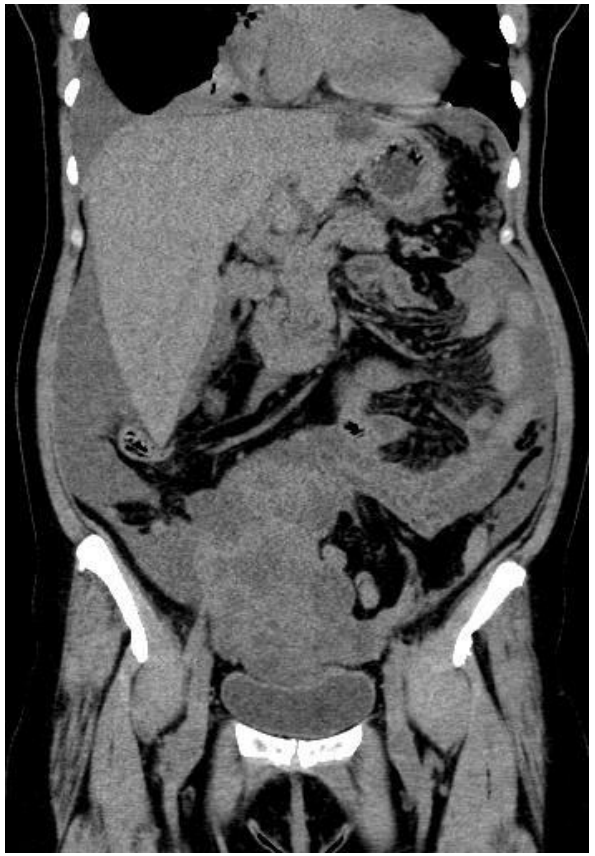
↑RT Effusion → Tunneled Pleural Catheter

PEG-Liposomal Doxorubicin x3 cycles → PD with hepatic metastases, hydronephrosis, partial SBO, PS = 3

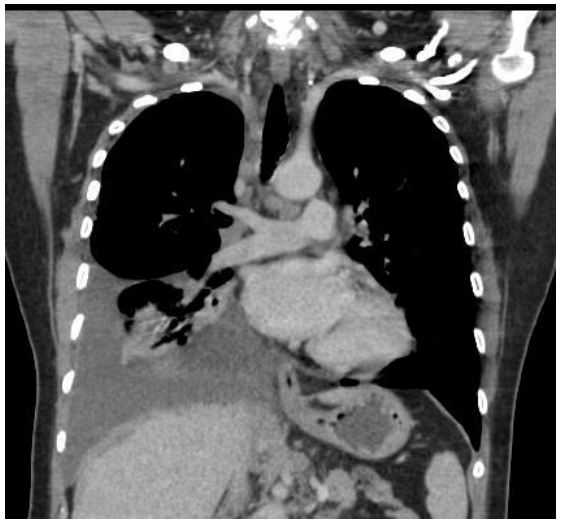
Your Recommendation:

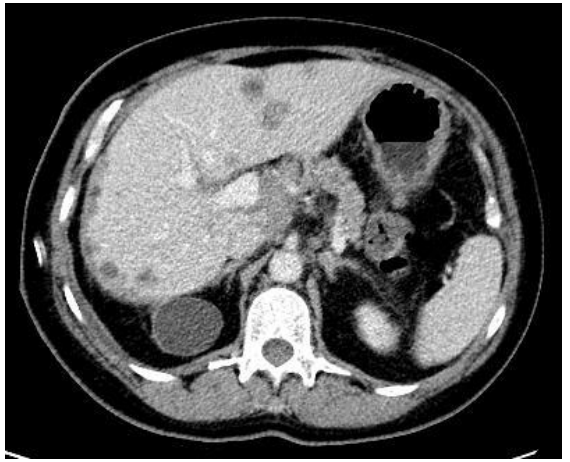
A. Additional non-platinum chemotherapy
B. Supportive care, transition to hospice
C. Lenvatinib + Pembrolizumab
D. Evaluate for ADC (FOLR1 and HER2)

Initial Presentation (FIGO IVB)



Progression Post-PARPi + Bevacizumab





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Carboplatin-Paclitaxel x6 → Clinical PR

NGS: Ovary (70% tumor content), *TP53* p.C176W (VAF 70%), MS Stable, TMB Low, LOH+ (HRD)

PARPi + Bevacizumab maintenance x4 months → PD

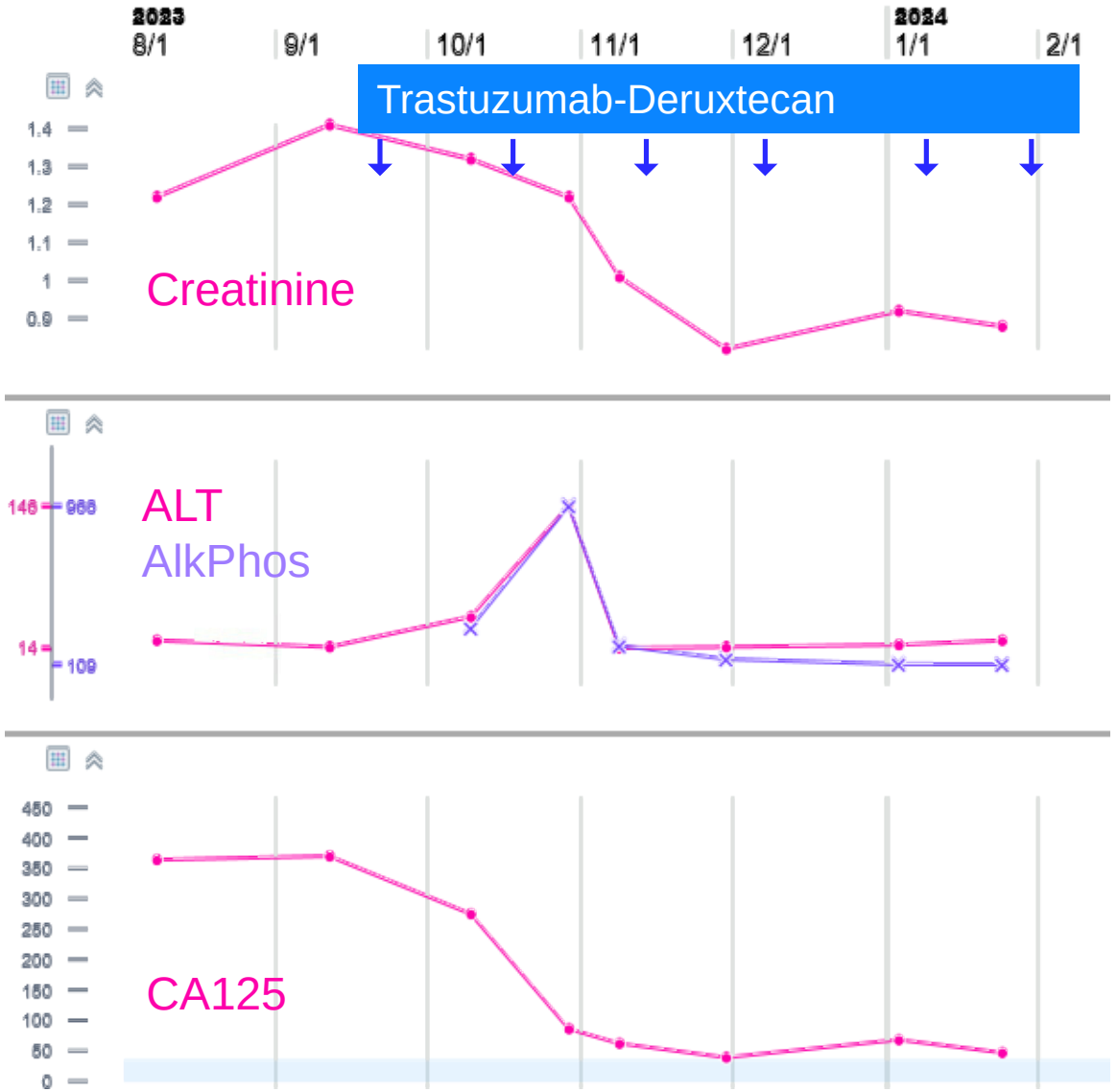
↑RT Effusion → Tunneled Pleural Catheter

PEG-Liposomal Doxorubicin x3 cycles → PD with hepatic metastases, hydronephrosis, partial SBO, PS = 3

IHC FOLR1 80% (2+/3+) and IHC HER2 2+

Trastuzumab-Deruxtecan → Sustained PR, PS = 0, Pleural catheter removed, hydronephrosis resolved, ↓CA125

International travel, no progression of disease



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Summary and Opportunities for Collaboration

- Treatment is increasingly defined by molecular subtypes and tumor biology
- Many “ovarian” cancers arise from extra-ovarian sites. The ovary is a favored site for implantation, due to cyst formation, angiogenesis, hormones, and other factors. “Synchronous” endometrial and ovarian tumors are monoclonal maligancies.
- Screening tests (IHC MMR and P53) can be discordant with NGS in a proportion of tumors, and it is important to distinguish “risk factors” (such as Lynch Syndrome) from tumor-causing events
- “Double Classifiers” merit careful evaluation to determine the primary molecular driver, including pathogenic mutations in BRCA1/2, which may not be cancer-causing or PARPi sensitive, without confirmation of HRD-LOH
- Hypermutated states (MSI and POLEmut), as well as HRD-LOH, are distinct at a molecular level, but secondary mutations can make it difficult to indintify the primary molecular driver
- Availability of functional HR assays (RAD51 focus-forming) and detection of BRCA1/2 revertant clones could identify tumors that are PARPi resistant
- Single-agent immune checkpoint inhibitors (anti-PD1 or PD-L1) are not effective in HGSC
- The emergence of antibody-drug conjugates has provided a valuable treatment strategy, but each one is different (target, linker, payload)


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