

From Research to Practice: What's New in Gynecologic Cancers?



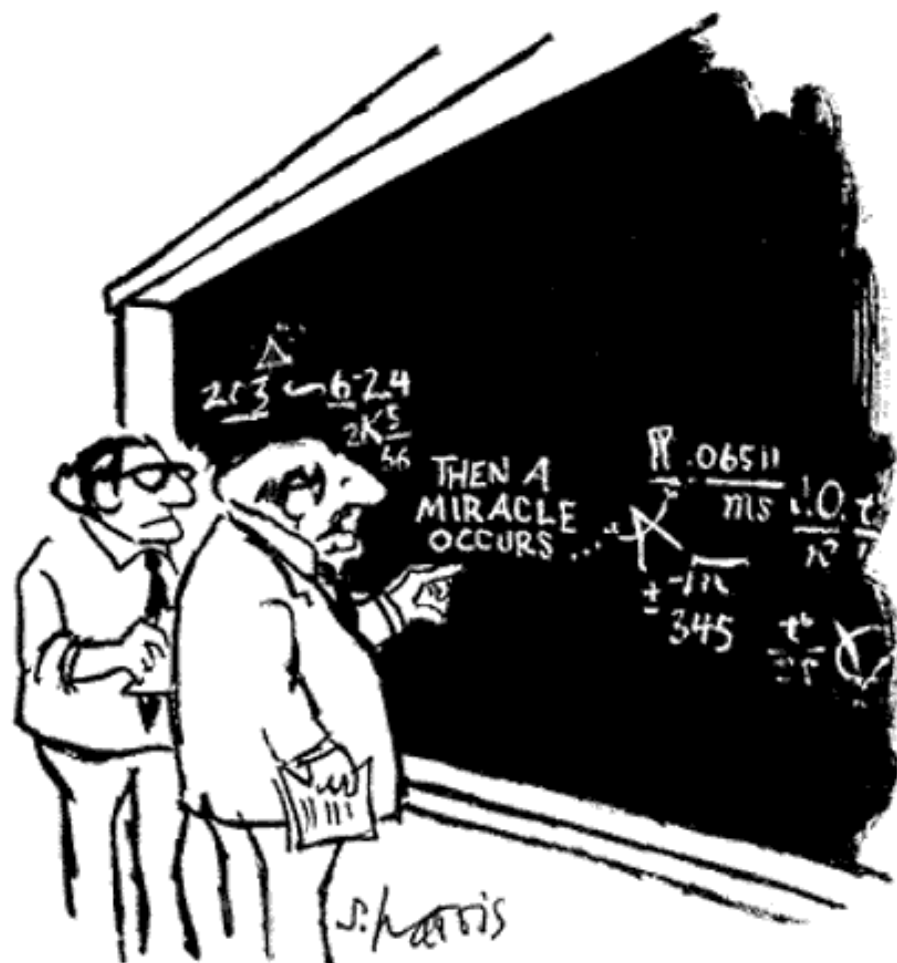
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Disclosure

- Speakers Bureau: AstraZeneca

Outline

- New cancer basics
- Ovarian cancer achievements
 - Surgical modifications
 - Chemotherapy and targeted therapy
- Cervical and endometrial cancer surgery
 - Robotic
 - Sentinel node sampling
- Targeted therapy for cervical cancer
- NCI Match trial



"I think you should be more explicit here in step two."

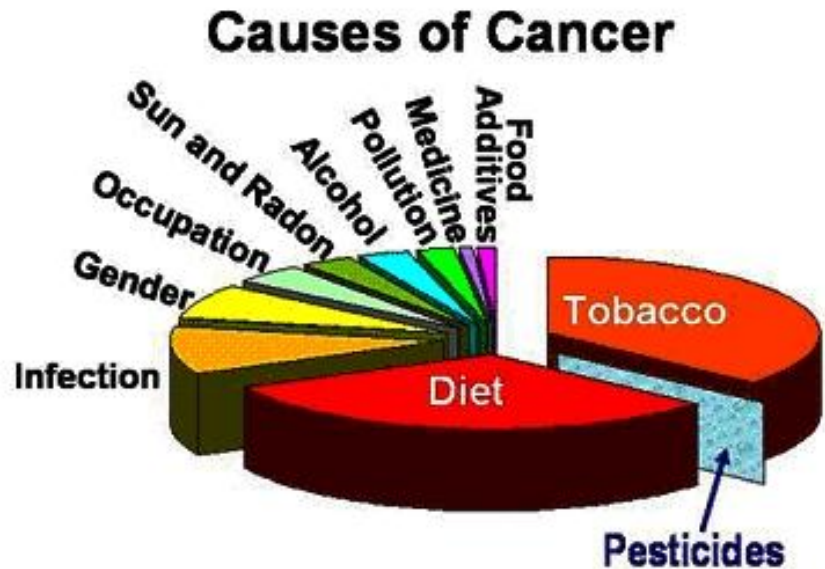
Precision Medicine



“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?”

- President Obama, January 30, 2015

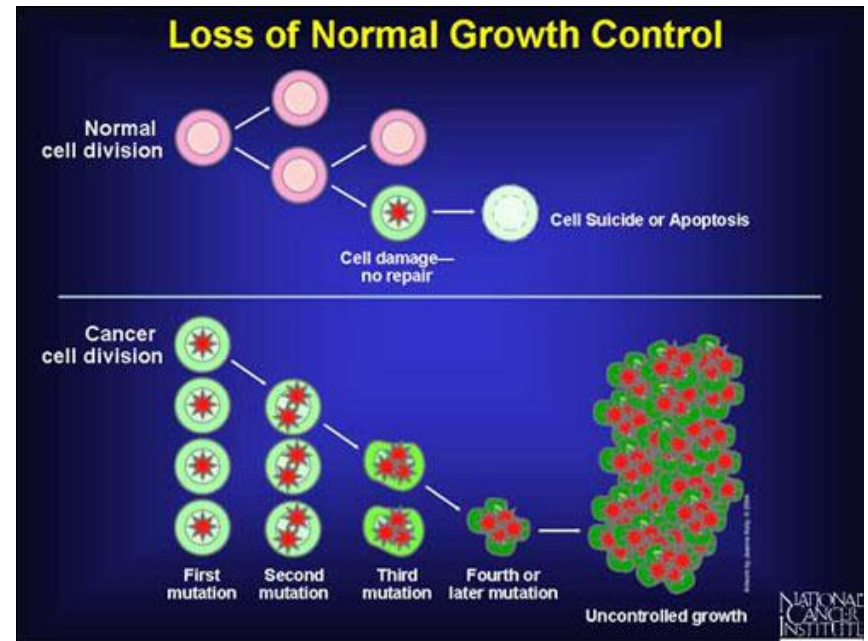
- Cancer is an infectious disease
- Cancer is a disease of aging
- Cancer is an environmental disease



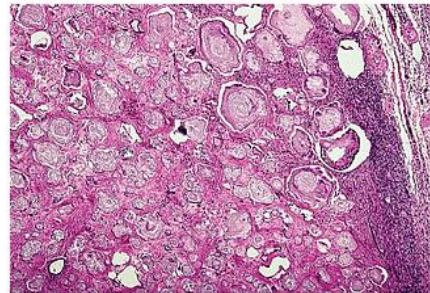
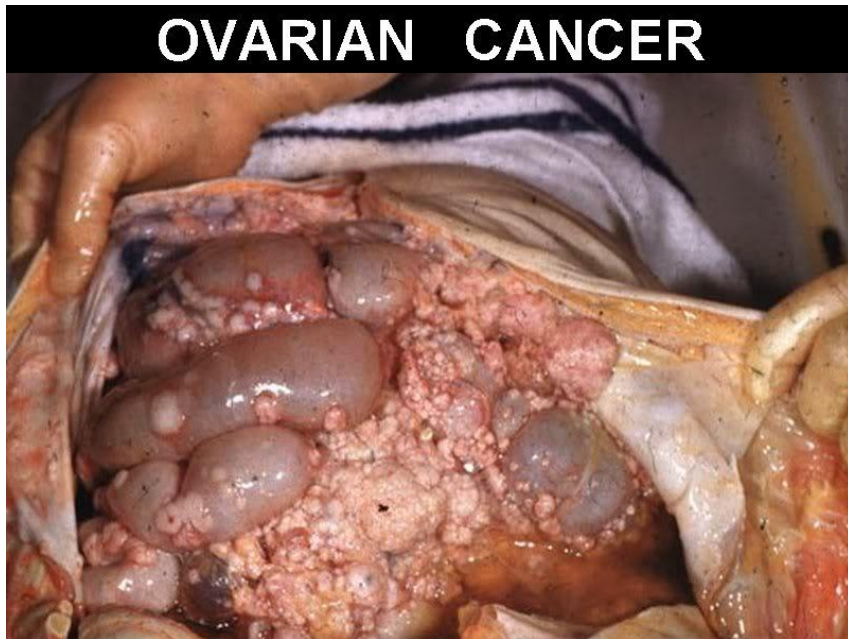
Ultimately, all cancers are a genetic disease

Genetic Basis of Cancer

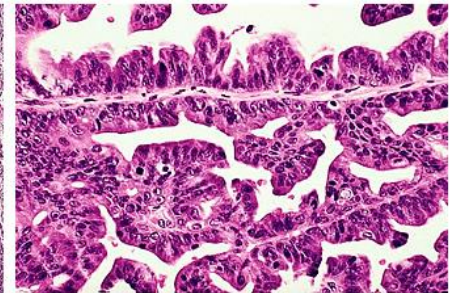
- Germline mutations - inherited
- Somatic mutations - occur in individual cells after conception
- Cancer is caused by an accumulation of mutations that affect gene expression in a single cell
- Cancer is an immortalized cell line that no longer responds to the normal mechanism that control cell proliferation



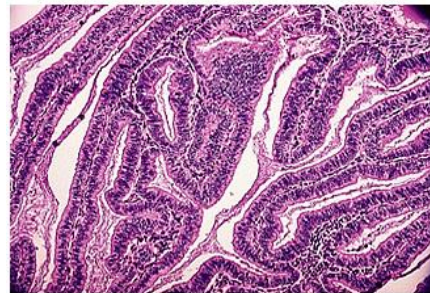
Our concept of ovarian cancer until 2011



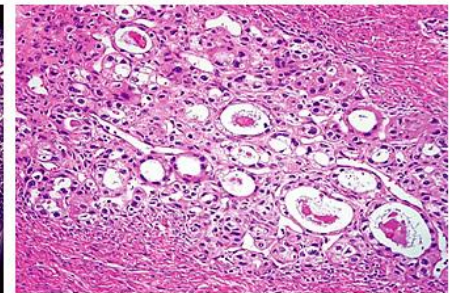
Serous cystadenocarcinoma



Mucinous Cystadenocarcinoma



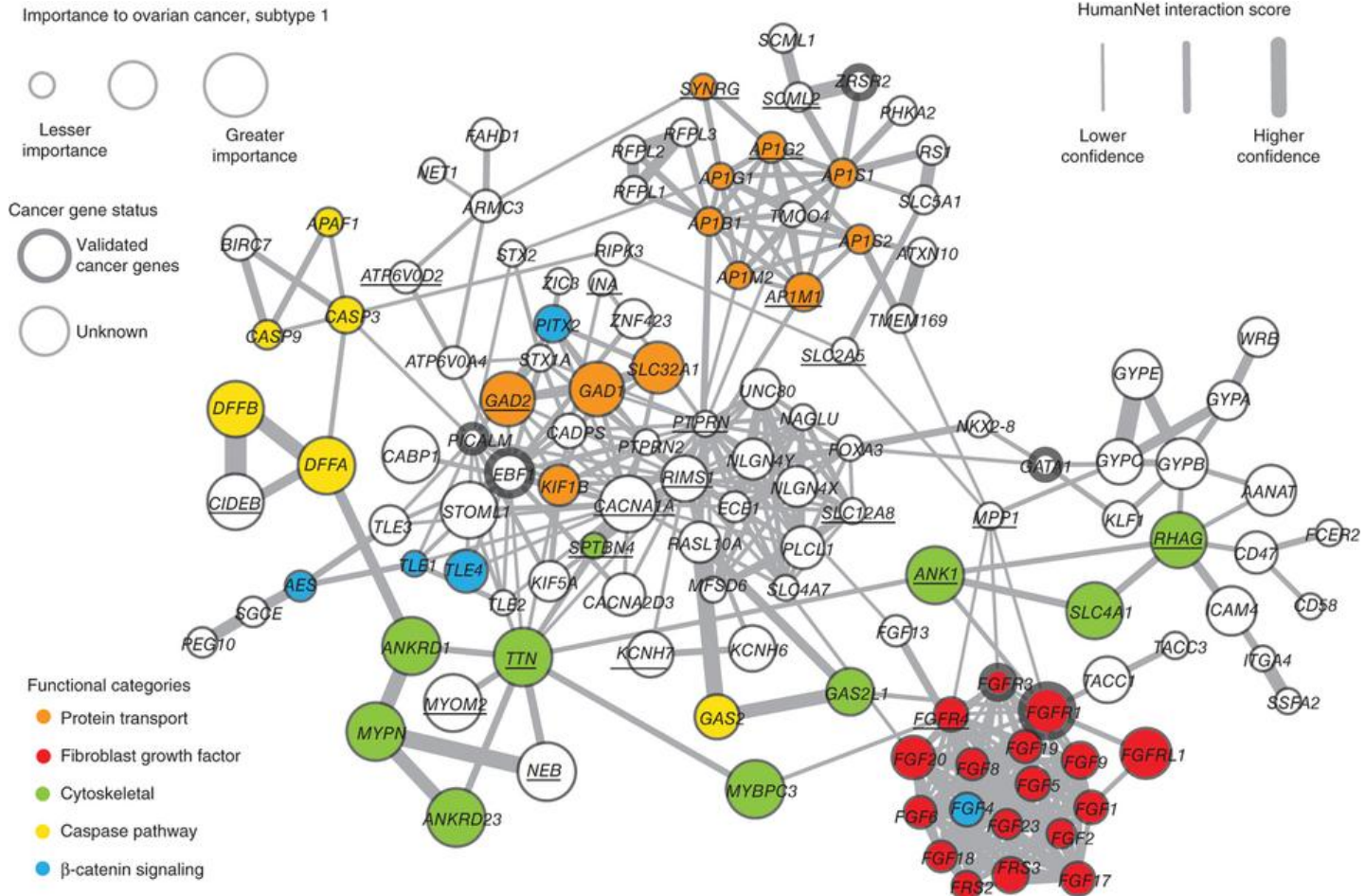
Endometrioid Ovarian Carcinoma



Clear Cell Carcinoma

Integrated genomic analyses of ovarian carcinoma

The Cancer Genome Atlas Research Network*



Transformation of the Fallopian Tube Secretory Epithelium Leads to High-Grade Serous Ovarian Cancer in *Brca*;*Tp53*;*Pten* Models

Ruth Perets,^{1,4,6} Gregory A. Wyant,^{2,4} Katherine W. Muto,² Jonathan G. Bijron,³ Barish B. Poole,² Kenneth T. Chin,² Jin Yun H. Chen,² Anders W. Ohman,² Corey D. Stepule,² Soongu Kwak,¹ Alison M. Karst,¹ Michelle S. Hirsch,³ Sunita R. Setlur,² Christopher P. Crum,³ Daniela M. Dinulescu,^{2,3,5,*} and Ronny Drapkin^{1,3,5,*}

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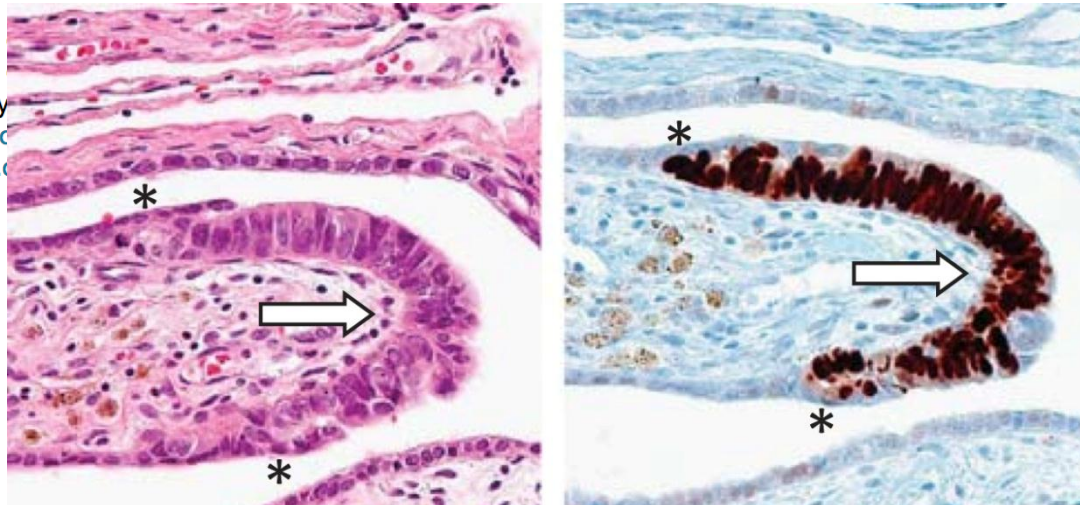
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⁶Present address: Oncology

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<http://dx.doi.org/10.1016/j.ccr.2016.04.011>



Documented preinvasive to invasive HGSOC



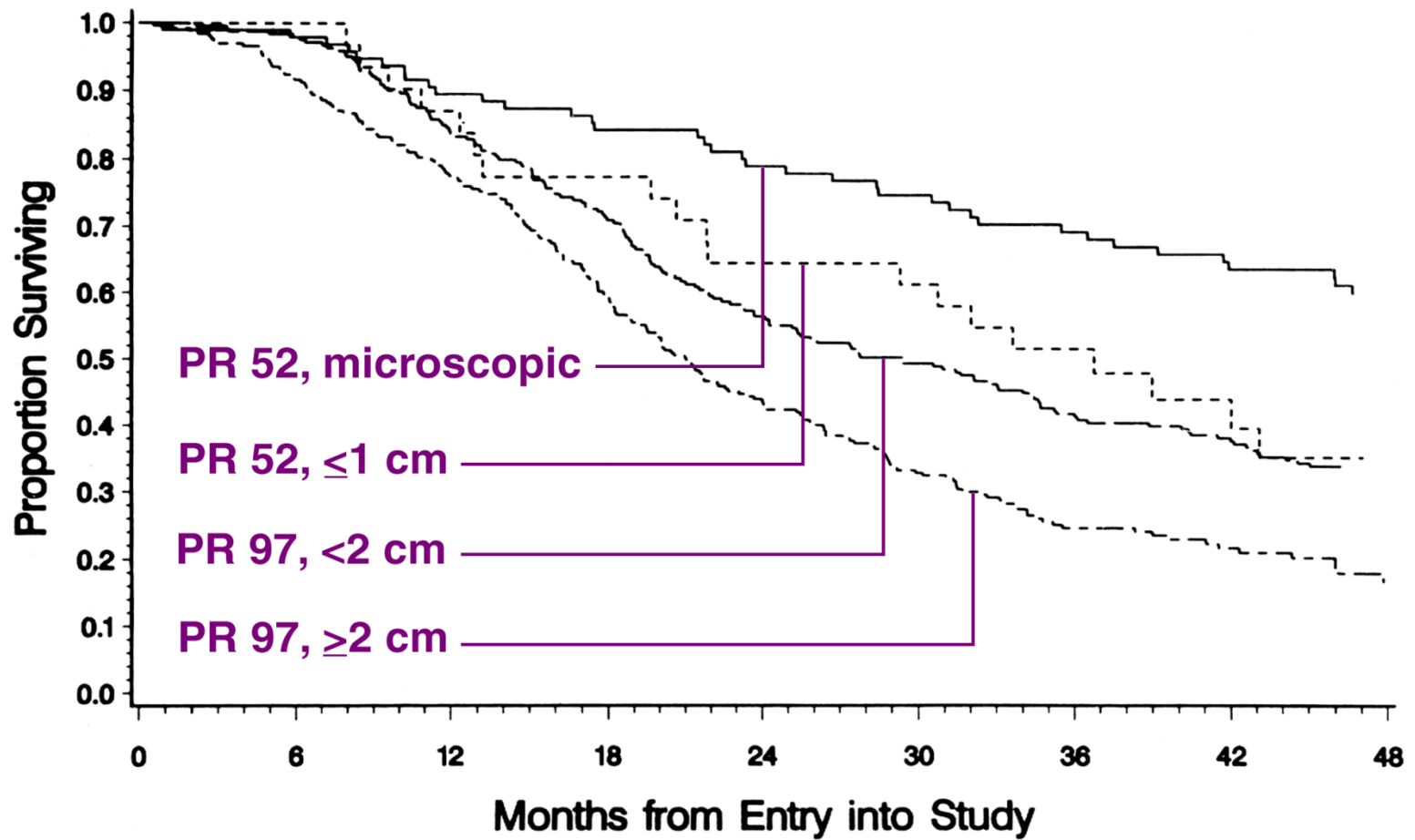
"Whoa! That was a good one! Try it, Hobbs — just poke his brain right where my finger is."

Ovarian Cancer:

Surgical Treatment for Advanced Disease

- Significant survival advantage for women who are optimally cytoreduced
- Procedures may include:
 - *En bloc* resection of uterus, ovaries and pelvic tumor
 - Omentectomy
 - Bowel resection
 - Removal of diaphragmatic and peritoneal implants
 - Splenectomy, appendectomy
 - Possible intraperitoneal port placement

Ovarian Cancer: Survival by Residual Disease



GOG Protocols (PR) 52 and 97

MSK Experience

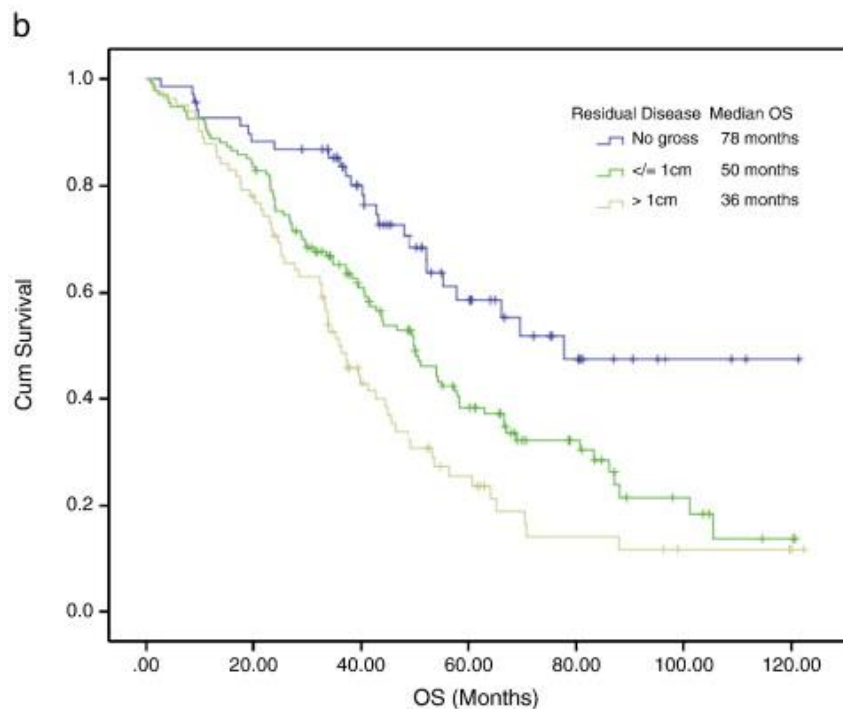
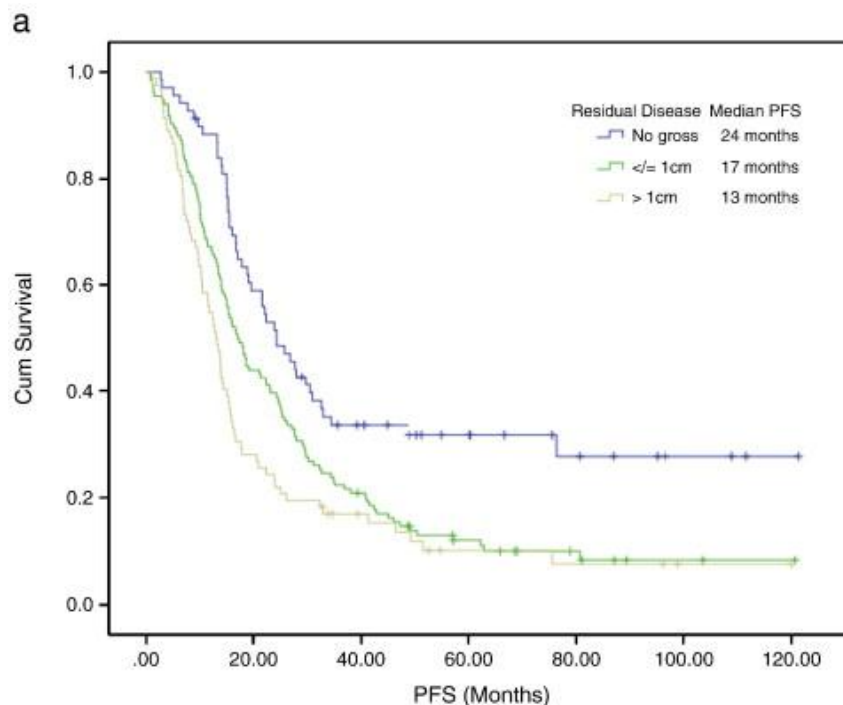
9/98 to 12/06

No gross 69

Residual \leq 1 cm 134

Residual $>$ 1 cm 82

Chi et al Gynecol Oncol 2012



EORTC Neoadjuvant Chemotherapy Trial

- Randomization to primary debulking vs 3 cycles of therapy, surgery, and 3 more cycles
- 632 subjects with extensive St IIIc or St IV disease – lesions > 5 cm in 74% and > 10 cm in 62%
- Residual tumor \leq 1 cm in 42% of primary surgical cases and in 81% following interval debulking
- PFS (median: 12 vs 12 mo) and OS (median: 29 vs 30 mo) were no different between the two groups
- Complete resection of all gross disease was the strongest predictor of survival for primary and interval surgery

MRC CHORUS Trial

- Randomization similar to the EORTC trial
- 552 stage III/IV subjects randomized, 25% w/ stage IV
- Median tumor size: 8 cm, 20% WHO PS of 2 or 3
- Residual tumor burden
 - No gross dz: 16% primary surg vs 40% neoadjuvant
 - ≤ 1 cm: 41% primary surg vs 75% neoadjuvant
- Fewer complications in the neoadjuvant arm
- No difference in median PFS (10.3 vs 11.7 mo) or median OS (22.8 vs 24.5 mo)

Ovarian Cancer Surgery

MD Anderson Cooper Protocol

- Goal: complete resection of gross disease
- Physical examination
- CT imaging of chest, abdomen and pelvis
 - Mesenteric implants are particularly ominous
 - Moderate or large pleural effusions – pleural implants
- Laparoscopic evaluation
 - Six item scoring system
 - If not a candidate for laparotomy, obtain a biopsy of the tumor and place an IV portacath

Laparoscopic Scoring System

- Laparoscopic Features: 2 pts/finding

Peritoneal Carcinomatosis	Omental Cake
Diaphragmatic Carcinomatosis	Bowel and/or Stomach Infiltration
Superficial Spleen &/or Liver Carcinomatosis	Mesenteric retraction

- Preliminary study by Fagotti indicated that for a score ≥ 8 , 100% could not be debulked
- Evaluation in Houston yielded an increase in complete resection with primary surgery from 20% to 88%



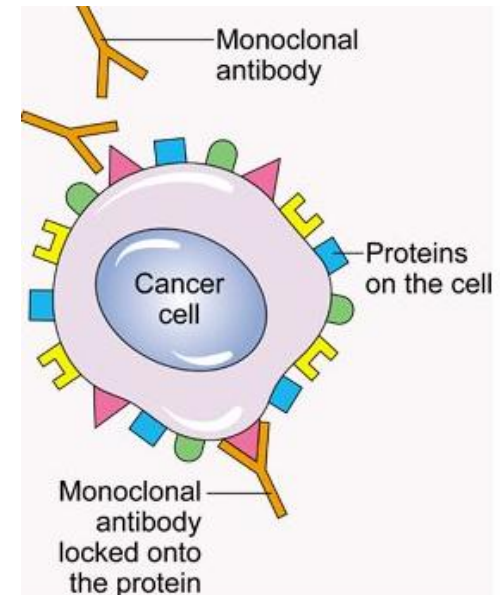
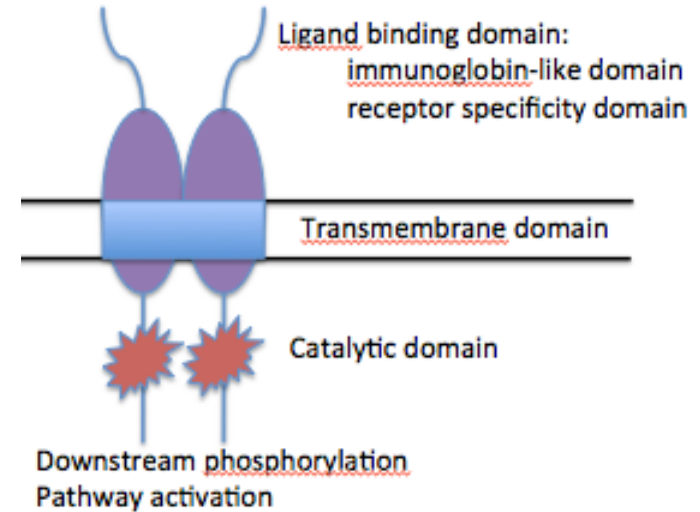
“We’ve found a mass. The good news is we have weapons of mass destruction.”

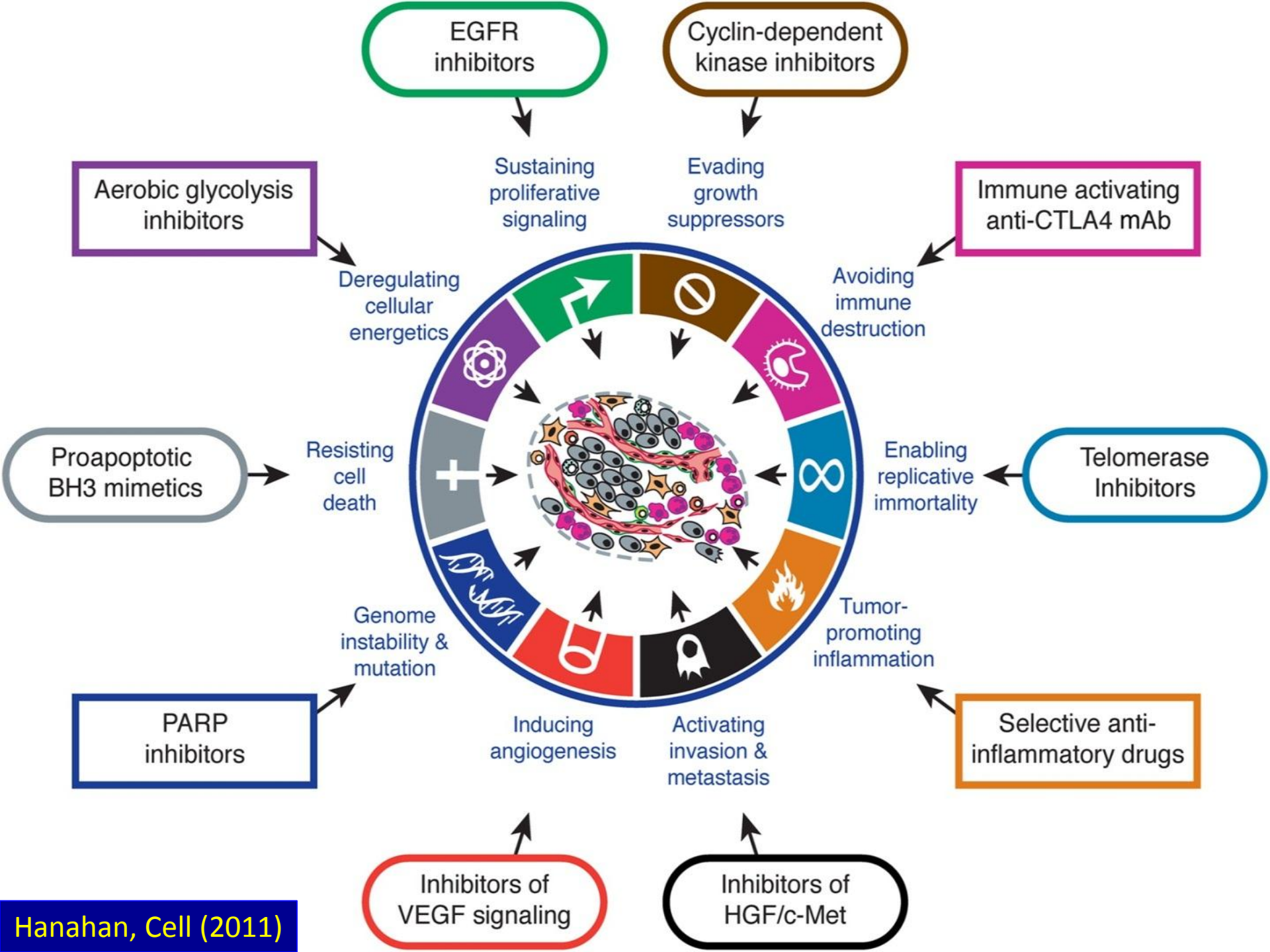
Primary Chemotherapy for Ovarian Cancer

- Primary therapy
 - Carboplatin/taxane q3 wks x 6 cycles
 - Carboplatin q3 wks*/Taxol wkly x 6 cycles
 - Cisplatin/Taxol IV/IP q3 wks x 6 cycles
- Bevacizumab (Avastin) can be added to the IV regimens and is continued as consolidation therapy
- Response rate of approximately 80%
- 75% of patients will recur

Targeted Therapy

- ACTIONABLE
- Small molecule drugs (-ib)
 - Enter cells and interact with target proteins
- Monoclonal antibodies (-mab)
 - Bind to target proteins on surface of cancer cells so immune system can locate and destroy





Biomarkers: Functional Definitions

Prognostic Markers

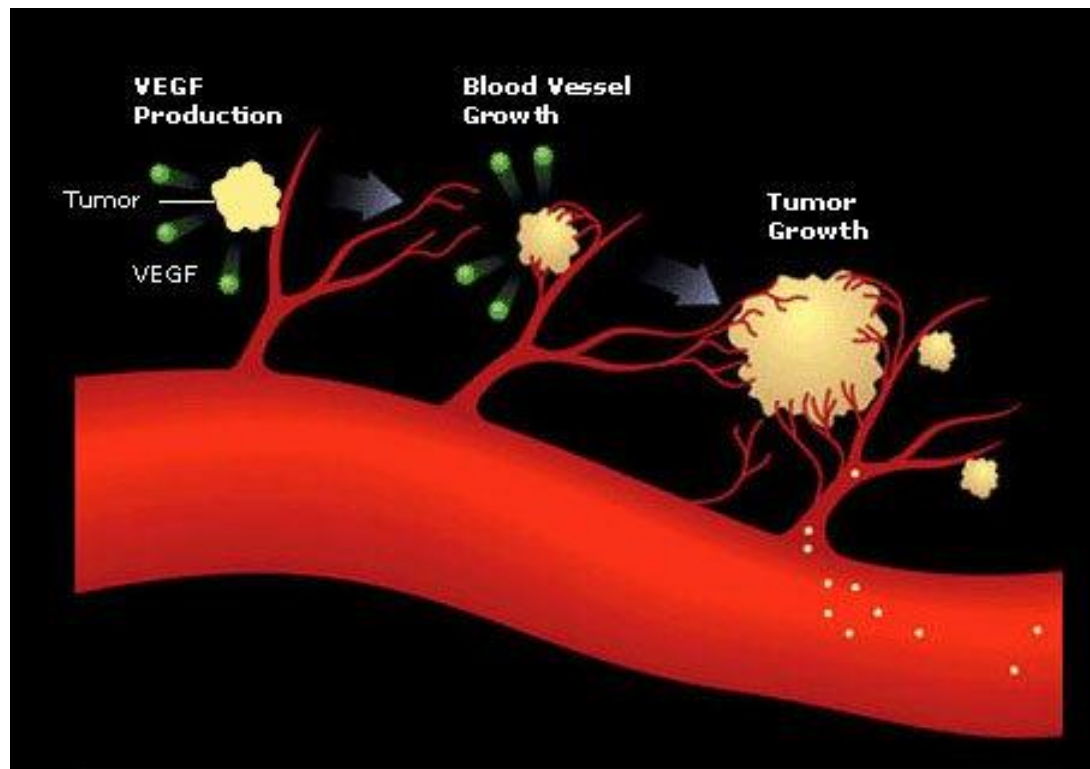
- Correlate with disease outcome regardless of intervention
- e.g. Clinical: stage, PS
- e.g. Lab: LDH in non-Hodgkin's lymphoma

Predictive Markers

- Predict outcome with specific therapy - match drugs with appropriate pts
- e.g. KRAS mutations and anti-EGFR monoclonal antibodies in colorectal cancer

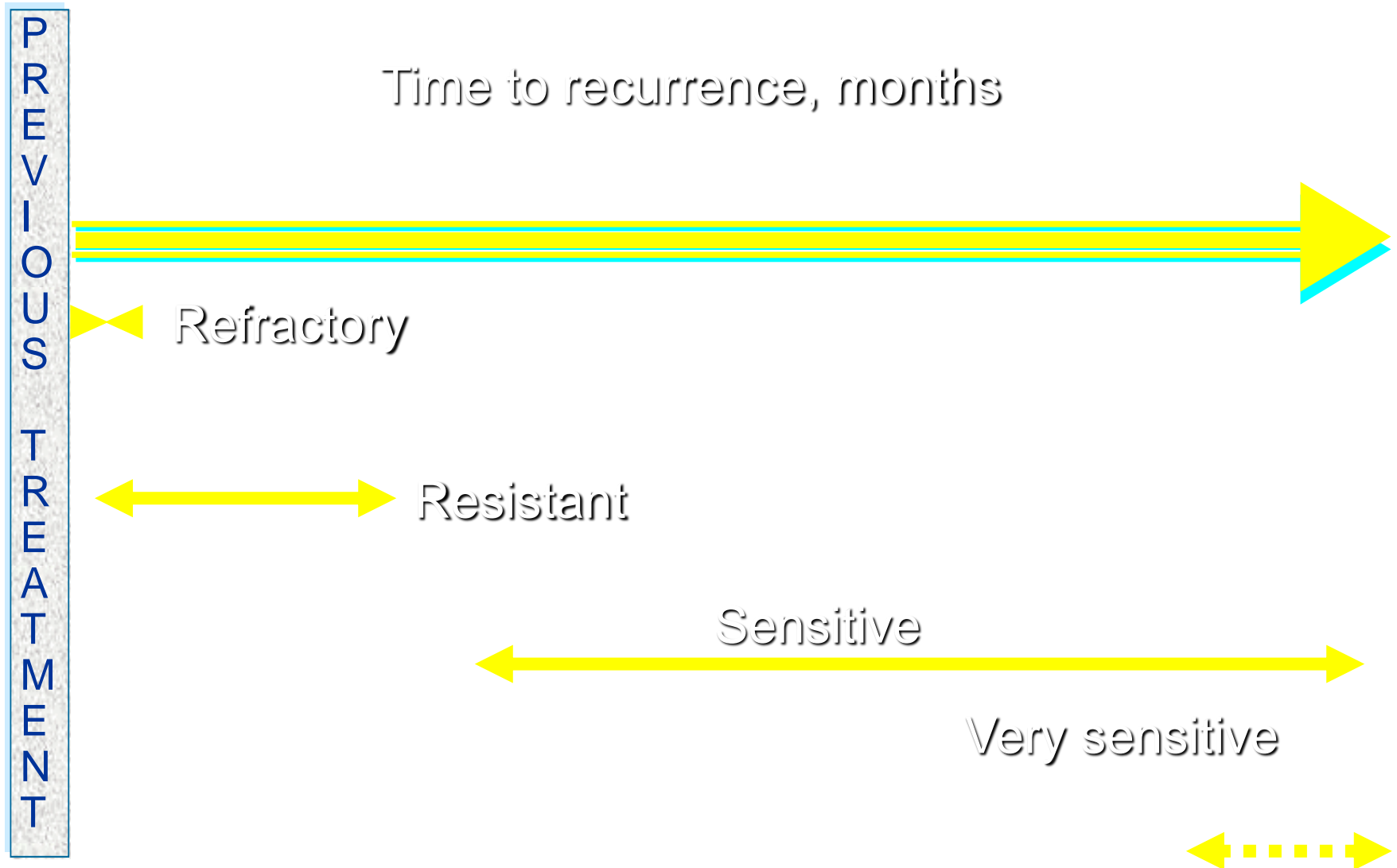
Pharmacodynamic Markers

- Confirm biologic activity
- e.g. ↓ pERK with a targeted agent (such as a MEK inhibitor)



- Cancers secrete vascular endothelial growth factor (VEGF) to stimulate the development of new blood vessels
- Bevacizumab is an antibody that binds to VEGF to reverse angiogenesis
- Primary therapy: no effect on overall survival

Recurrent Ovarian Cancer— Definition of Disease Sensitivity



ACCEPTABLE RECURRENCE THERAPIES (1 OF 2)^a

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Single Agents or Combinations	Platinum-Sensitive Disease^{b,c} Carboplatin ¹ Carboplatin/docetaxel ^{2,3} Carboplatin/gemcitabine ¹ Carboplatin/gemcitabine/bevacizumab ^{d,e} (category 2B) ⁴ Carboplatin/liposomal doxorubicin ⁵ (category 1) Carboplatin/paclitaxel (category 1) ⁶ Carboplatin/paclitaxel (weekly) ⁷ Cisplatin ⁶ Cisplatin/gemcitabine ⁸		Bevacizumab ^{d,e,17,18} Olaparib ^{9,19,20}	
	Platinum-Resistant Disease Docetaxel ⁹ Etoposide, oral ¹⁰ Gemcitabine ^{11,12} Liposomal doxorubicin ^{11,12} Liposomal doxorubicin/bevacizumab ^{d,e,13} Paclitaxel (weekly) ¹⁴ Paclitaxel (weekly)/bevacizumab ^{d,e,13} Topotecan ^{15,16} Topotecan/bevacizumab ^{d,e,13}		Bevacizumab ^{d,e,17,18} Olaparib ^{9,19,20}	
Other Potentially Active Agents ^f	Single Agents²¹ Altretamine Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Aromatase inhibitors Leuprolide acetate Megestrol acetate Tamoxifen		Palliative localized radiation therapy

Antiangiogenesis Agents for Recurrent Ovarian Cancer

Table 2. Efficacy Comparisons: Angiogenesis Inhibitors in Platinum-Pretreated Ovarian Cancer

Trial	TRINOVA-1 ⁸		AURELIA ^{5,6}		OCEANS ⁴	
Regimen	trebananib + paclitaxel	paclitaxel	Avastin + Chemo	Chemo	Avastin + carboplatin + gemcitabine	carboplatin + gemcitabine
Platinum-Free Interval (PFI)	< 12 months		< 6 months		≥ 6 months	
mPFS (months)	7.2	5.4	6.7	3.4	12.4	8.4
PFS HR, p-value	HR: 0.66, p<0.001		HR: 0.48, p<0.001		HR: 0.484, p<0.001	
mOS (months)	19.0	17.3	16.6	13.3	33.3	35.2
OS HR, p-value	HR:0.86, p=0.19*		HR: 0.85, p=0.174		HR: 1.027*	
Toxicity	Edema Ascites Pleural Effusion		Hypertension Proteinuria GI Perforation		Hypertension Proteinuria Bleeding Thromboembolic event	

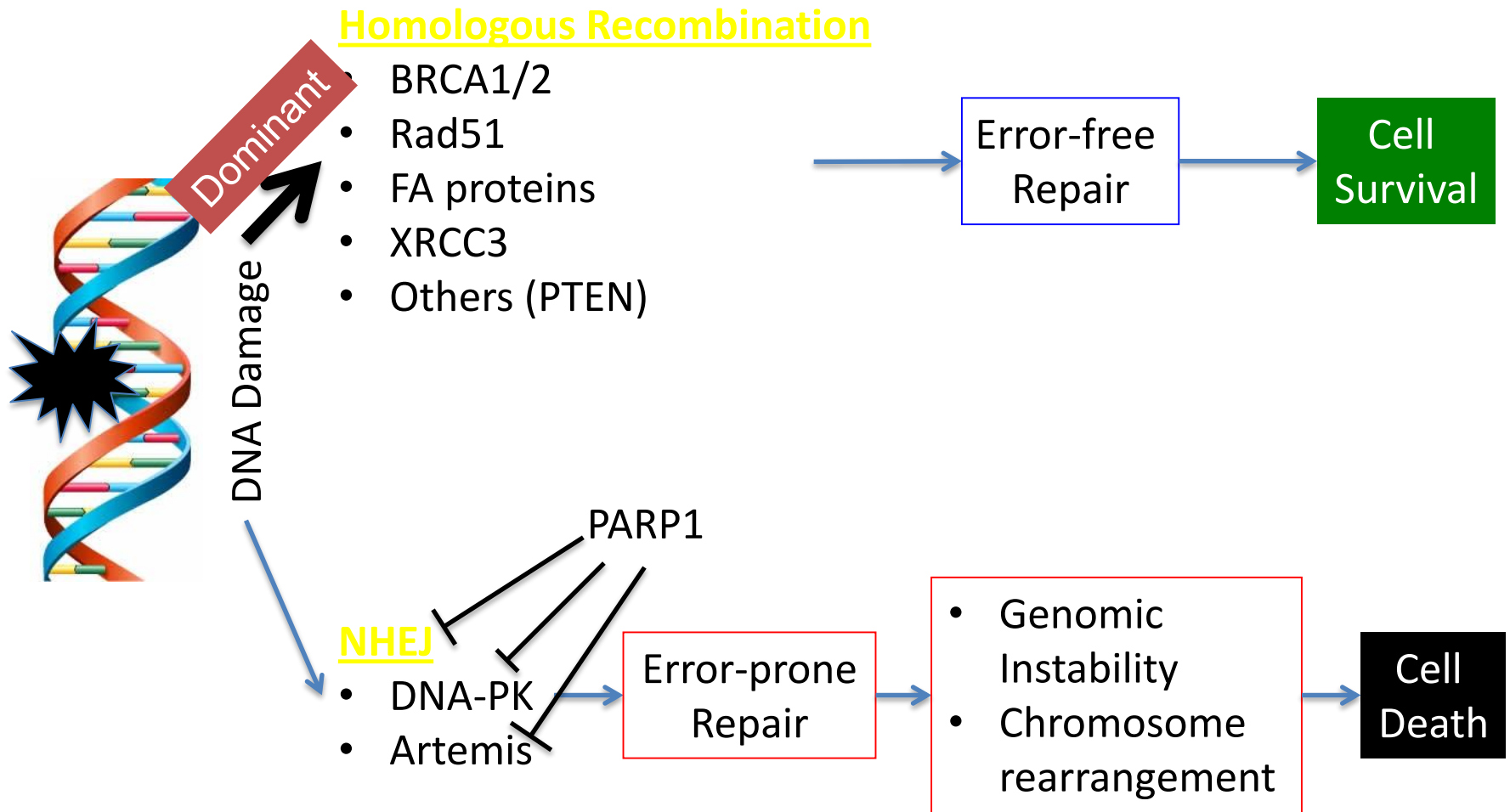
*Based on an interim analysis, data are not yet mature

Exploratory analysis of Aurelia results: wTaxol v. wTaxol/bev

PFS: 3.9 v 9.6 mo (HR 0.47 CI 0.31, 0.72)

OS: 13.2 v 22.4 mo (HR 0.64 CI 0.41, 1.01)

PARP Inhibitors: Mechanism of Action



Study 19: Maintenance Olaparib

Patient eligibility:

- Platinum-sensitive high-grade serous ovarian cancer
- ≥ 2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
 - Time to disease progression on penultimate platinum therapy
 - Objective response to last platinum therapy
 - Ethnic descent
- Primary ENDPOINT: PFS

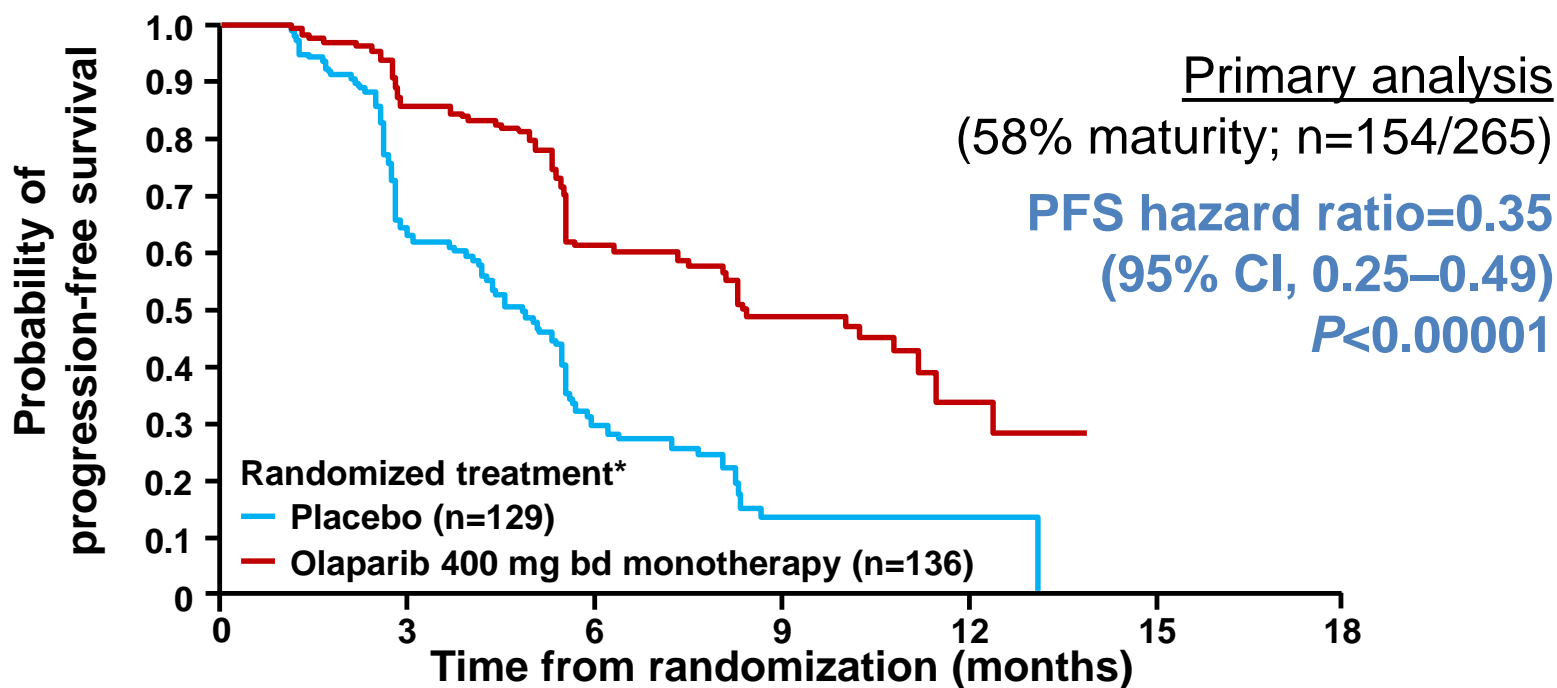
Olaparib
400 mg po bid

Placebo
po bid

Treatment until
disease
progression

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

- Patients were randomized after response to platinum-based chemotherapy

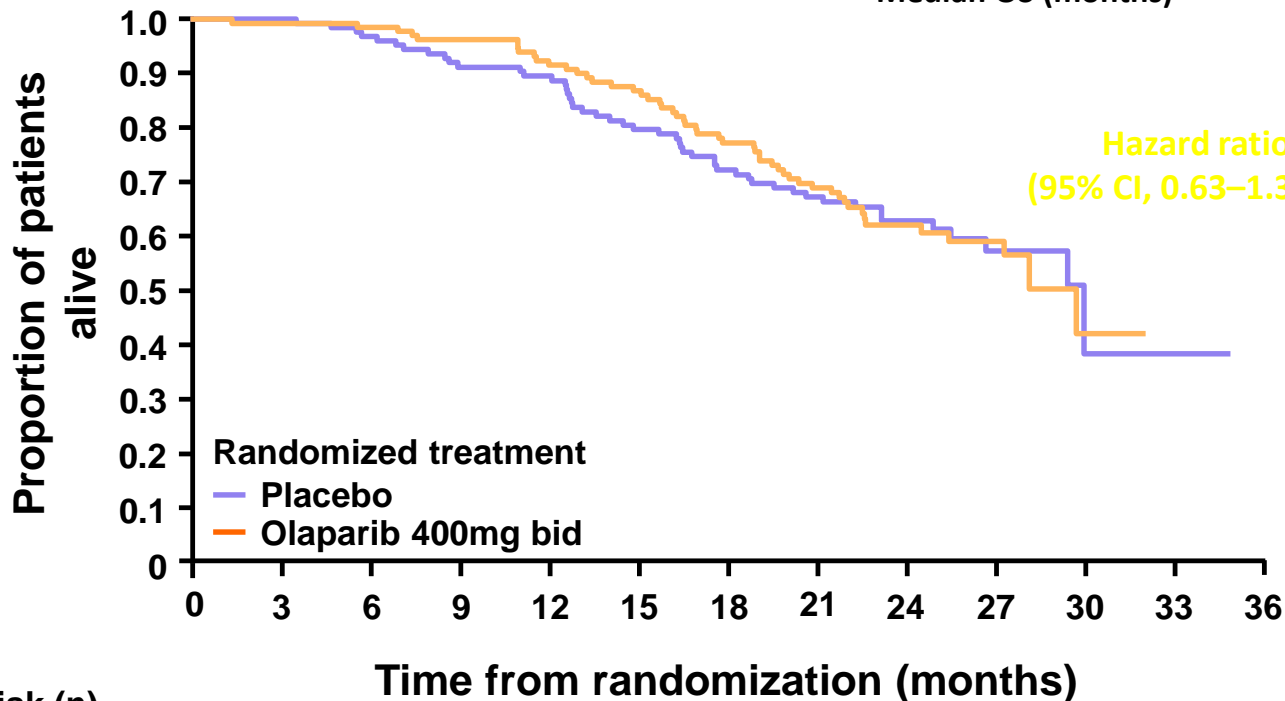


- Interim OS analysis (38% maturity): HR=0.94; 95% CI, 0.63–1.39; *P*=0.75

*Patients were treated until disease progression

Overall survival: interim analysis*

	Olaparib	Placebo
No. of events: Total patients (%)	52:136 (38.2)	49:129 (38.0)
Median OS (months)	29.7	29.9

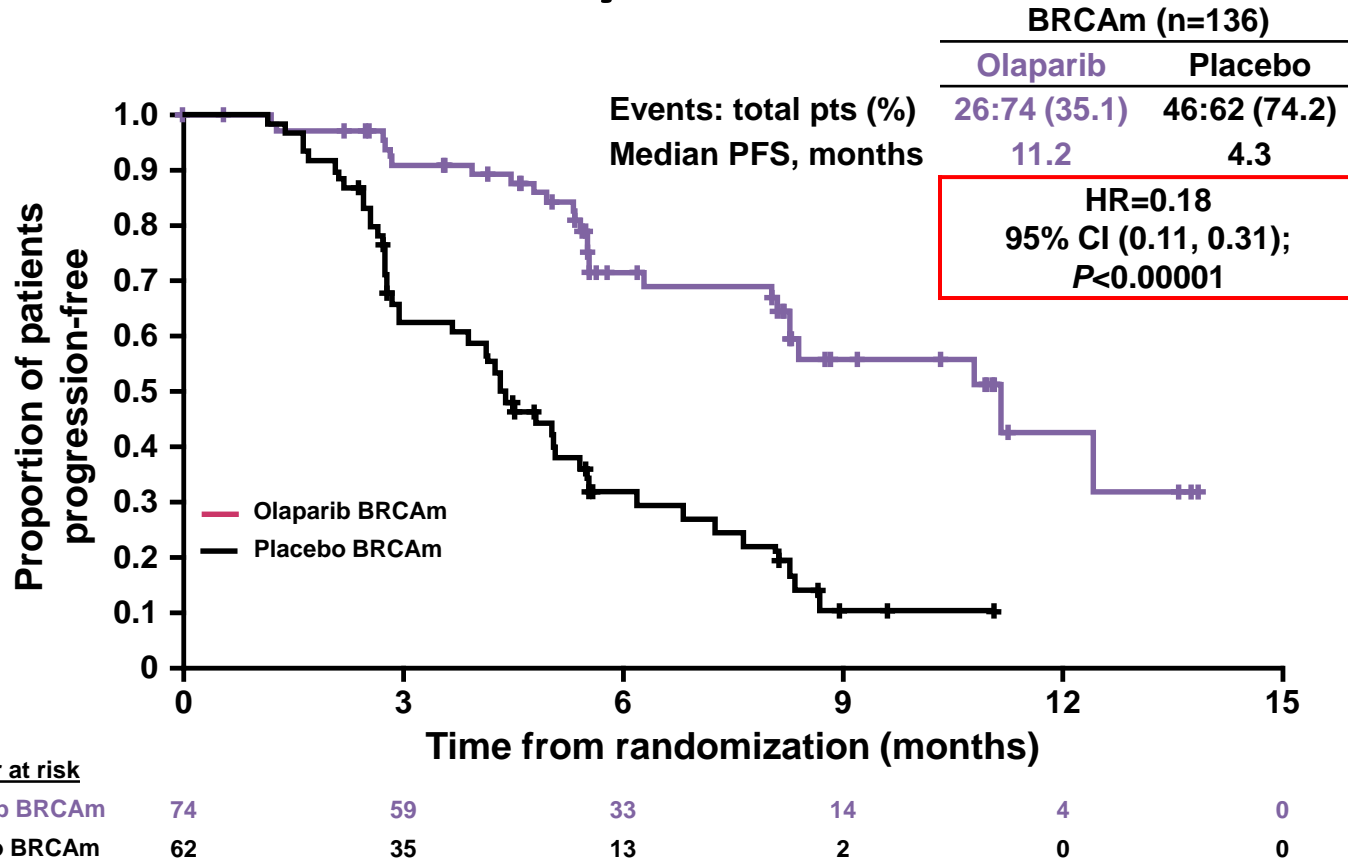


At risk (n)	0	3	6	9	12	15	18	21	24	27	30	33	36
Olaparib	136	132	128	124	117	109	94	79	45	24	4	0	0
Placebo	129	127	120	111	108	96	86	78	44	21	3	1	0

38% events
67% planned

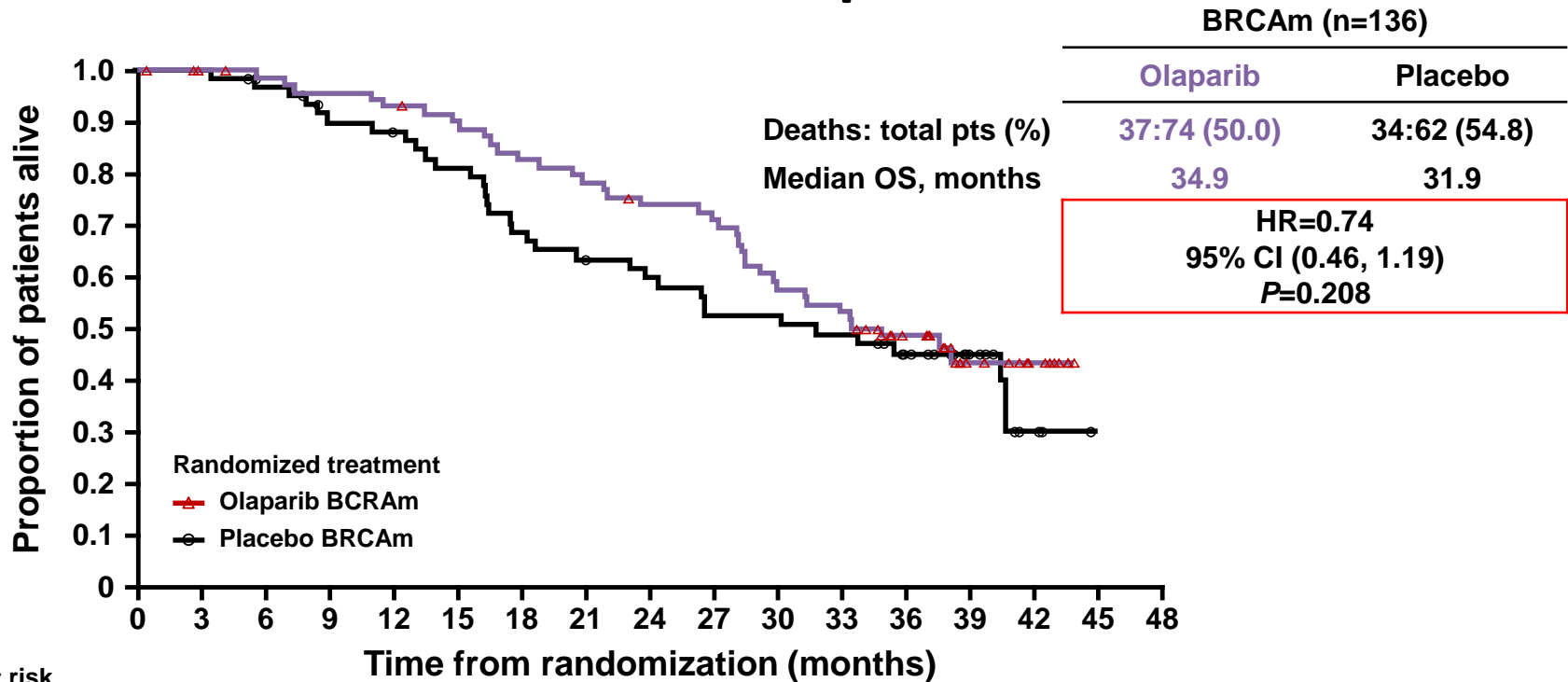
*Performed at 38% maturity

PFS by BRCAm status



- 82% reduction in risk of disease progression or death with olaparib

OS in BRCAm patients



Number at risk

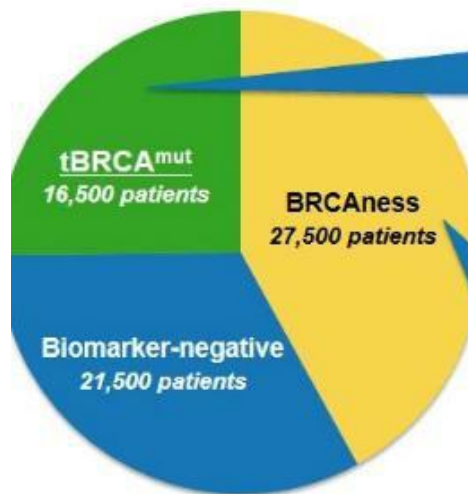
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Olaparib BRCAm	74	71	69	67	65	62	57	54	50	48	39	36	26	12	7	
Placebo BRCAm	62	62	58	52	50	46	39	36	33	29	29	27	21	12	4	

- OS in BRCAwt patients: HR=0.98; 95% CI, 0.62–1.55; $P=0.946$
 - Median OS: olaparib, 24.5 months; placebo, 26.2 months
- 14/62 (22.6%) placebo patients switched to a PARP inhibitor

ARIEL2: Evaluation of BRCAness Signature

Treatment of recurrent ovarian cancer with Rucaparib

The optimal companion diagnostic in ovarian cancer looks beyond gBRCA mutations



RR 8%

- Patients with germ-line (17%) and somatic (8%) BRCA mutations respond equally to rucaparib
- Tissue test (not blood) required to identify somatic mutations

RR 70%

- Tissue test also required to detect BRCAness (42%)
- Clovis developed a proprietary BRCAness signature
- Signature prospectively and successfully applied in an interim look at 200-patient ARIEL2 study
- Signature allows analysis of archival or fresh tissue – interesting differences observed
- Signature being applied prospectively in ARIEL3
- Foundation Medicine a key collaborator

RR 40%

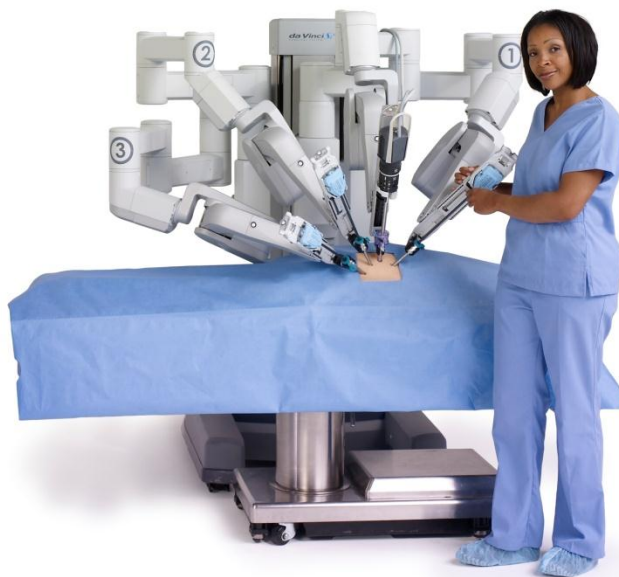
tBRCA: tissue BRCA, incorporating both germline BRCA and somatic BRCA

Sources: Estimated annual incidence of ovarian cancer for US and EU is 65,500; Globocan 2012; Clovis Oncology estimates

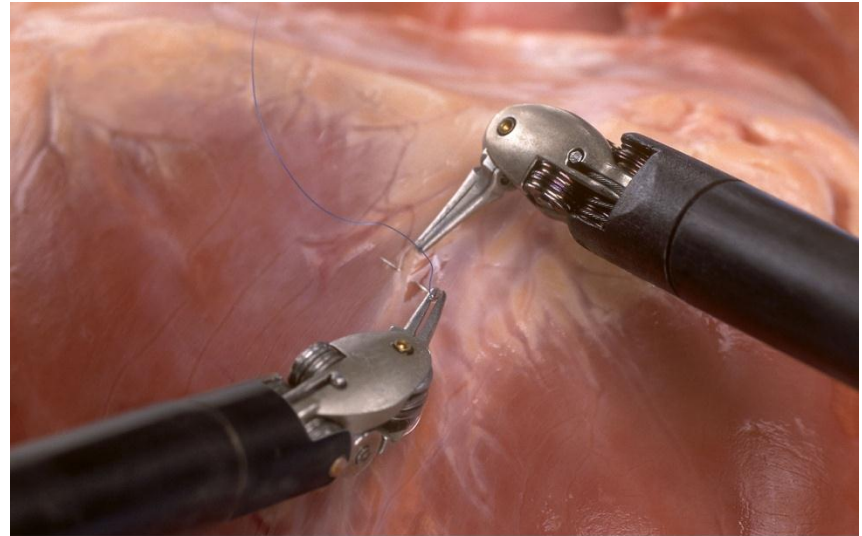
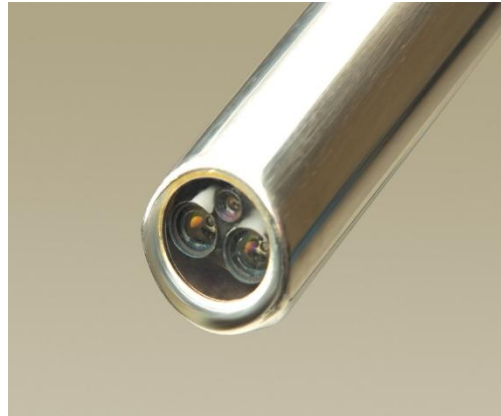
Famous Robots From History



da Vinci Robot System



da Vinci Features



Minimally Invasive Surgery

Benefits

- Faster recovery with shorter hospitalization
- Less time to resumption of normal daily activities
- Decreased blood loss
- Less postoperative pain
- Improved cosmesis

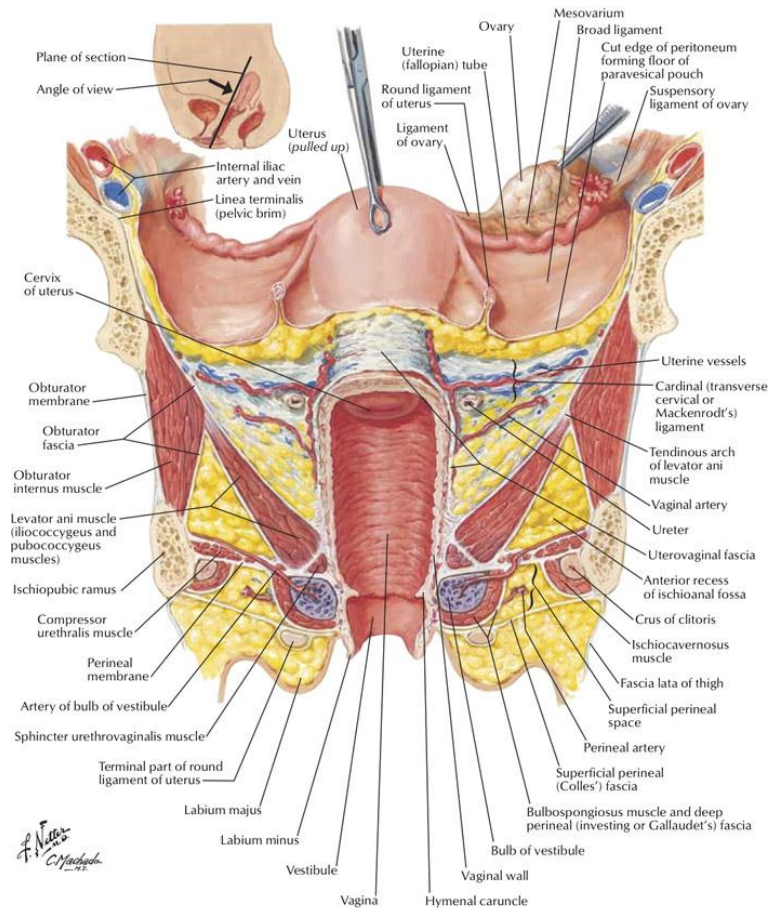
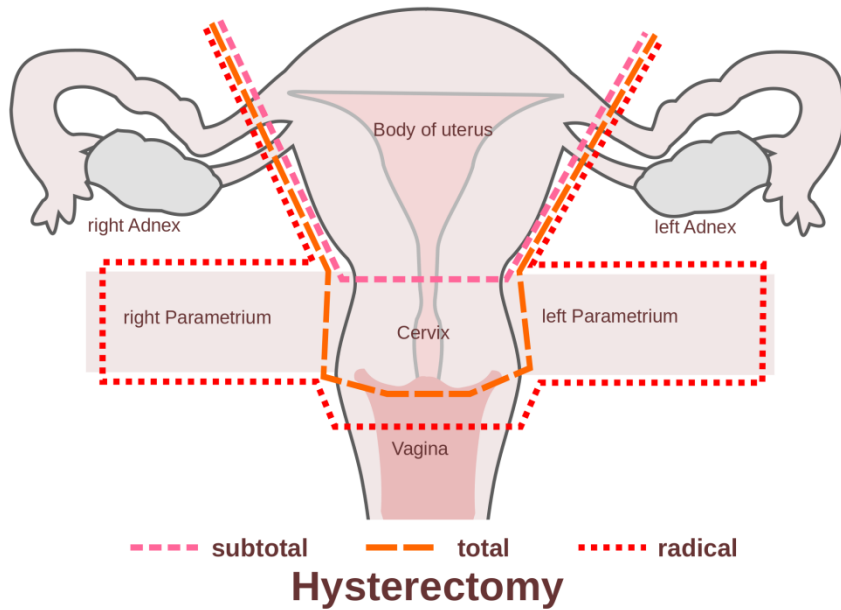
Robotic Advantages

- 3-D visualization
- “Wristed” instruments with 7 degrees of freedom
- Natural movements
- Downscaling of surgeon’s movements (i.e.. 3:1 ratio)
- Improved ergonomics

Management Early Stage Cervical Cancer

Radical hysterectomy – standard since mid1900's

Associated with a high complication rate



GOG Study 278 – Cervical Cancer

- St Ia1 (LVSI) – Ib1 (≤ 2 cm), DOI ≤ 10 mm, clean margins
- Simple hysterectomy (cone biopsy if fertility desired) with pelvic lymph node dissection
- Risk for parametrial involvement with these parameters is $< 1\%$ with a relapse rate of 4%. Our Cooper data corroborates this.
- This study assumes simple hysterectomy to be the equivalent of a radical hysterectomy in regard to disease control
- Purpose is to evaluate QOL parameters

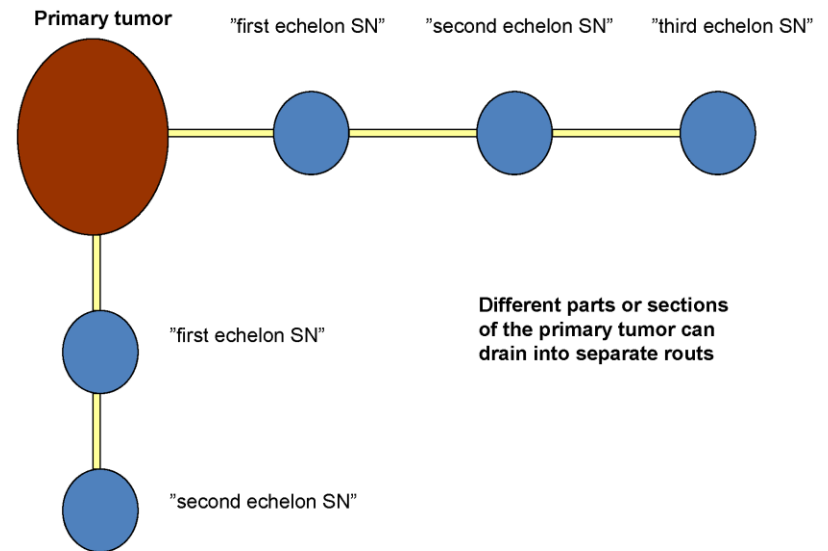
Lymph Node Dissection for Endometrial Cancer

Mayo Clinic Criteria

- Frozen section criteria allowing omission of nodal dissection
 - Type I endometrial cancer
 - Grade 1 or 2 histology
 - <50% myometrial invasion
 - Gross lesion size ≤ 2 cm
 - Lesion confined to the uterine corpus

Sentinel Node Concept

This concept is based on the orderly and sequential progression of tumor cells through the lymphatic system. The first set of nodes to receive drainage from a tumor are referred to as the sentinel nodes. If spread of disease has occurred, a sentinel node should be involved.



(a)

Sentinel Node Sampling

- Established in melanoma, breast and vulvar cancers
- Minimizes morbidity such as lymphedema associated with a full lymphadenectomy
- More accurate identification of the 10% of sentinel nodes in non-standard locations
- Radioactive tracer, blue dye or near-infrared fluorescence imaging (NIR) used
- Ongoing studies in cervical and uterine cancers demonstrate high sensitivity for nodal detection and a low false negative rate

Bevacizumab for Cervical Cancer

GOG 240

- 252 subjects randomized to either cisplatin/Taxol or Topotecan/Taxol +/- bevacizumab
- Improved PFS & OS with bevacizumab
- No difference was noted between the two chemo regimens

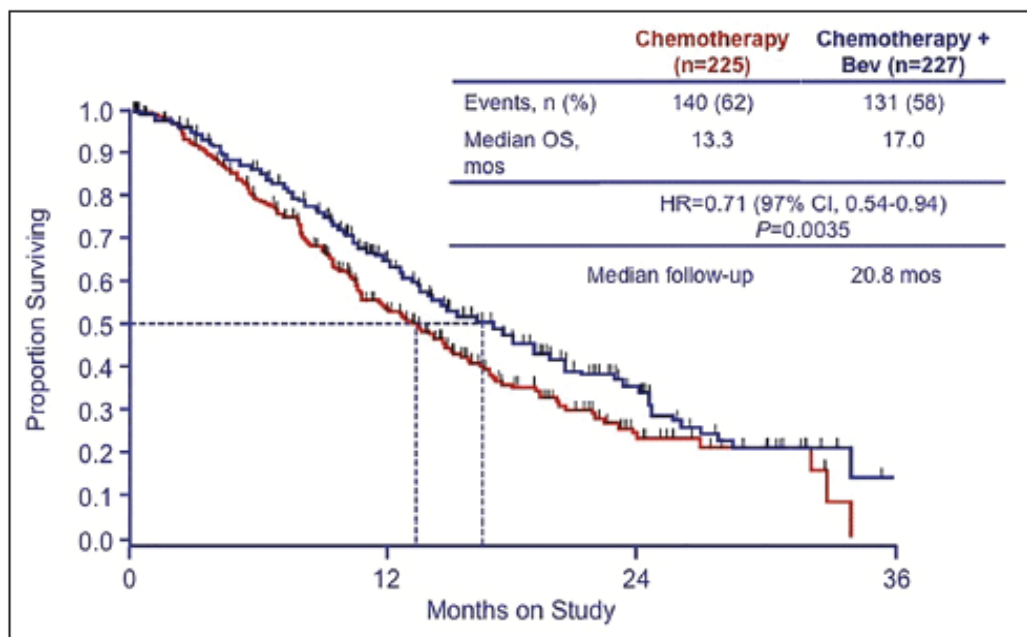


Figure 2: The Overall Survival Curve From GOG 240[60] Provides a Demonstration of the Promise of Anti-Angiogenesis Therapies In Gynecologic Malignancies —There was a 3.7-month improvement with the addition of bevacizumab. Bev = bevacizumab; CI = confidence interval; GOG = Gynecologic Oncology Group; HR = hazard ratio. © Massachusetts Medical Society; reproduced with permission from Tewari KS et al.

NATIONAL CANCER INSTITUTE NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL
EXPLORES TREATING PATIENTS
BASED ON THE MOLECULAR
PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:

- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment



ABOUT 3,000
CANCER PATIENTS
WILL BE
SCREENED WITH A
TUMOR BIOPSY

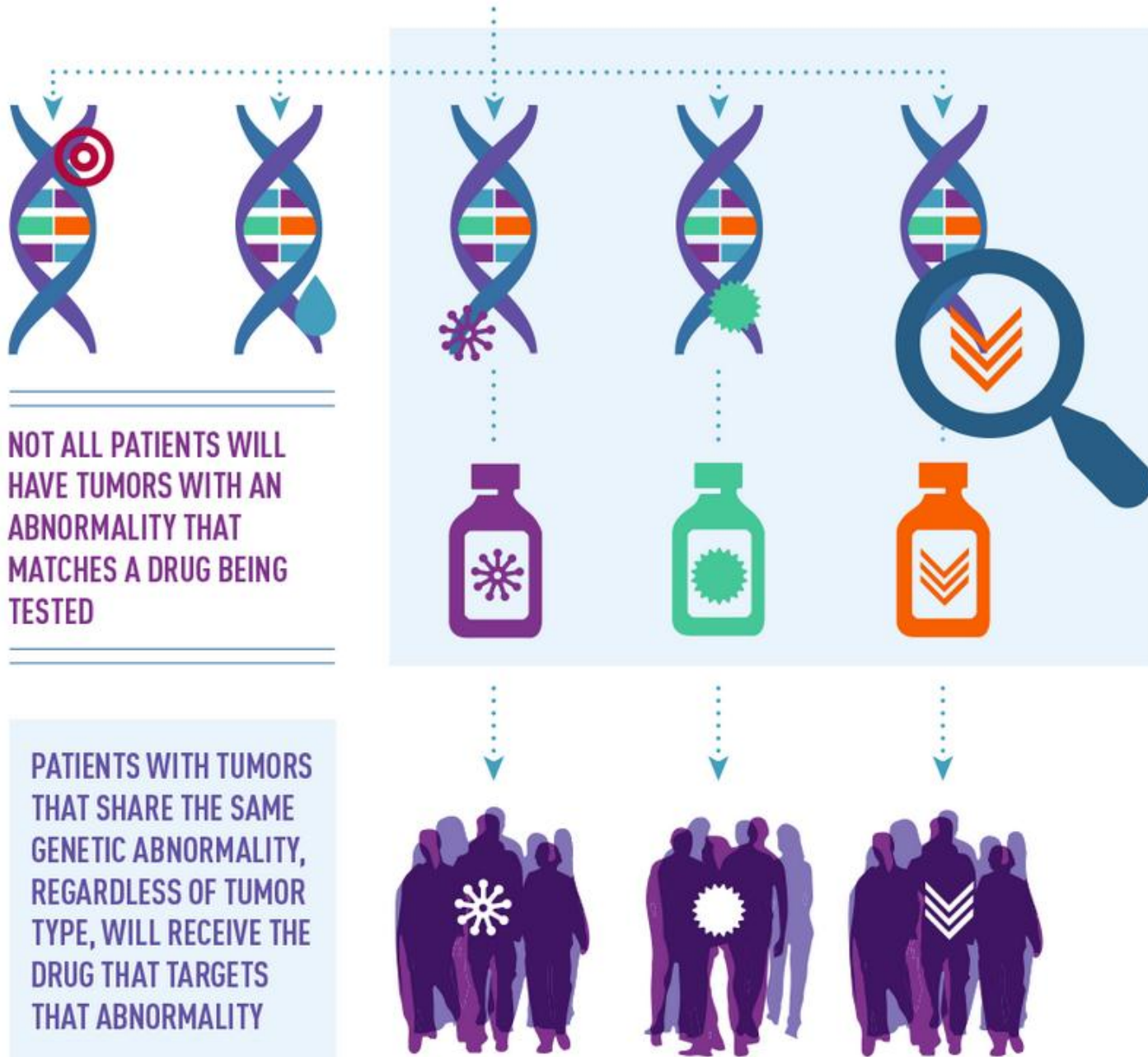


GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

THE BIOPSIED
TUMOR TISSUE
WILL UNDERGO
GENE
SEQUENCING



IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH



NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY



Thank You