THE CLEARITY FOUNDATION

Transforming treatment and improving survival for ovarian cancer patients

March 25, 2012

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Overview

- Introduction to Clearity Foundation
- Clearity profiling panel
- Interpretation of results utilizing the Diane Barton Database
- Case studies
  - Patient in second recurrence that went on to receive chemotherapy
  - Patient in first recurrence that went onto a clinical trial of a molecular-targeted agent combined with chemotherapy
  - Recurrent vs primary specimens
- Utilizing the TCGA groupings for selection of clinical trials
  - Case study of BRCAness
- Q&A

THE CLEARITY FOUNDATION

The Clearity Foundation launched as a non-profit organization in 2008 to:

- **Bring molecular profiling to the forefront of ovarian cancer diagnosis and treatment**
- **Assist doctors in priorizing therapy for recurrent ovarian cancer informed by their patient's tumor molecular profile**
- **Expedite the clinical development of novel targeted agents for ovarian cancer**
- **Increase the probability of success by utilizing molecular profiling to select patients for clinical trials**

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Leading advisors and scientific findings presented

Scientific Advisory Board	
Beth Karlan, MD, Chair	Cedars Sinai & UCLA Medical Center
Doug Levine, MD	Memorial Sloan Kettering Cancer Center
Johnathan Lancaster, MD	Moffitt Cancer Center
Julie Cherrington, PhD	Pathway Therapeutics
Ursula Matulonis, MD	Dana Farber Cancer Center & Harvard Medical School
Deb Zajchowski, PhD	Clearity Foundation Scientific Director

Mol Cancer Ther; 11(2) February 2012: **Treatment-related protein biomarker expression differs between primary and recurrent ovarian carcinomas** DA Zajchowski, BY Karlan and LK Shawver

ASCO 2011: Expression Profiles in Matched Primary and Recurrent Ovarian Carcinomas DA Zajchowski, BY Karlan and LK Shawver,

AACR 2011: Molecular Profiling in Recurrent Ovarian Cancer Patients DA Zajchowski, C Bentley, J Gross, BY Karlan and LK Shawver

AACR 2010: Selecting Patients for Ovarian Cancer Clinical Trials by Profiling Tumors against a Broad Panel of Molecular Markers DA Zajchowski, J Gross, BY Karlan, K Bloom, D Loesch, A Alarcon and LK. Shawver

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Accomplishments in less than four years

- Developed diagnostic protocols with latest technologies and input from expert advisors
- Created the Diane Barton Database, a platform for:
  - Compiling test results from multiple labs
  - Tracking patient outcomes
  - Establishing assay cut-points to prioritize treatment options
  - Utilizing markers for clinical trial enrollment
  - Comparing tumor profiling results from patient to patient
- Formed web-based informational tools and patient support process
- Provided access to molecular profiling for ~200 women with ovarian cancer

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How we work

Oncologists and Patients

Clearity Profiling Services:

- Physician and patient education
- Coordination with CLIA labs to test
- Secure database for patient data
- Data integration/ analysis
- Results reporting

Medical team utilizes molecular profiles to prioritize therapeutic options

6

Multiple choices for recurrent disease

Can we inform the treatment decision?

NCCN Guidelines for Epithelial Ovarian Cancer/Fallopian Tube Cancer/Peritoneal Cancer 2.2.2011

ACCEPTABLE RECURRENCE THERAPIES (1 of 2)[1]

Agents	Cytotoxic Therapy	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Agents	Combination if platinum sensitive Carboplatin/paclitaxel (category 1)[2,3] Carboplatin/weekly paclitaxel[2,4] Carboplatin/docetaxel[2,5,6] Carboplatin/gemcitabine[2,7] Carboplatin/liposomal doxorubicin[2,8] Cisplatin/gemcitabine[2,9] Single-agent if platinum sensitive Carboplatin[7] Cisplatin[7] Single-agent non-platinum based if platinum resistant Docetaxel[10] Etoposide, oral[11] Gemcitabine[12,13] Liposomal doxorubicin[12,13] Paclitaxel, weekly[14] Topotecan[15]		Bevacizumab	
Other Potentially Active Agents	Single Agents[16] Altretamine Capecitabine Cyclophosphamide Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Anastrozole Letrozole Leuprolide acetate Megestrol acetate Tamoxifen		Palliative localized radiation therapy

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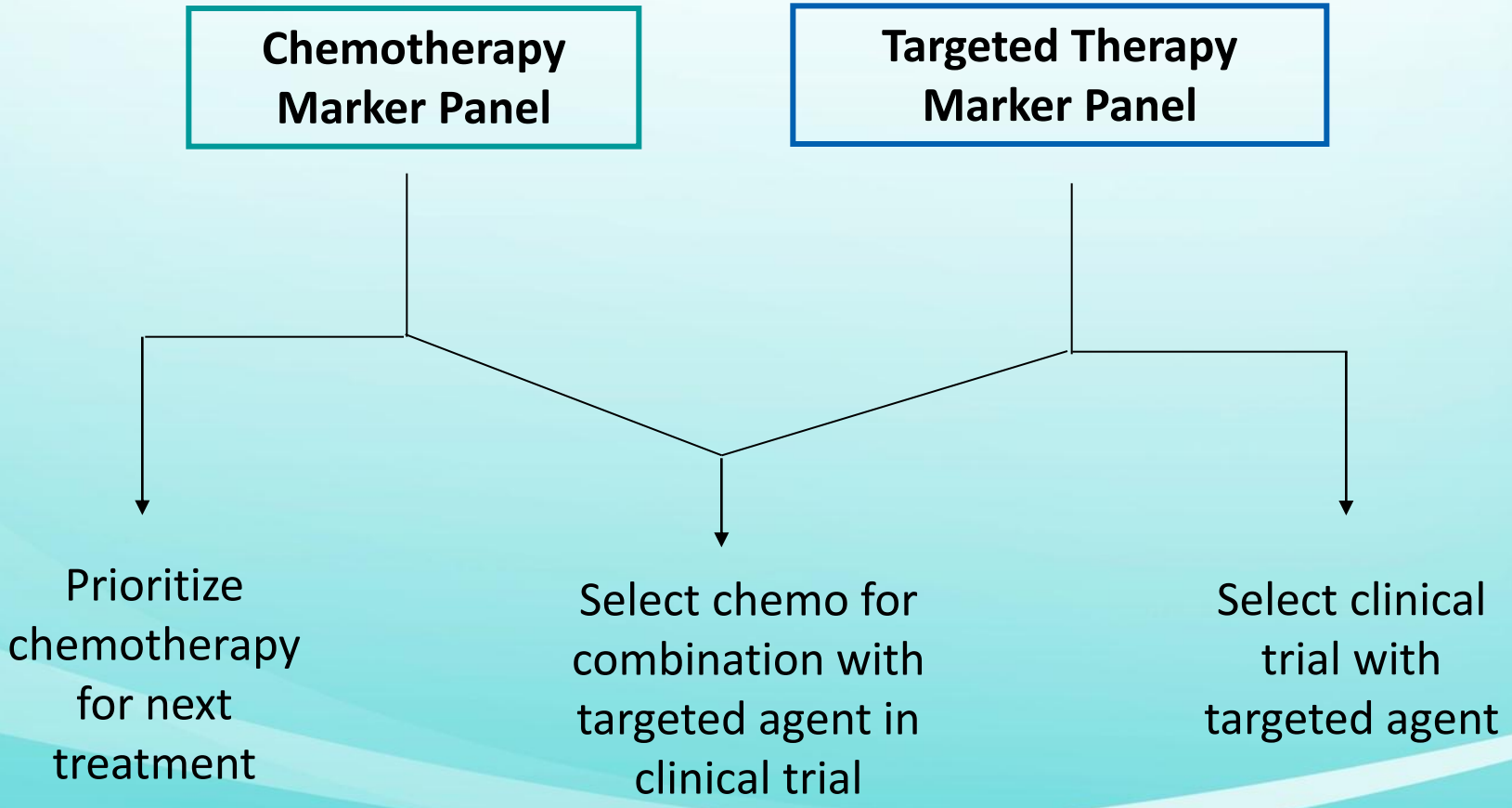
Use tumor molecular profiles to prioritize choice of chemotherapy and/or clinical trial



Current panel of tests

Growth Factors/ Receptors					
EGFR*	Her2*	IGF1R	c-Met	VEGF	PDGFR

Cytoplasmic Signal Transducers and Apotosis Regulators						
K-ras**	B-raf**	PIK3CA**	PTEN	Bcl-2	Survivin	Cox-2

Nuclear Signaling Proteins							
Hormone Receptors/Transcription Factors				Cell Cycle			
ER	AR	PR	HIF1A	Ki67	p21	p16	Rb

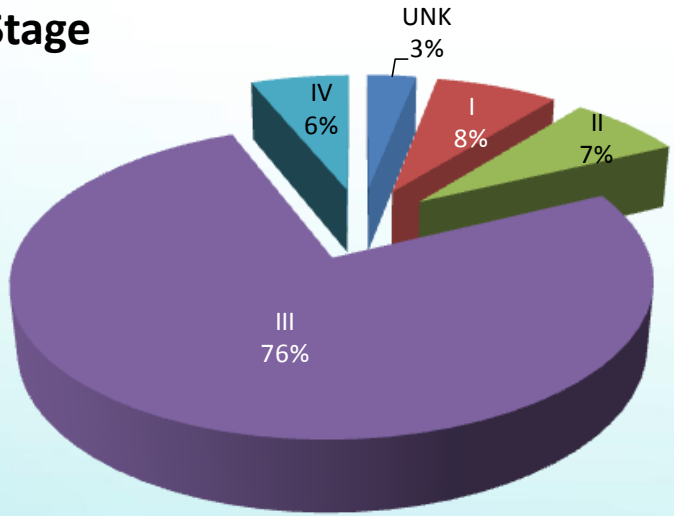
Chemotherapy Sensitivity Markers			
DNA Synthesis/Transcription			ECM
TLE3	Topo1	Top2A	SPARC

Chemotherapy Resistance Markers							
Drug Transporters			DNA Repair/ Modification		DNA Synthesis/Cell Division		
BCRP	MRP1	MDR1/PGP	ERCC1	MGMT	RRM1	TS	TUBB3

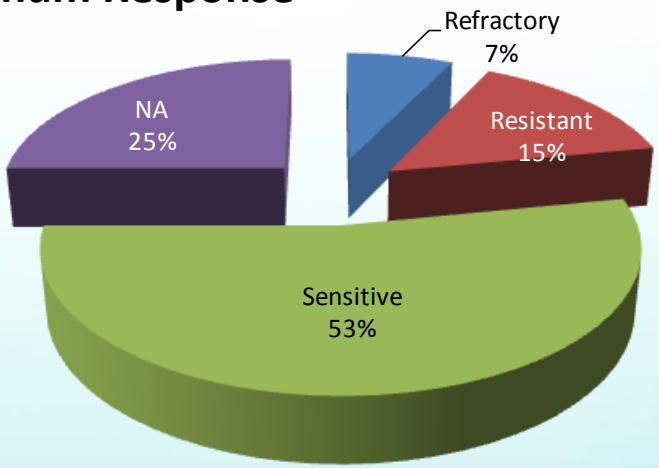
* DNA amplification ** DNA mutational analysis

Data stored and analyzed in Diane Barton Database

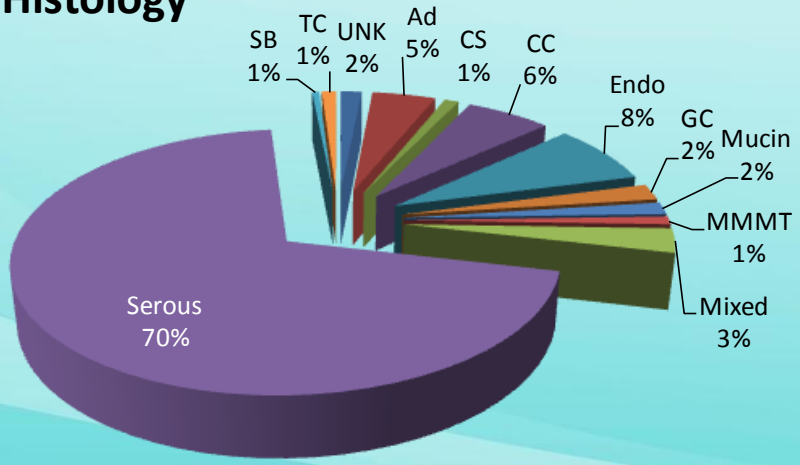
Stage



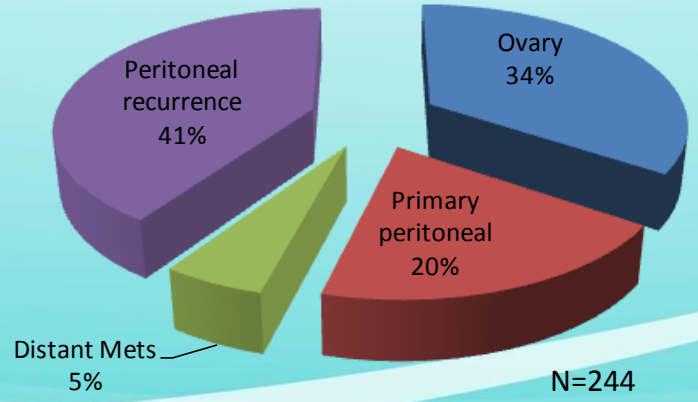
Platinum Response



Histology



Specimen Source



*196 patients, February, 2012

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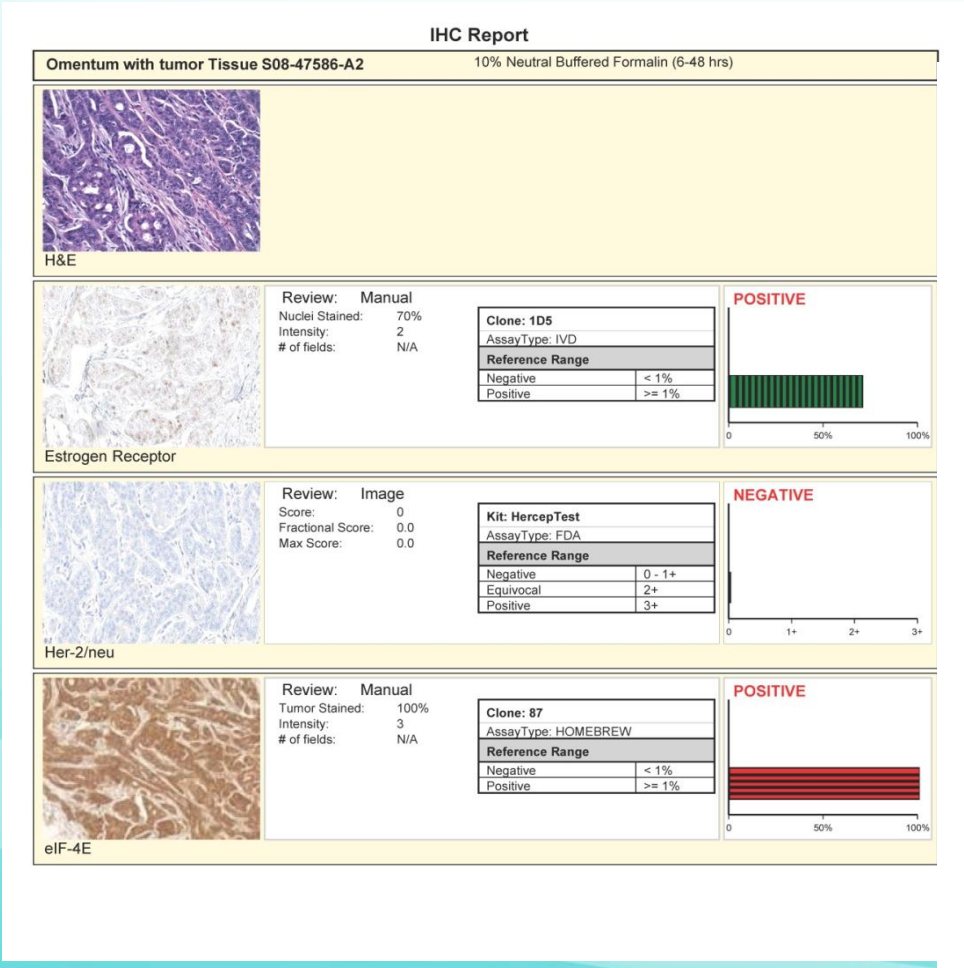
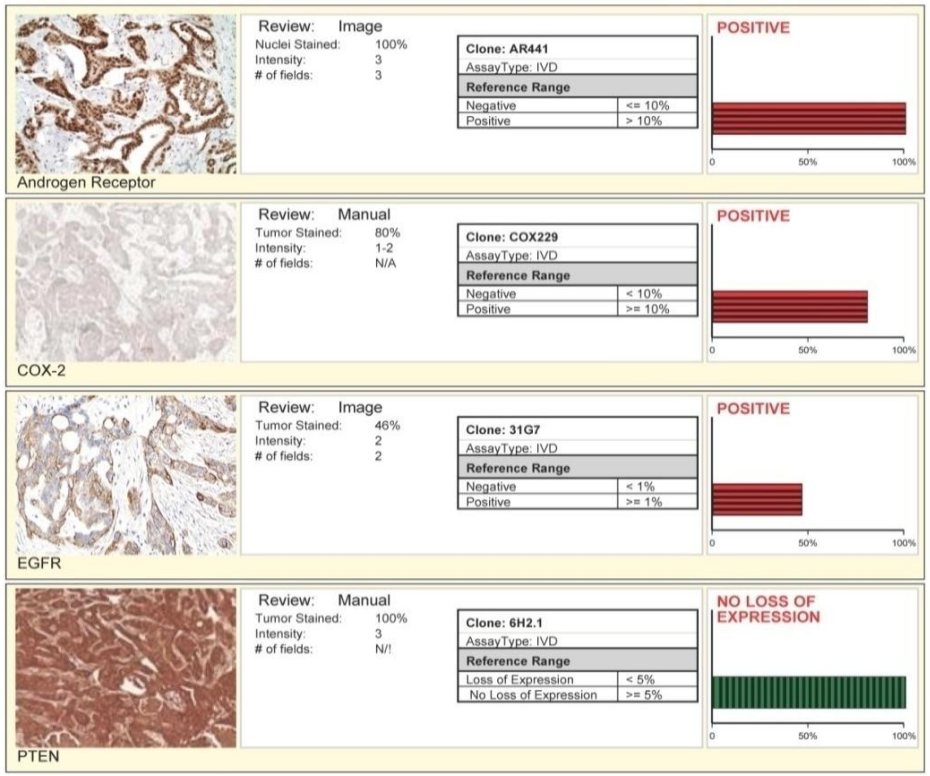
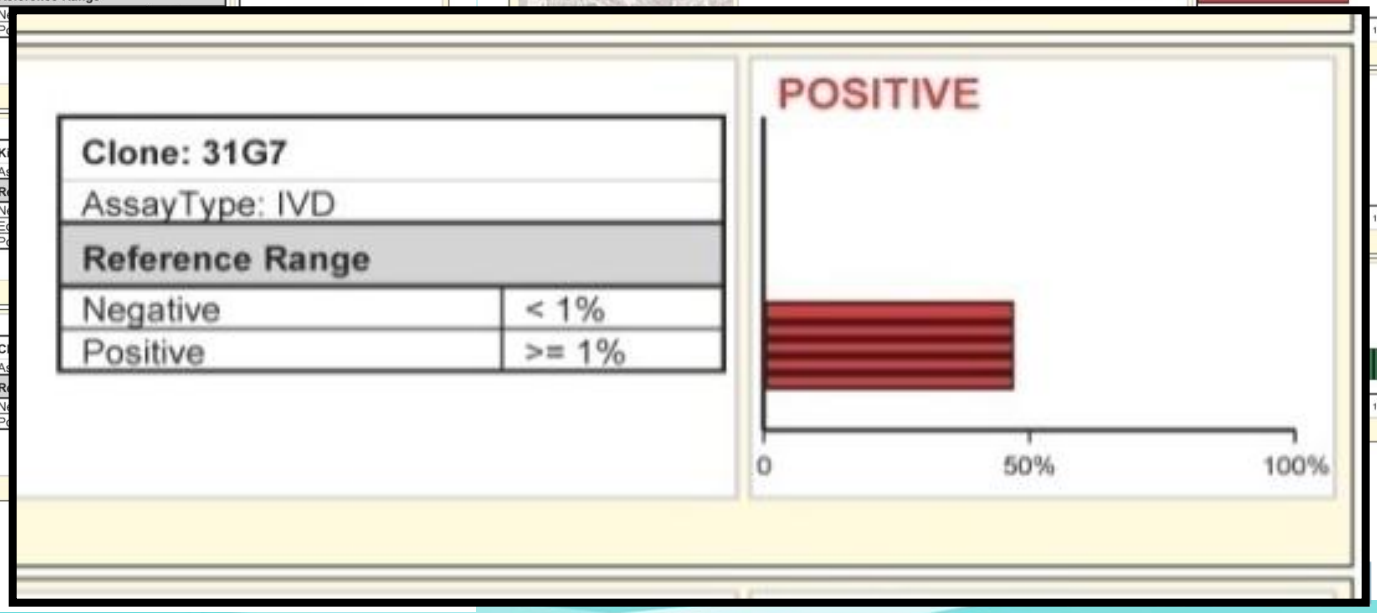
Example laboratory read-out for IHC





Data collected as histoscores

Histoscore =
% tumor stained x
Intensity =92



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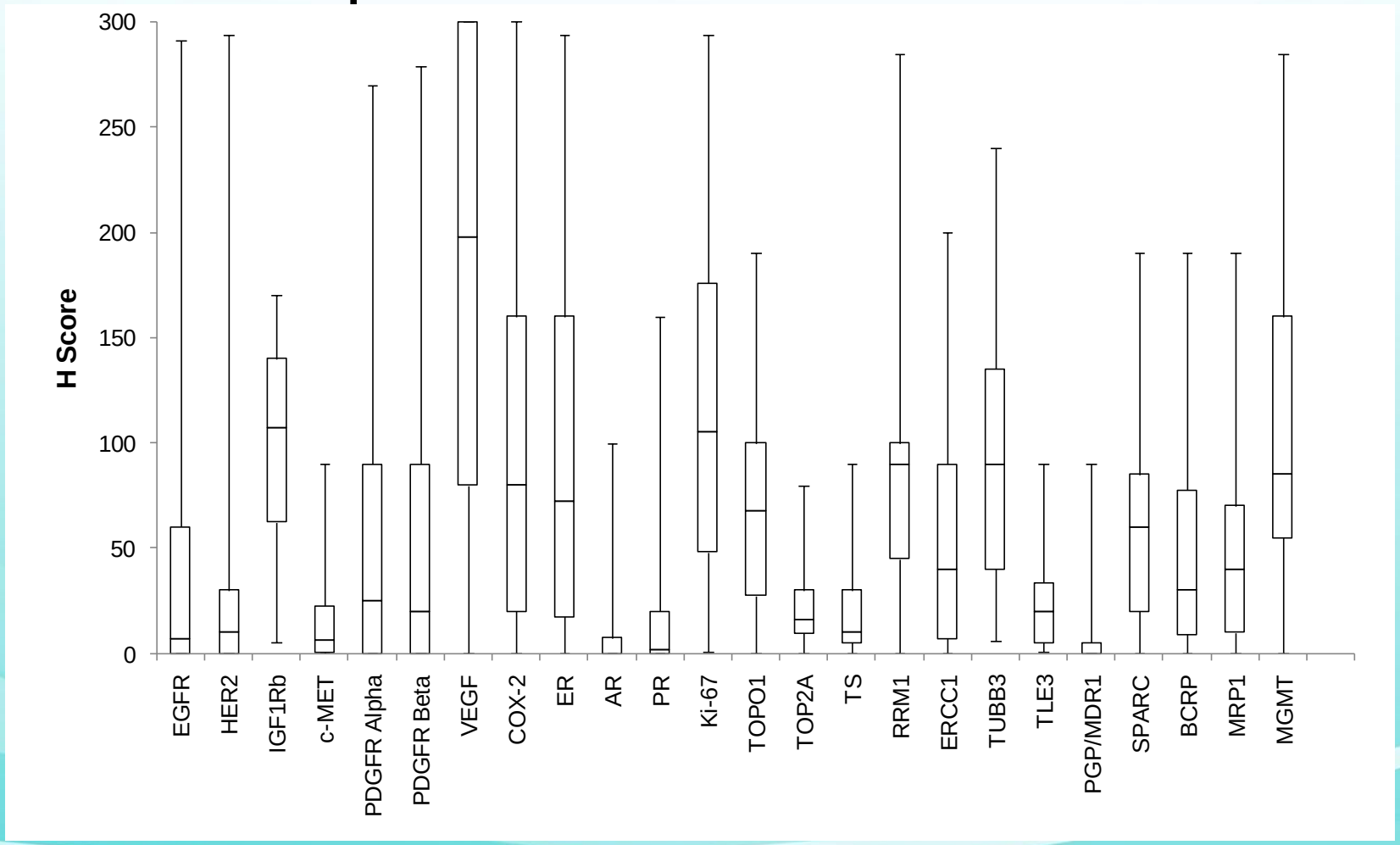
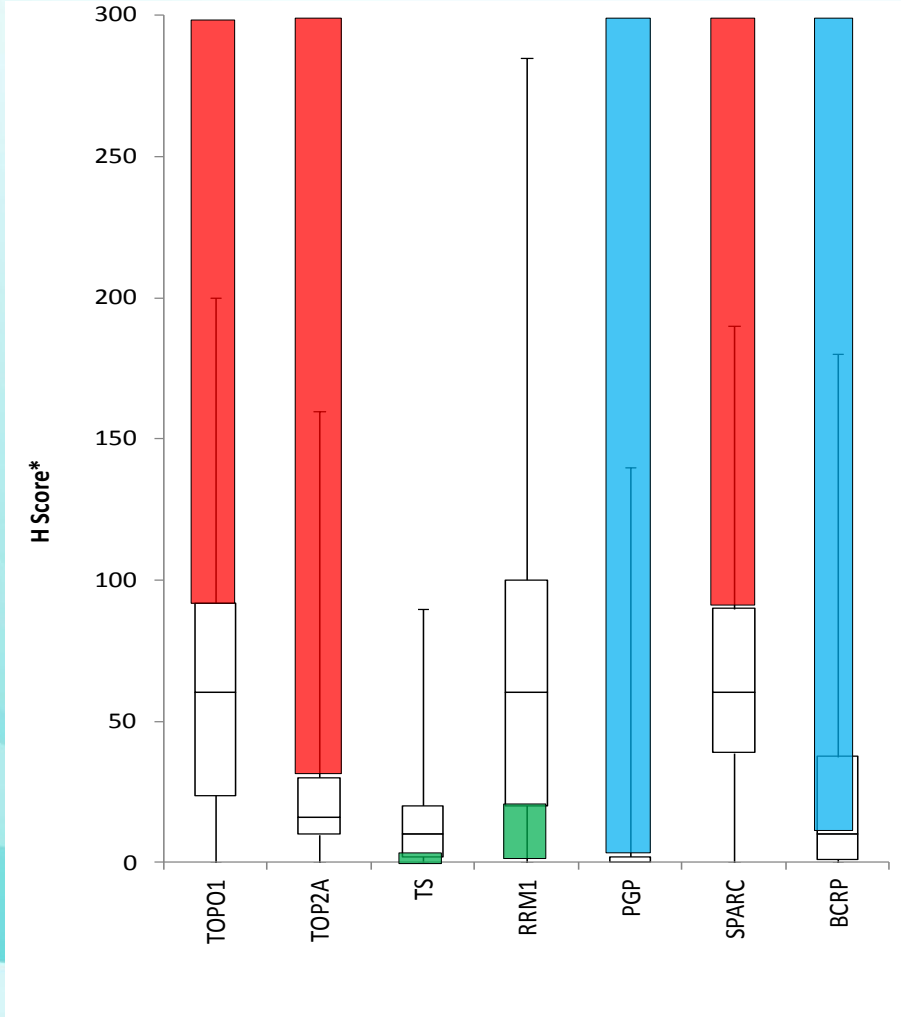
Marker expression in all patients provides basis for interpretation of individual results



Box, inter-quartile range; line, median; whiskers, maximum and minimum values

Chemotherapy selection using published evidence and expression cut-offs derived from current database



High Topo I → Irinotecan, topotecan

High Topo II → Doxorubicin, etoposide

Low RRM1 → Gemzar

Low TS → Fluoropyrimidines

High SPARC→ nab-Paclitaxel

High PGP → No Taxane, no doxil

High BCRP → No Topotecan

Low: <25th percentile High: >75th percentile

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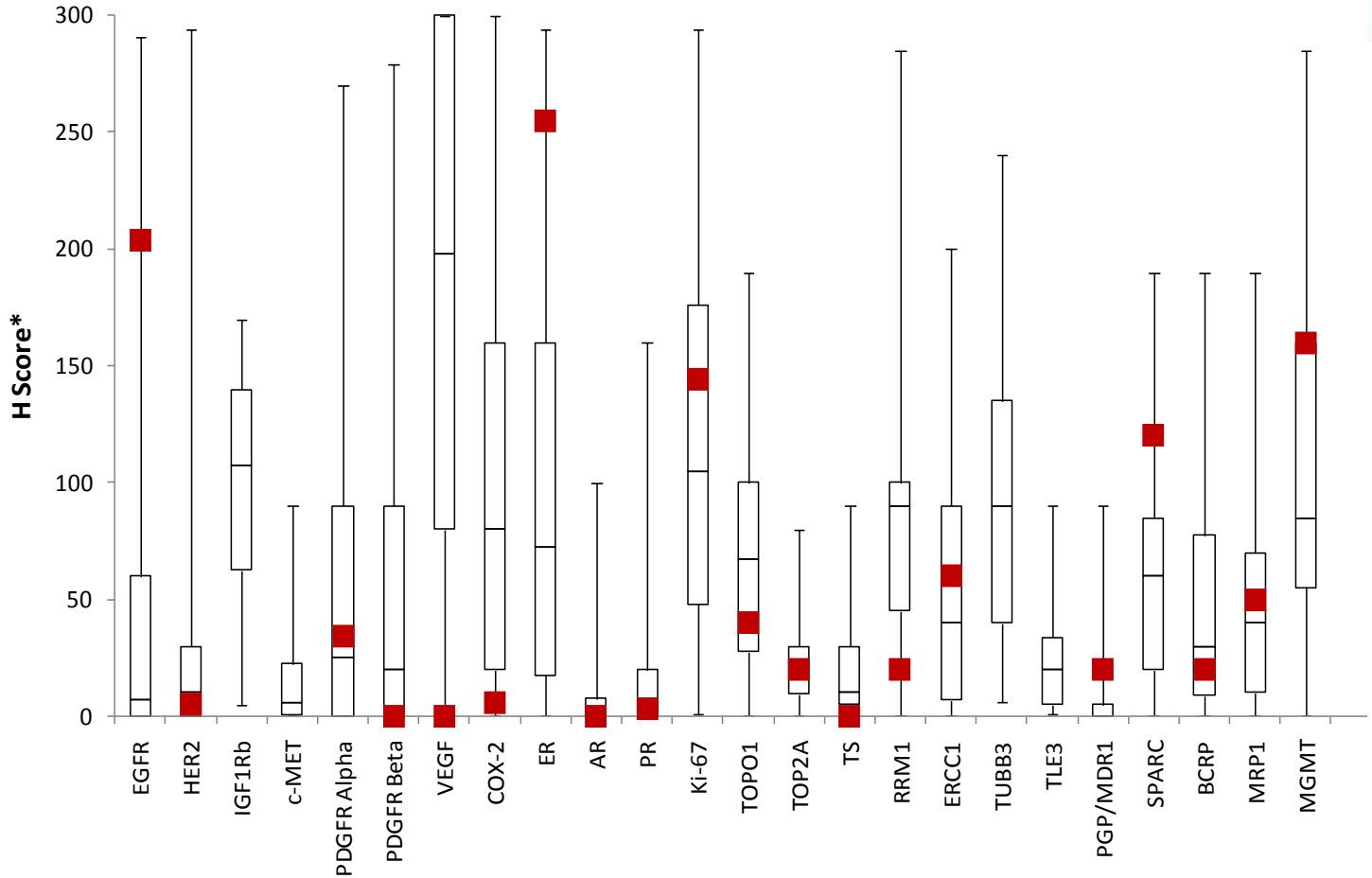
Case Study: profile for patient diagnosed in 3/2005 with stage IIIB papillary serous carcinoma



3/2005
Carbo/tax x6
↓
taxol 10 mos
↓
recurrence 12/2008
carbo/tax x 6
↓
carbo/tax/bev x3
↓
12/2009
Doxil x3
↓
Surgery 1/2010
↓
Tumor Profiled

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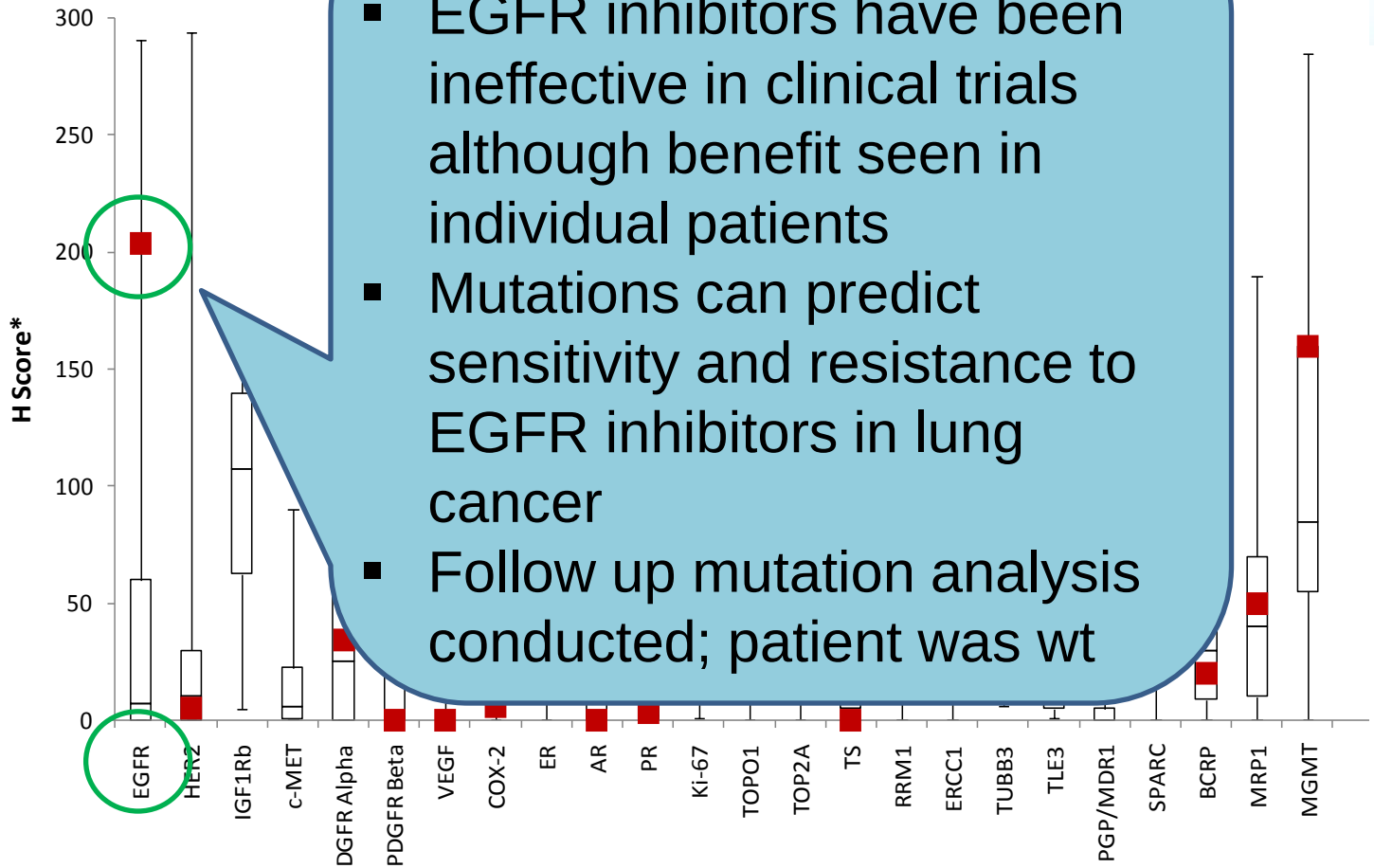
Case Study: profile for patient diagnosed in 3/2005 with [illegible]arcinoma



High EGFR (98th percentile)

- EGFR inhibitors have been ineffective in clinical trials although benefit seen in individual patients
- Mutations can predict sensitivity and resistance to EGFR inhibitors in lung cancer
- Follow up mutation analysis conducted; patient was wt

3/2005
Carbo/tax x6
↓
taxol 10 mos
↓
recurrence 12/2008
carbo/tax x 6
↓
carbo/tax/bev x3
↓
12/2009
Doxil x3
↓
Surgery 1/2010
↓
Tumor Profiled

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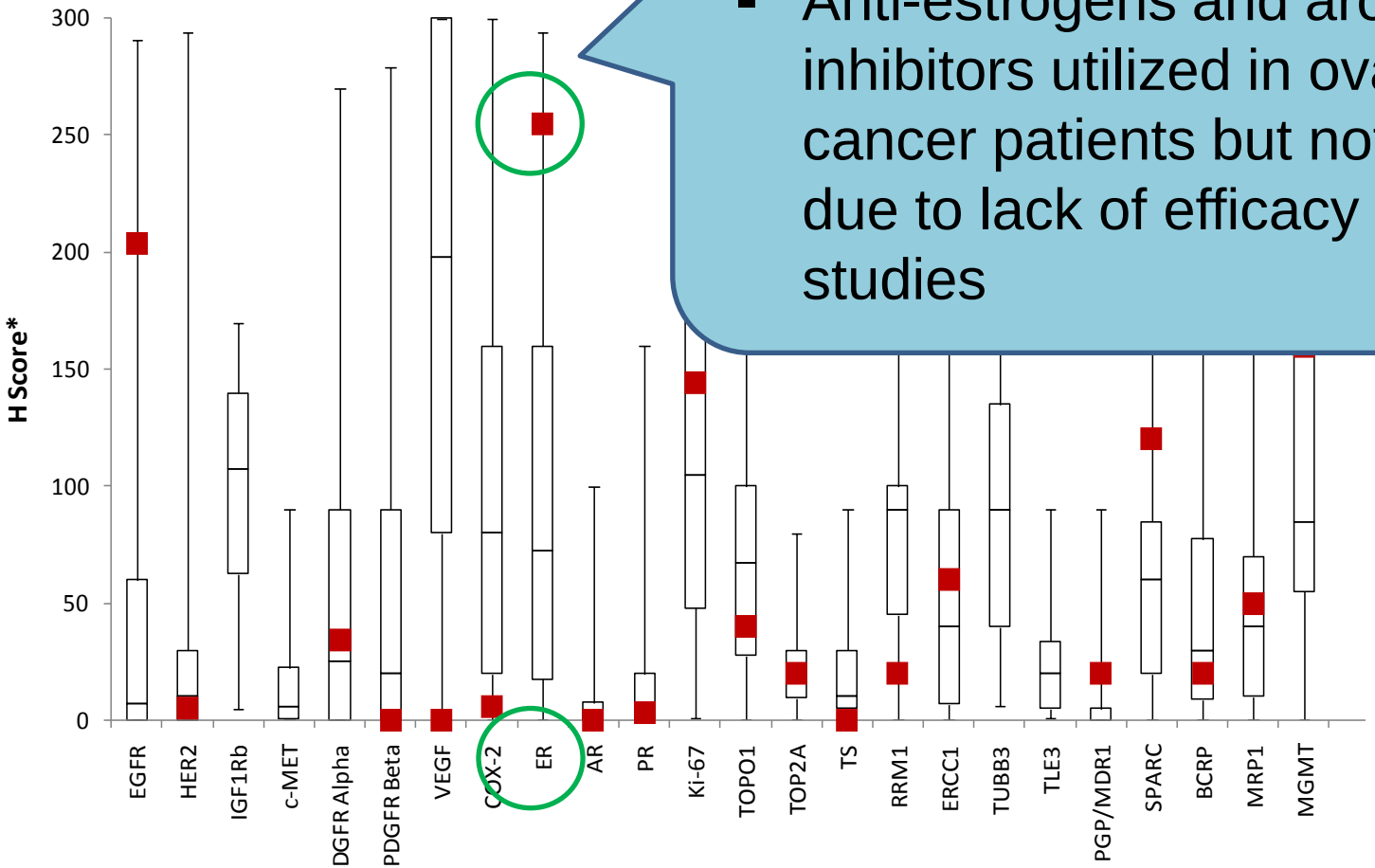
Case Study: profile for patient diagnosed in 3/2005 with stage IIIB

High ER

- Anti-estrogens and aromatase inhibitors utilized in ovarian cancer patients but not approved due to lack of efficacy in clinical studies



8

carbo/tax/bev x3

12/2009
Doxil x3

Surgery 1/2010

Tumor Profiled

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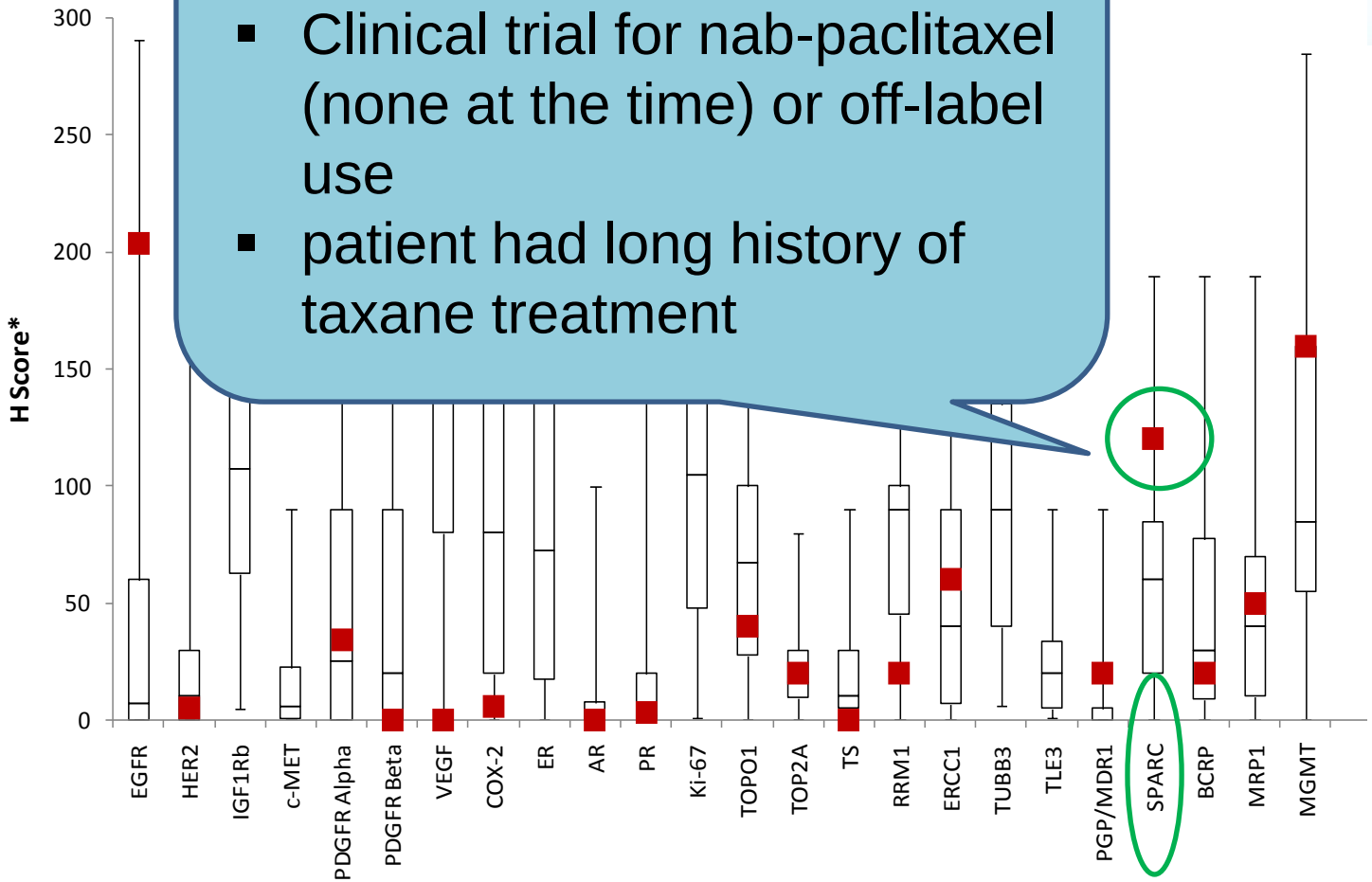
Case Study: profile for patient diagnosed in 3/2005 ... us carcinoma

High SPARC

- Clinical trial for nab-paclitaxel (none at the time) or off-label use
- patient had long history of taxane treatment



3/2005
Carbo/tax x6
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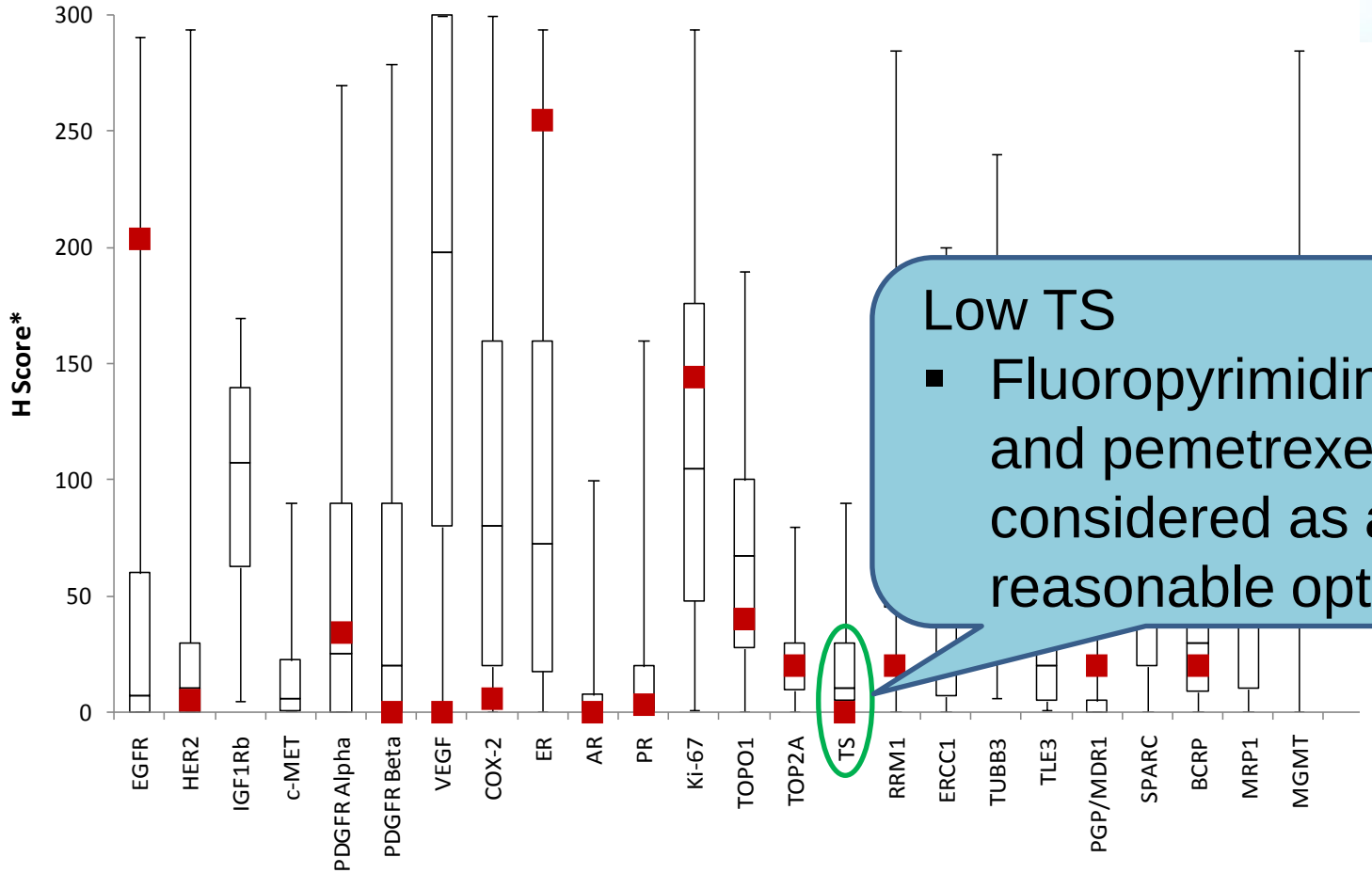
carbo/tax x 6
↓
carbo/tax/bev x3
↓
12/2009
Doxil x3
↓
Surgery 1/2010
↓
Tumor Profiled

Case Study: profile for patient diagnosed in 3/2005 with stage IIIB papillary serous carcinoma

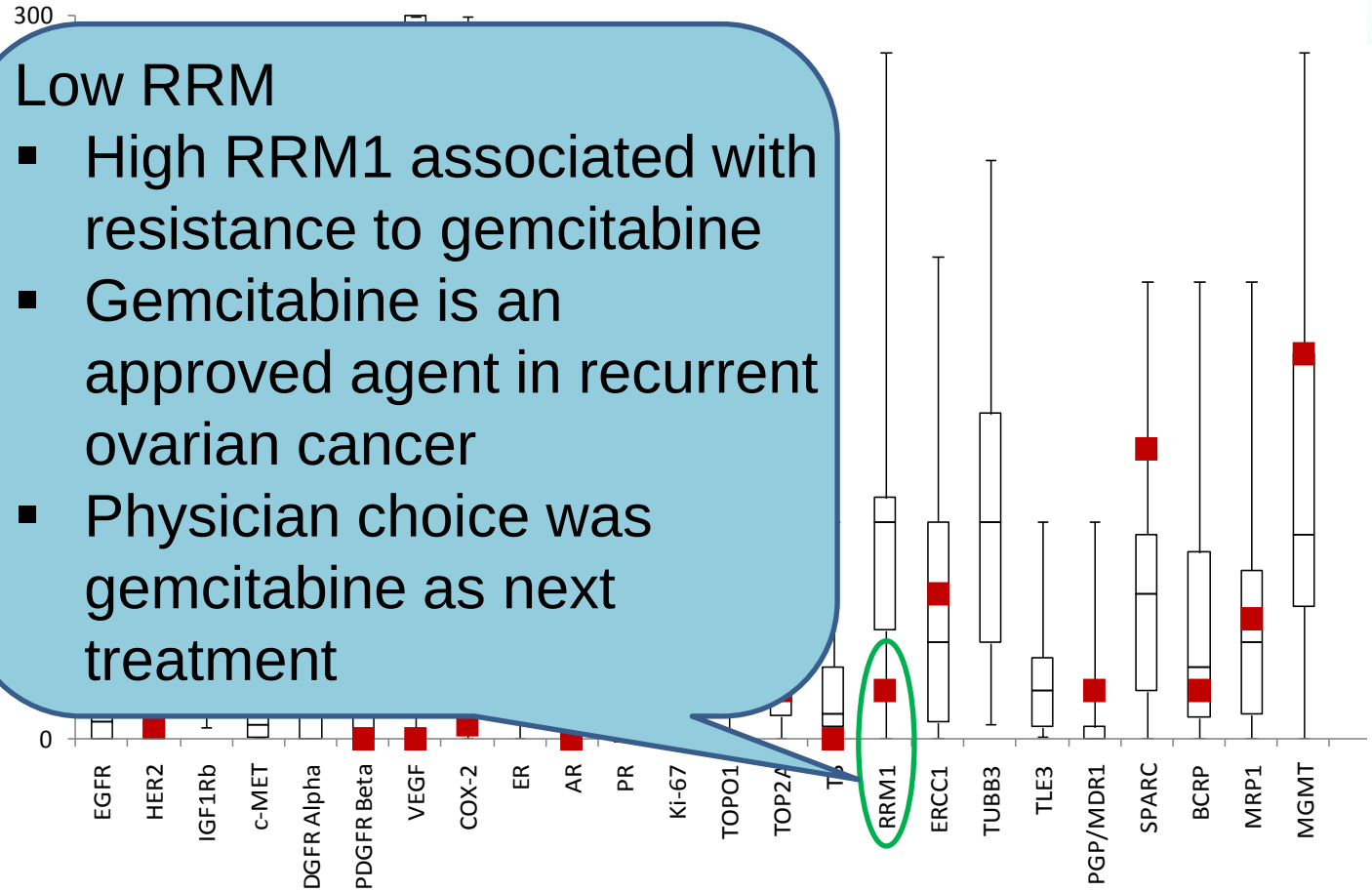


Low TS

- Fluoropyrimidines and pemetrexed considered as a reasonable option

3/2005
Carbo/tax x6
↓
taxol 10 mos
↓
nce 12/2008
o/tax x 6
↓
tax/bev x3
↓
2/2009
oxil x3
↓
Surgery 1/2010
↓
Tumor Profiled

Case Study: profile for patient diagnosed in 3/2005 with stage IIIB papillary serous carcinoma



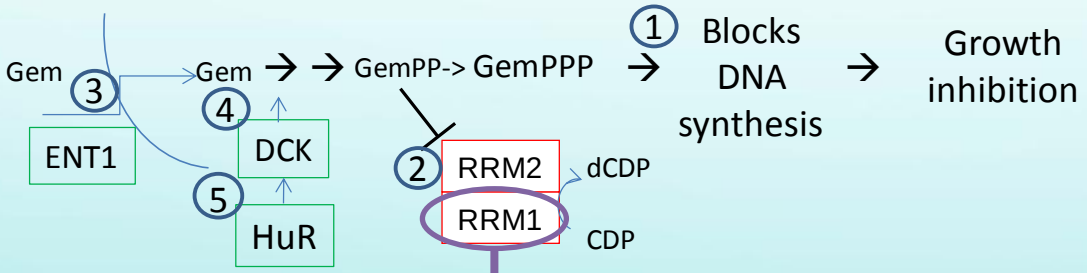
Low RRM

- High RRM1 associated with resistance to gemcitabine
- Gemcitabine is an approved agent in recurrent ovarian cancer
- Physician choice was gemcitabine as next treatment

3/2005
Carbo/tax x6
↓
taxol 10 mos
↓
recurrence 12/2008
carbo/tax x 6
↓
carbo/tax/bev x3
↓
12/2009
Doxil x3
↓
Surgery 1/2010
↓
Tumor Profiled

Chemotherapy as targeted agents - clinical research evidence

Drug	Mechanism of Action
Gemcitabine	Inhibits cell division by blocking DNA synthesis

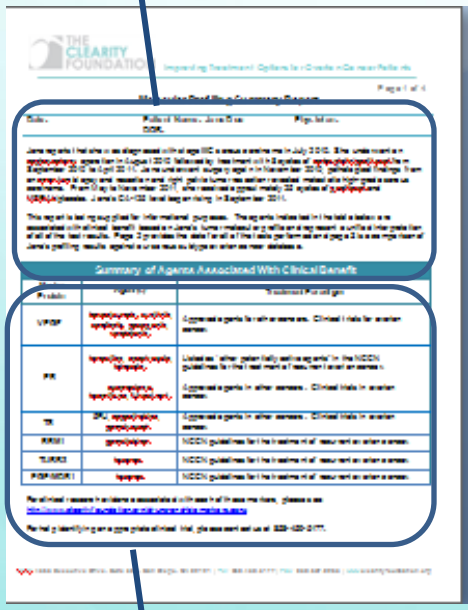


Gemcitabine Resistance Markers				
Marker	**Name**	**Biological Role**	**Evidence**	**References**
RRM1	ribonucleotide reductase, regulatory subunit M1	Enzyme synthesizes deoxyribonuceosides from ribonucleoside precursors	High protein levels associated with poor response and outcome in pancreatic, biliary, and NSCLC patients after gemcitabine-based therapy	Akita, Zheng et al. 2009; Reynolds, Obasaju et al. 2009; Nakamura, Kohya et al. 2010

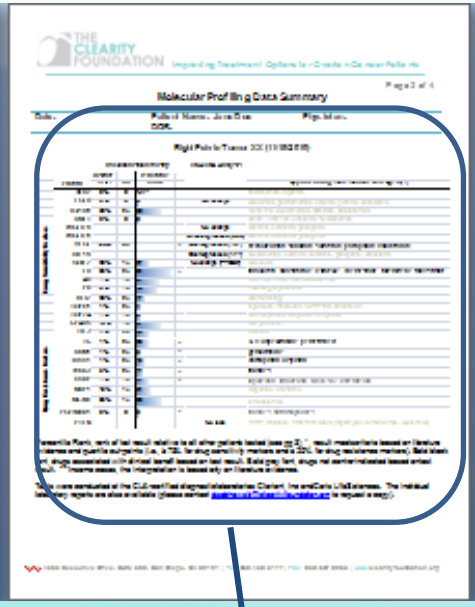
For information on each marker, visit http://www.clearityfoundation.org/drugs-and-biomarkers.aspx

Clearity molecular profiling summary report

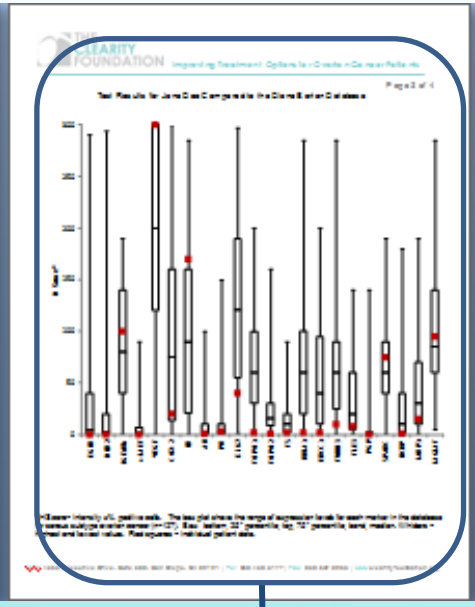
Summary of relevant patient medical history



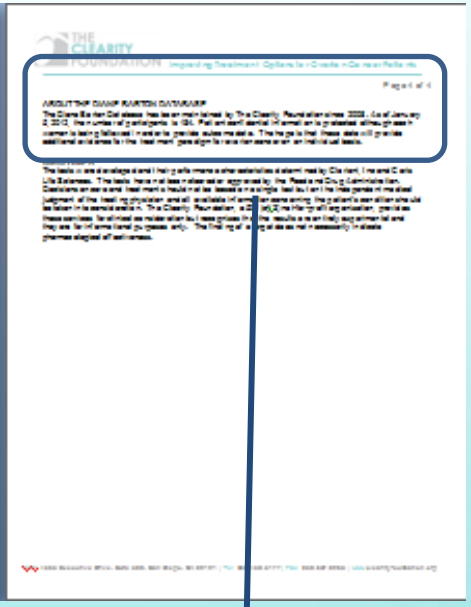
Summary of agents associated with clinical benefit extracted from pg 2



Compilation of data from all labs with interpretation (percentile rank, potential drugs)

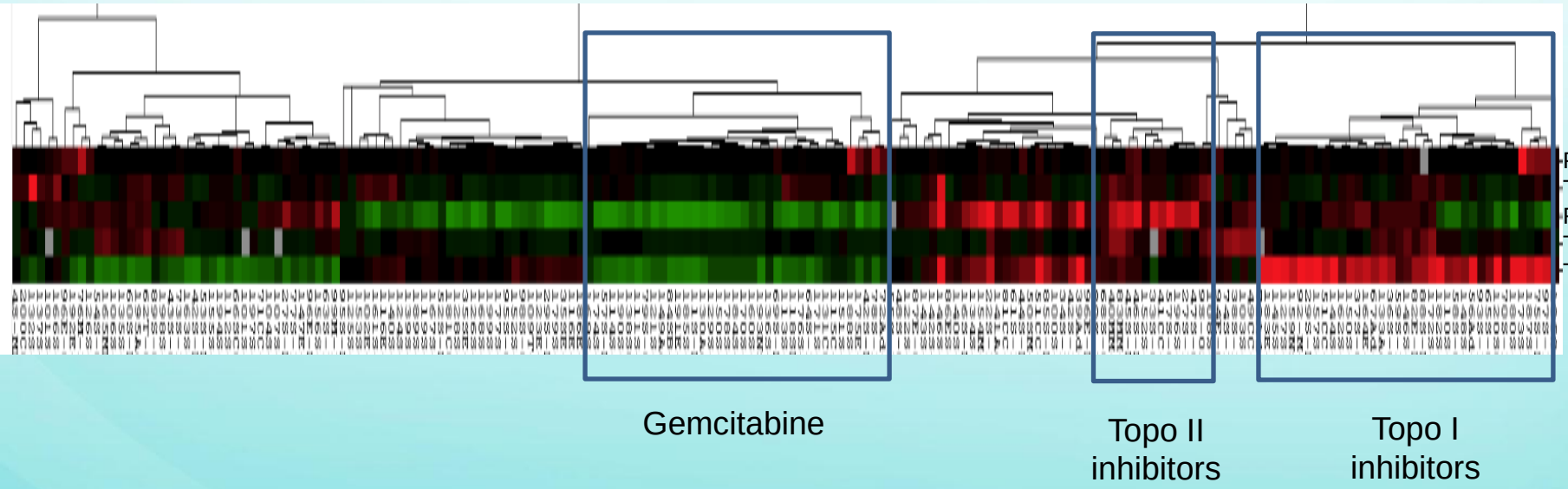


Individual profile compared to ovarian cancer population



Number of patients whose data are included in Diane Barton Database

Often, only one of the commonly used agents to treat recurrent ovarian cancer is prioritized by the profile



*Unsupervised hierarchical clustering analysis of protein expression (n=189)

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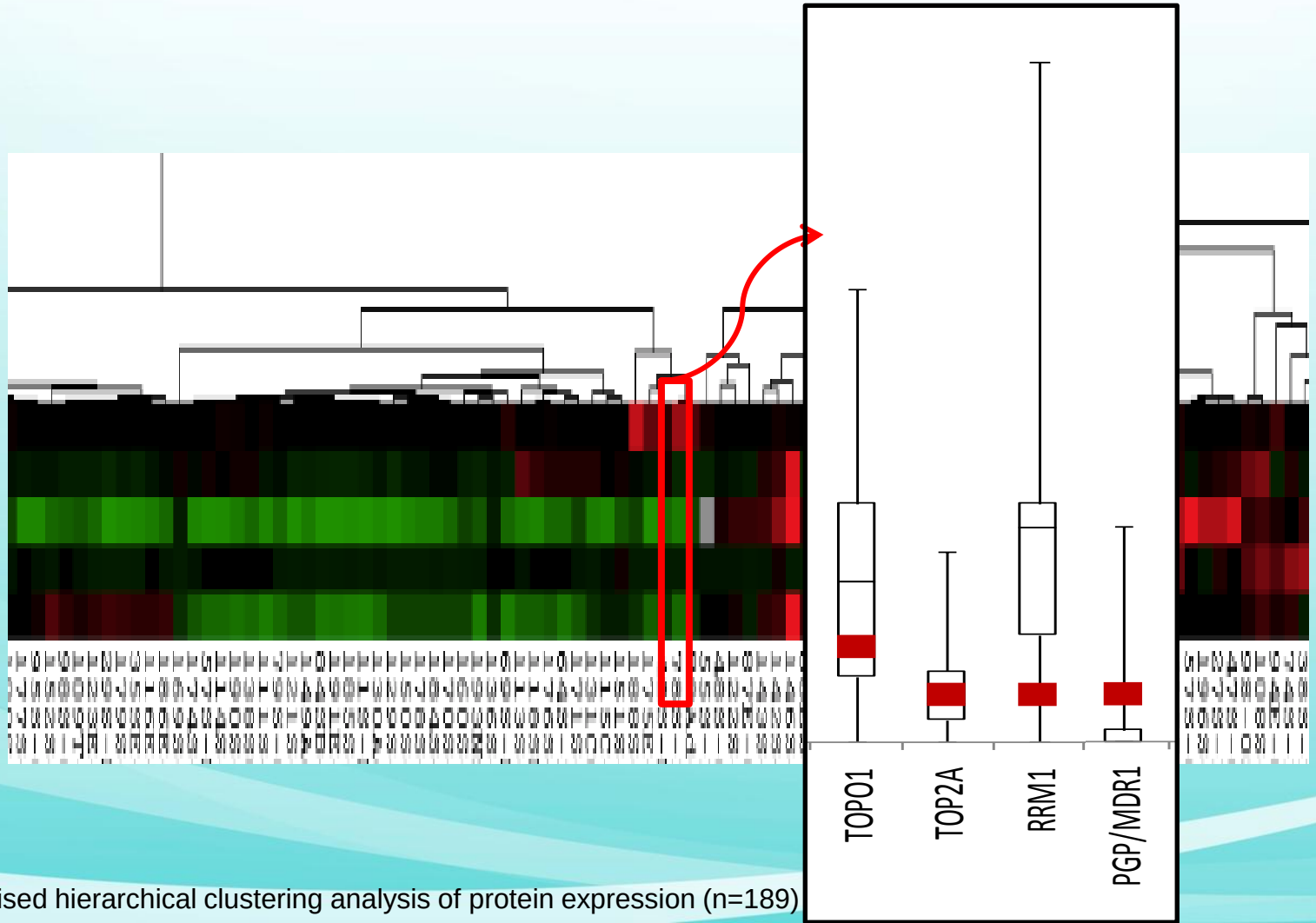
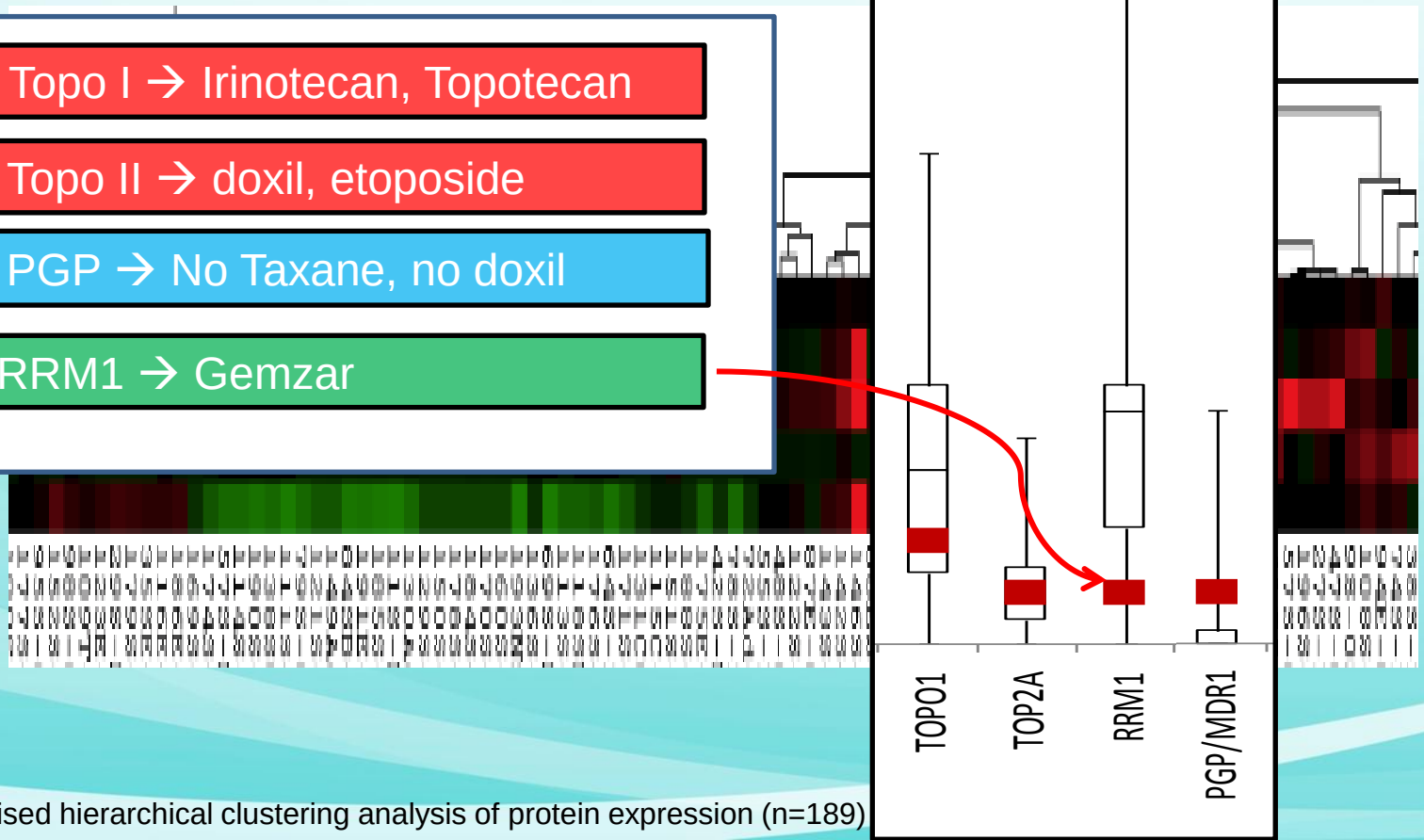
Often, only one of the commonly used agents to treat recurrent ovarian cancer is prioritized by the profile



*Unsupervised hierarchical clustering analysis of protein expression (n=189)

Often, only one of the commonly used agents to treat recurrent ovarian cancer is prioritized by the profile

- High Topo I → Irinotecan, Topotecan
- High Topo II → doxil, etoposide
- High PGP → No Taxane, no doxil
- Low RRM1 → Gemzar



*Unsupervised hierarchical clustering analysis of protein expression (n=189)

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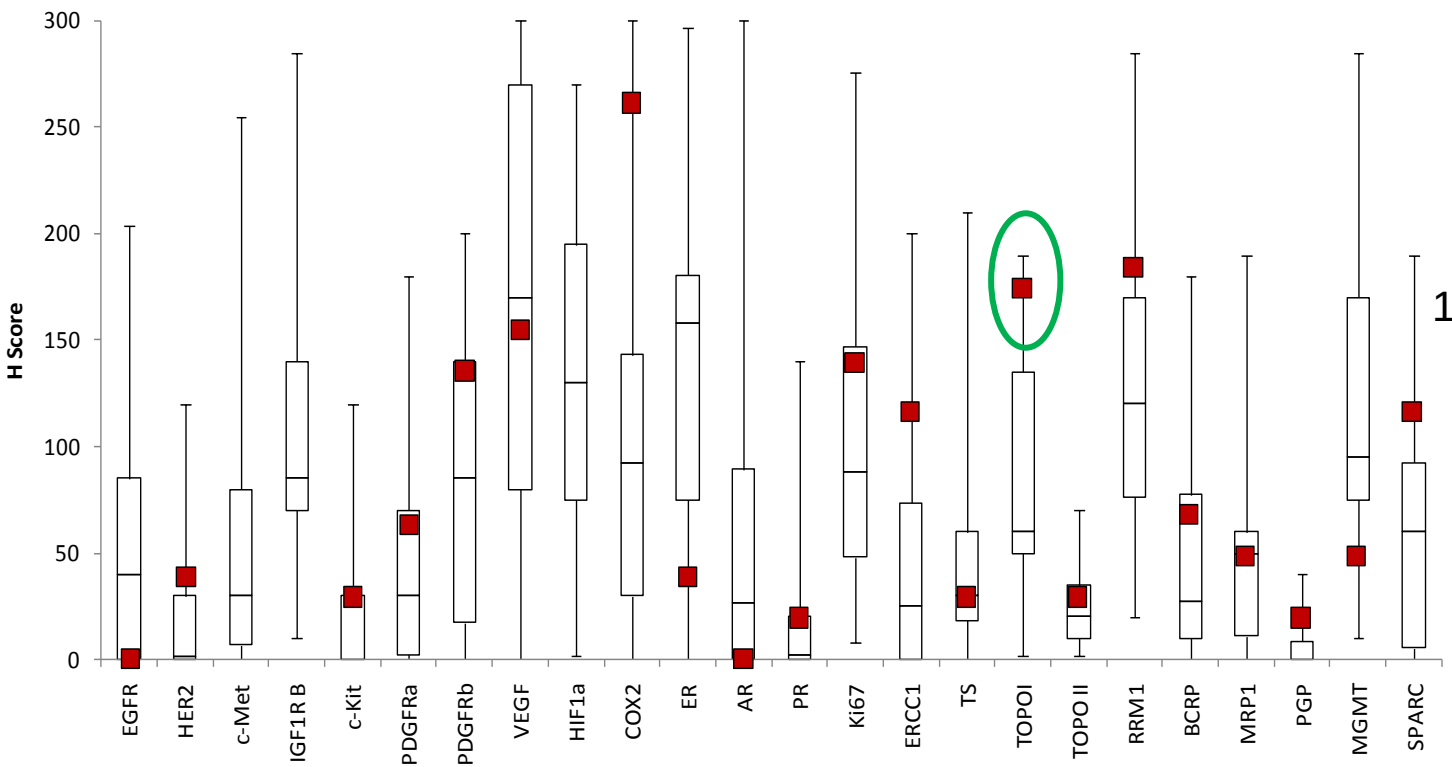
Case Study: profile for patient diagnosed in 2009 with stage IIIC clear cell carcinoma



4/2009
CDDP/tax (ip) x 3
Carbo/tax (iv) x3

↓

12/2009 recurrence

↓

Tumor profiled

↓

Topotecan +
AMG 386*
(clinical trial)

Biopsy of recurrent disease may be needed to obtain relevant profiling information

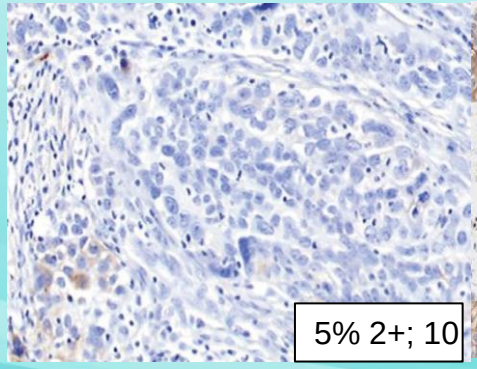
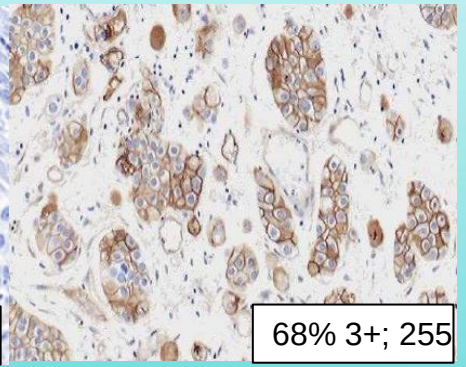
Mol Cancer Ther; 11(2) February 2012

Molecular Medicine in Practice

Molecular Cancer Therapeutics

Treatment-Related Protein Biomarker Expression Differs between Primary and Recurrent Ovarian Carcinomas

Deborah A. Zajchowski[1], Beth Y. Karlan[2], and Laura K. Shawver[1]

	Primary	Recurrence
EGFR	 5% 2+; 10	 68% 3+; 255

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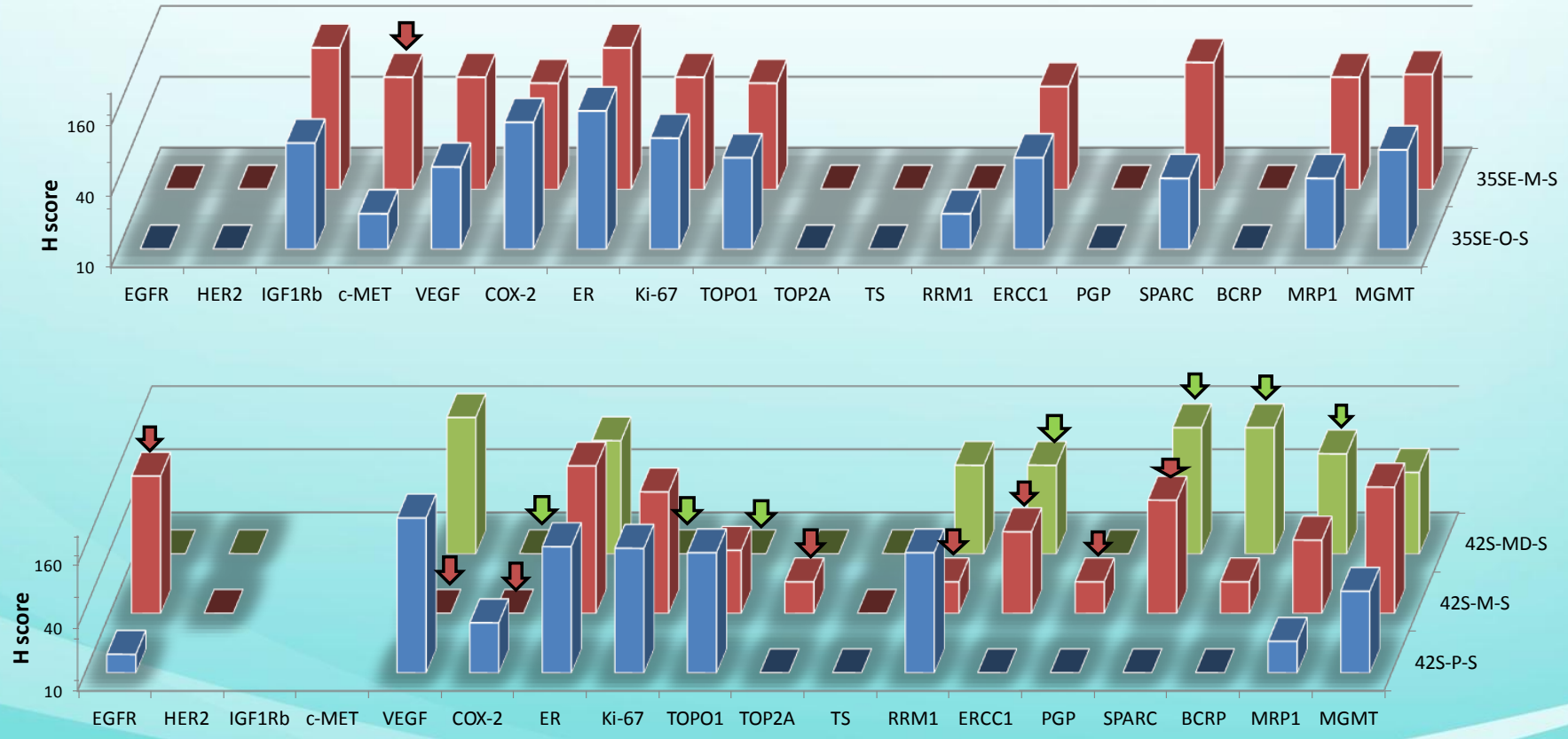
Marker expression differences in patient-matched primary and recurrent samples



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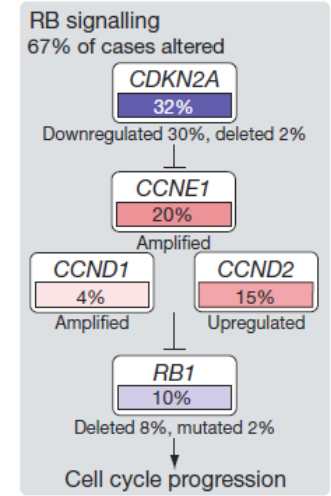
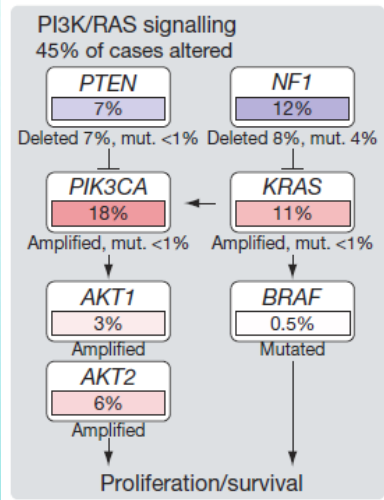
Low frequency of specific genetic aberrations → extensive interrogation necessary to characterize tumors

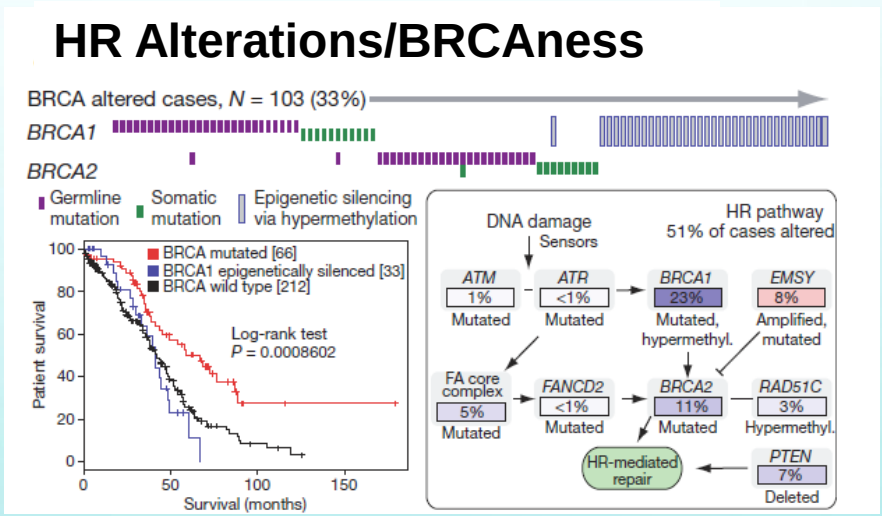
RB



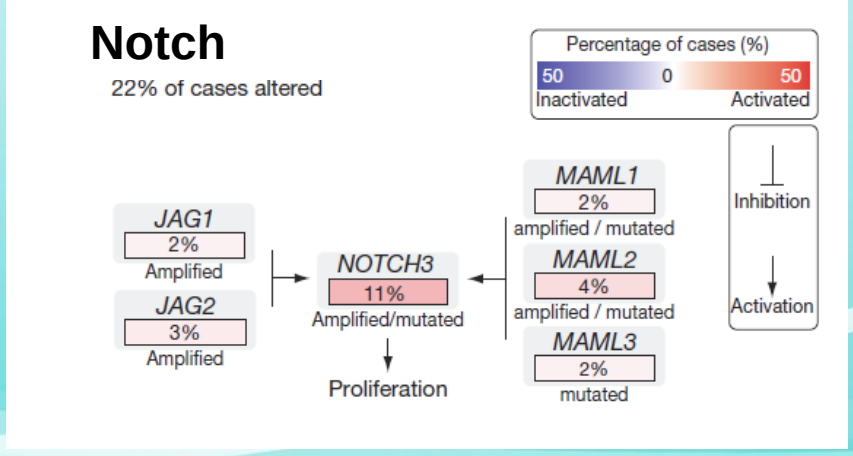
PI3K/RAS



HR Alterations/BRCAness



Notch



From TCGA study: Nature 474, 609- 615 (2011)

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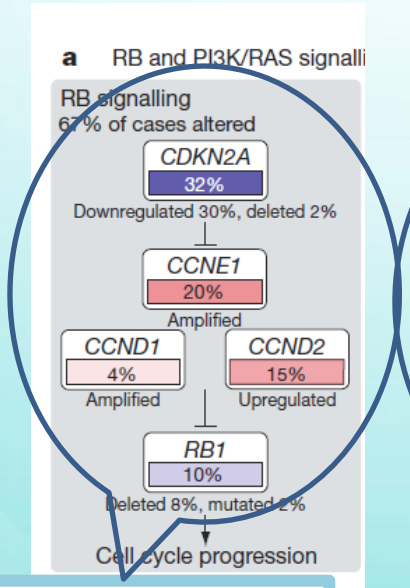
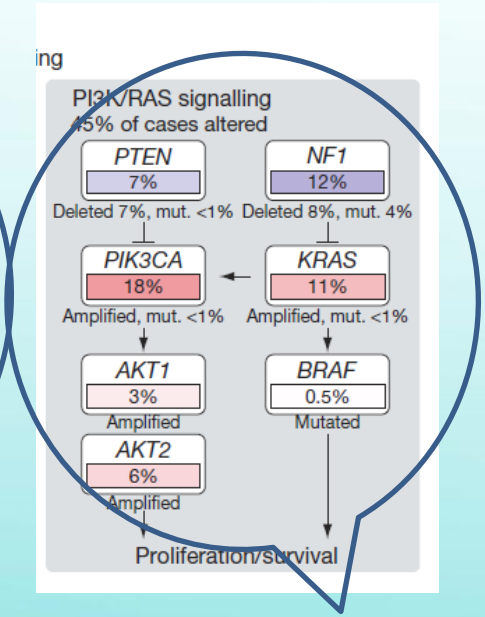
PARP inhibitors

Genomic markers can be used to assign patients to clinical trial agents

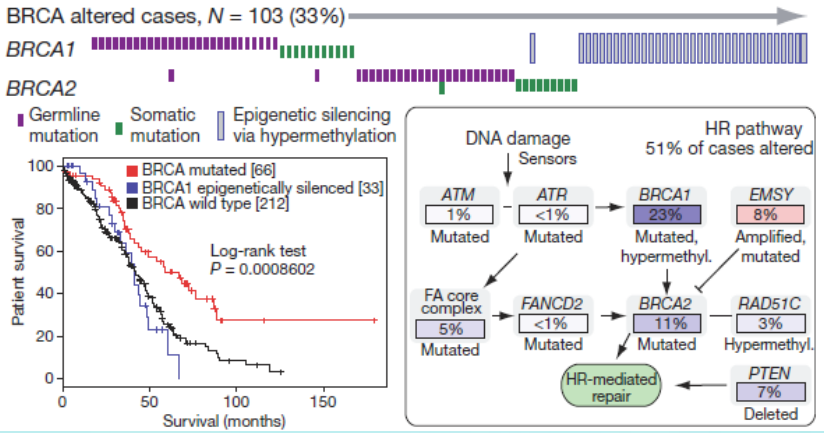
RB



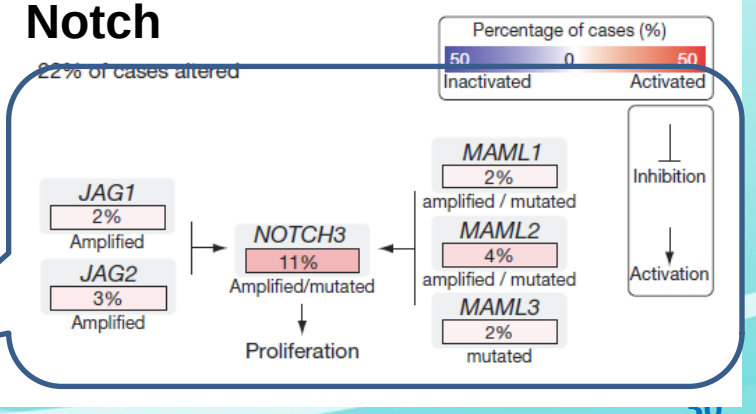
PI3K/RAS



HR Alterations/BRCAness



Notch



CDK inhibitors
AURK inhibitors

PI3K/AKT/mTOR inhibitors
MEK inhibitors

Notch inhibitors

From TCGA study: Nature 474, 609- 615 (2011)

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BRCAness Case Study

- **Stage IIIC diagnosed June 2007**
- **BRCA1 and 2 tested at Myriad – no mutations detected**
- **Carbo/docetaxel x 6 followed by 11 cycles of maintenance docetaxel the last 6 with the addition of bevacizumab**
- **Completed treatment in Nov 2008 and recurred in April 2009 (measurable disease by CT and increased CA125)**
- **No response to tamoxifen. 2nd remission achieved with Carbo/doxil**
- **Entered double-blind PARP inhibitor clinical trial Dec 2009 testing olaparib as maintenance to prevent recurrence**
  - **AZ announced 12.20.11 that the drug will not progress to Phase 3 but drug is provided for women who continue to benefit and**
  - **patient remains in remission and continues on study agent**
- **Sequencing of coding regions of ~200 genes implicated in cancer performed on tumor sample December 2011**
- **Somatic BRCA2 mutation detected**

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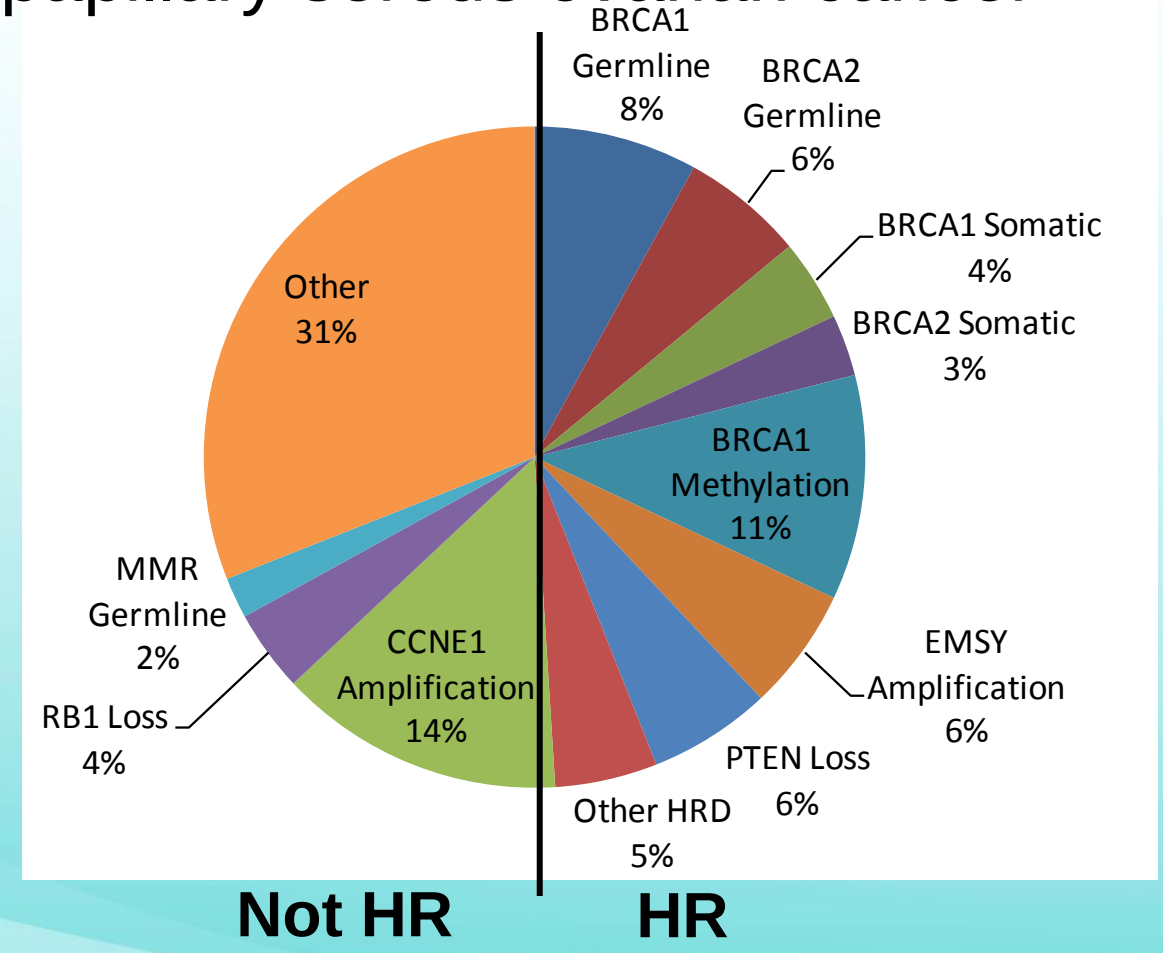
HR deficiencies may be identified in up to 50% of papillary serous ovarian cancer



Created by Douglas A. Levine, MD from data posted on the cBio Cancer Genomics Portal, MSKCC

Summary

- Ovarian cancer is heterogeneous and a broad profiling panel is needed to capture data relevant to each individual
- Commonly utilized agents for treatment of recurrent ovarian cancer can be prioritized using molecular markers
- Obtaining biopsies at recurrence is optimal
- Incorporation of molecular markers can help prioritize clinical trials for patients
  - Single agents
  - And combinations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