第21屆台灣癌症聯合學術年會
2016 Taiwan Joint Cancer Conference Speech Abstract

Choose your poison

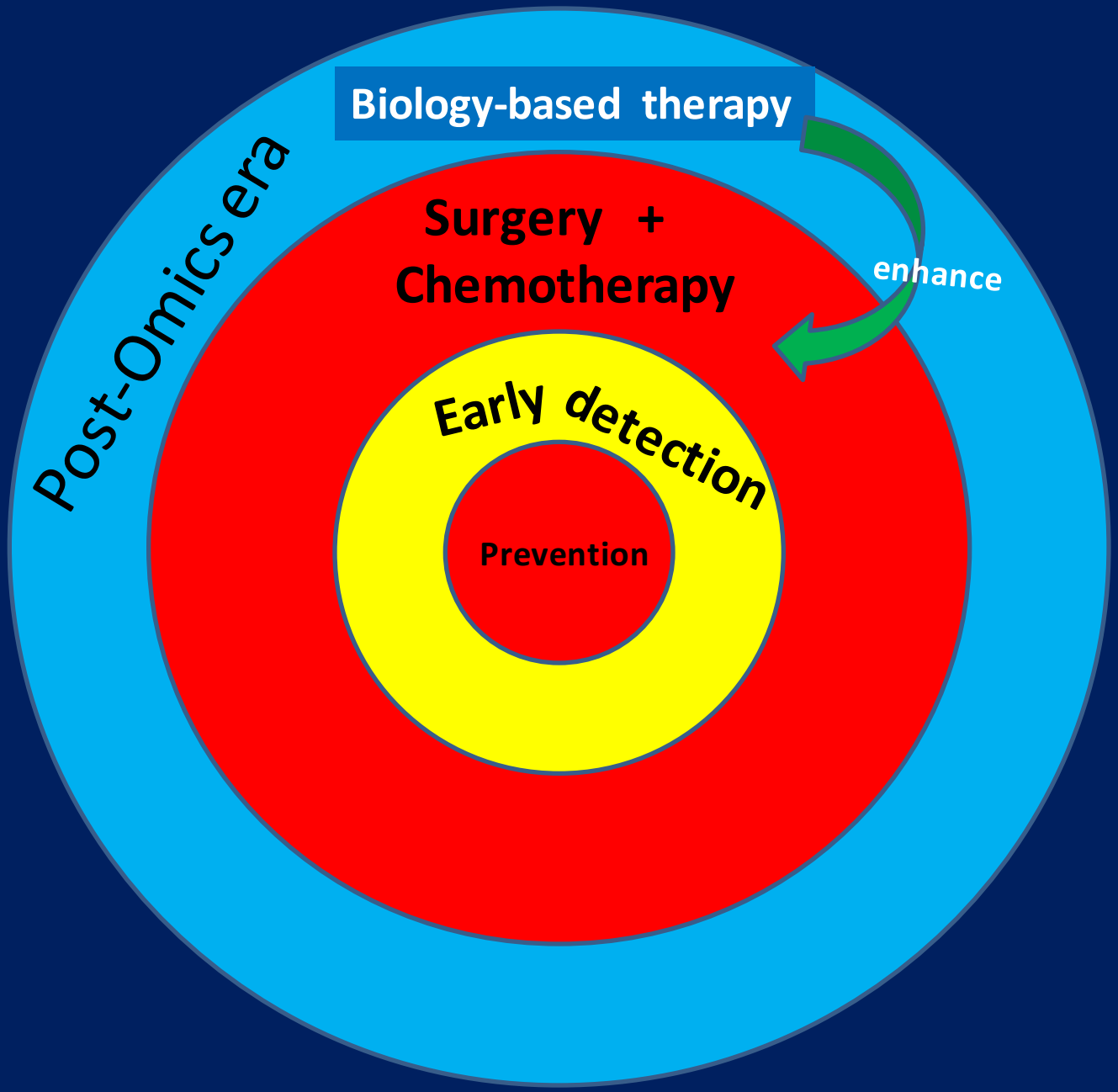
Ie-Ming Shih 施益民

www.gynecologycancer.org

JOHNS HOPKINS
MEDICINE

Outline

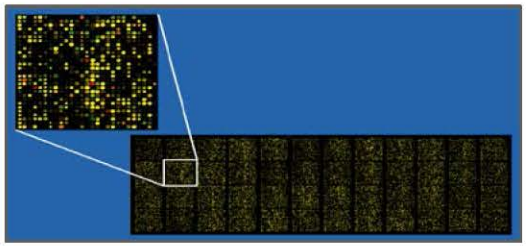
- Introduction
- PARP inhibitor- where are we now?
- Emerging molecular targets and pathways
- Challenges
- Summary and future perspectives


Post-Omics era
Biology-based therapy
enhance
Surgery +
Chemotherapy
Early detection
Prevention

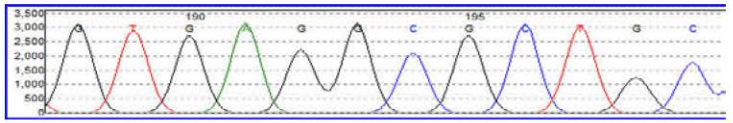
Omics

"A term encompassing multiple molecular disciplines, which involve the characterization of global sets of biological molecules such as DNAs, RNAs, proteins, and metabolites."

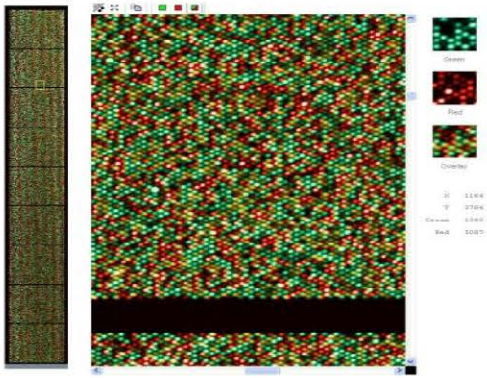
Affymetrix expression GeneChip



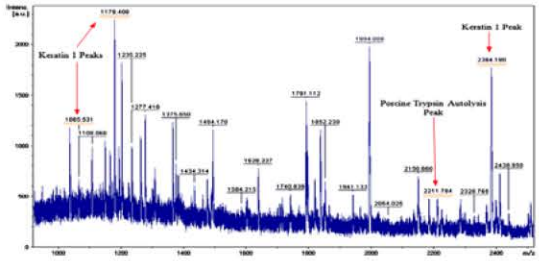
cDNA expression microarray



Mutation sequence surveyor trace

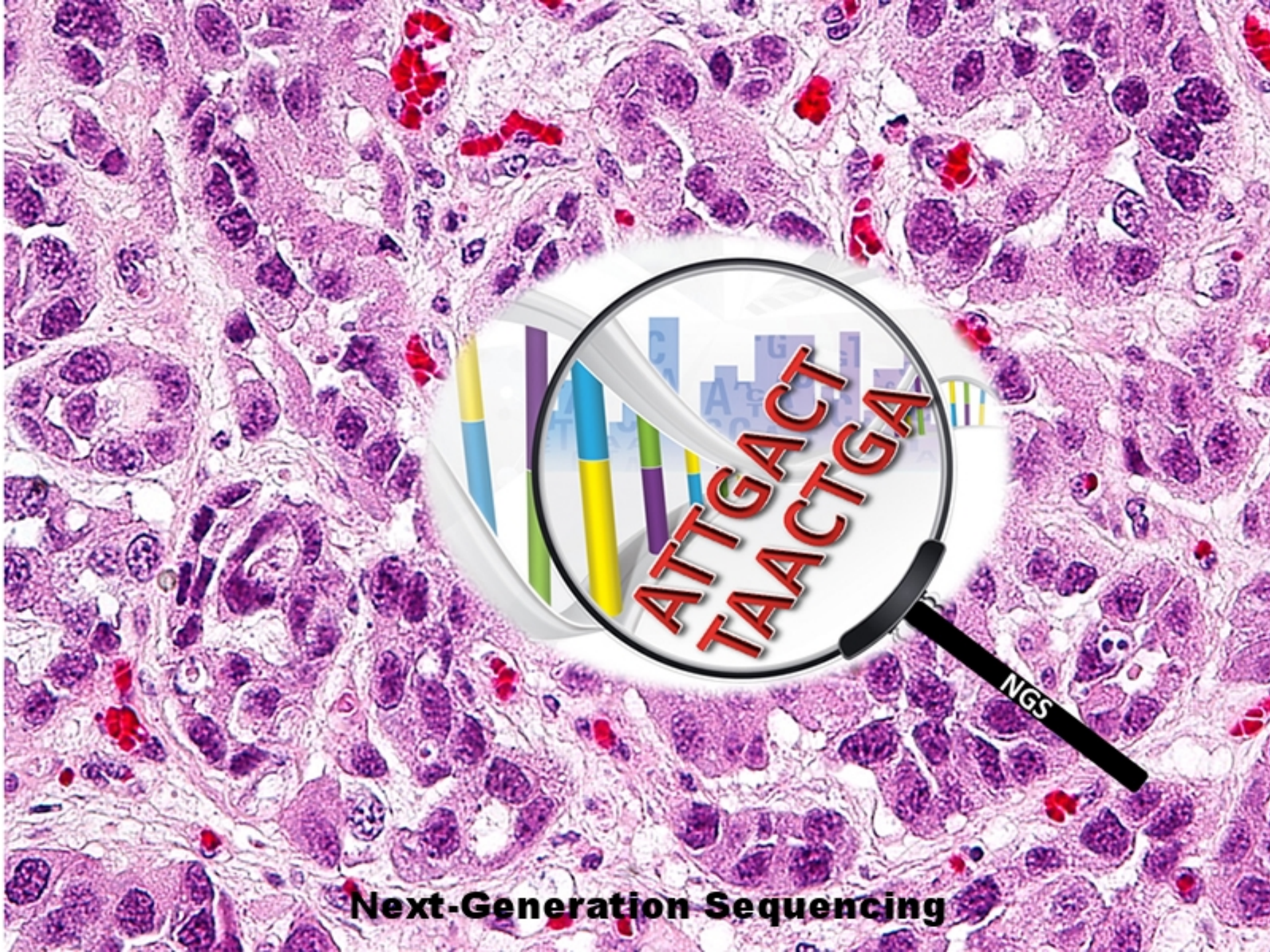


Illumina SNP bead array

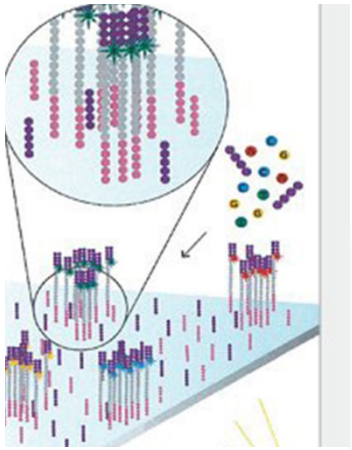


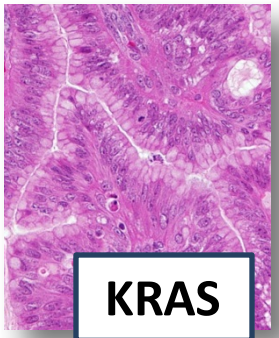
MALDI-TOF proteomic spectrum

http://www.iom.edu/Reports/2012/Evolution-of-Translational-Omics.aspx


ATTGACT
TAACTGA
NGS
Next-Generation Sequencing

Mutation Landscape





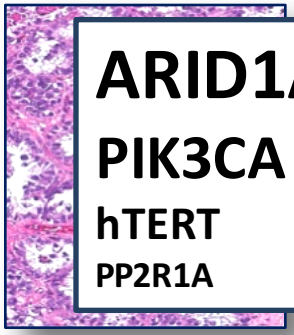
KRAS

Mucinous

ARID1A
PIK3CA
CTNNB1
PTEN
PP2R1A

TP53
BRCA1/2

ARID1A
PIK3CA
hTERT
PP2R1A

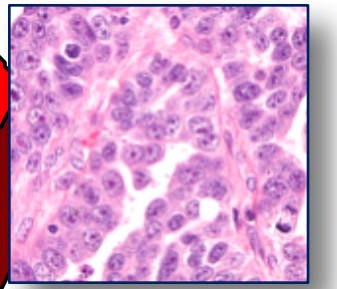


Endometrioid

Clear cell

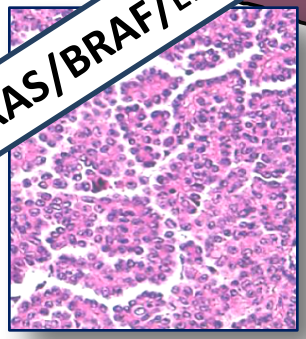
Low-grade serous

High-grade serous

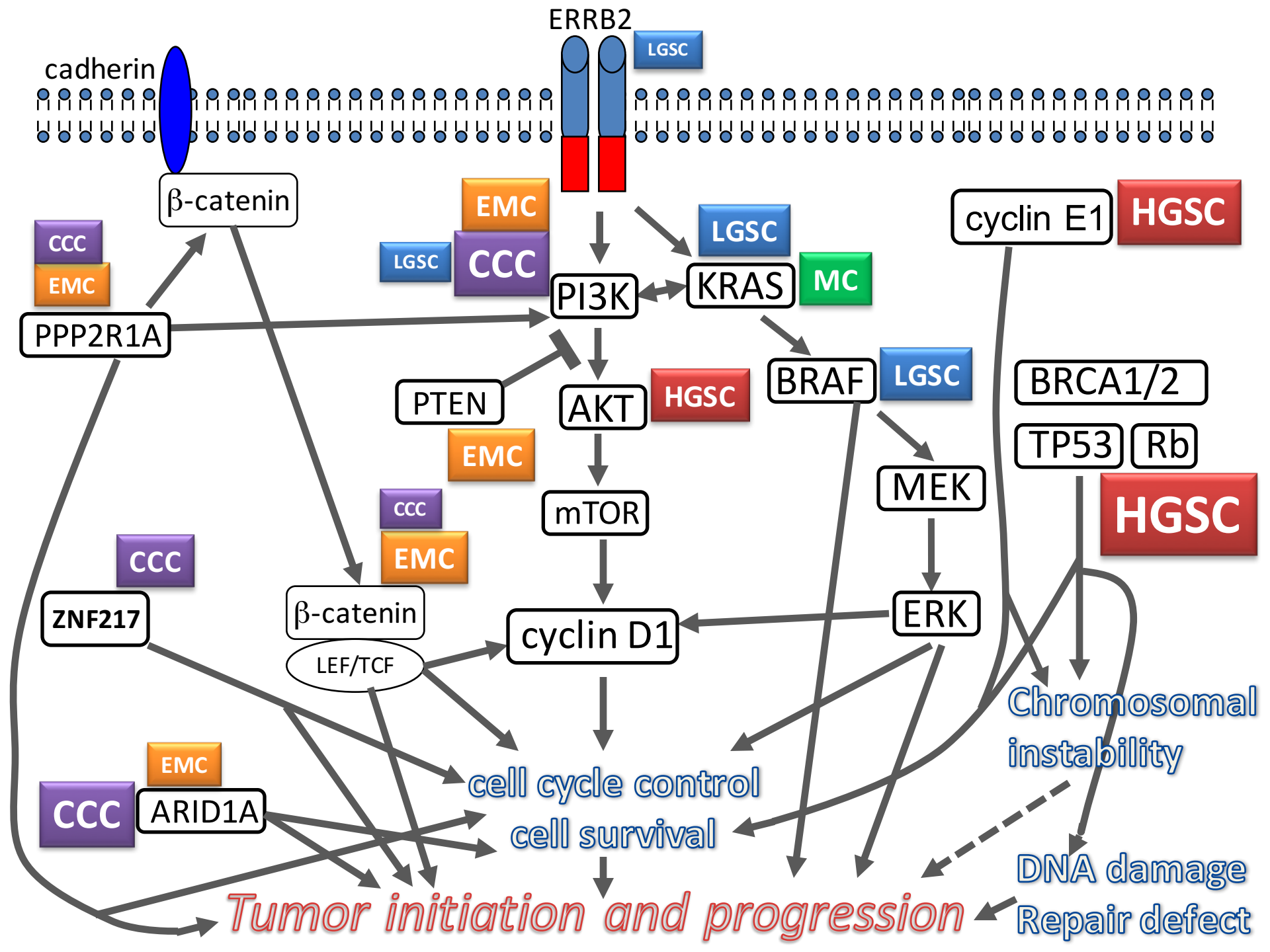


Primary ovarian carcinoma

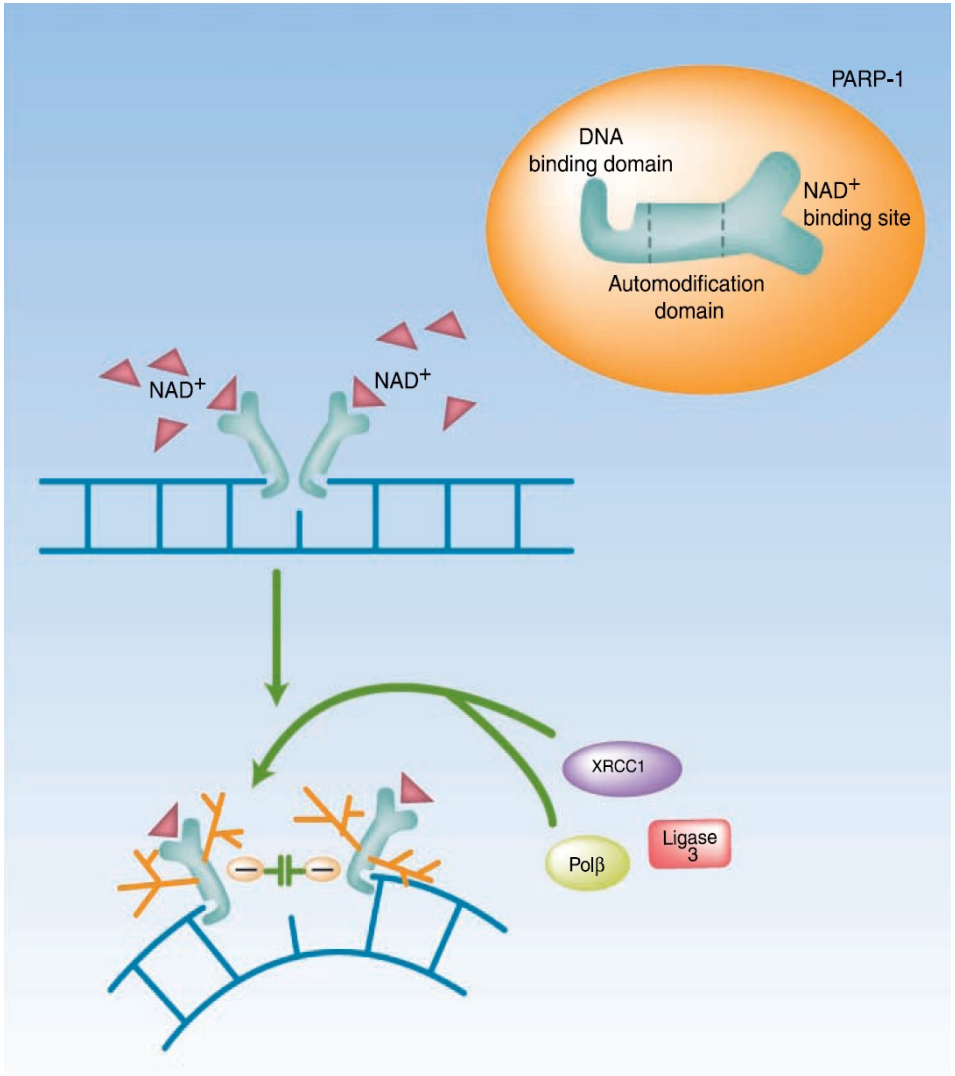
KRAS/BRAF/ERRB2



Lack of recurrent actionable mutations

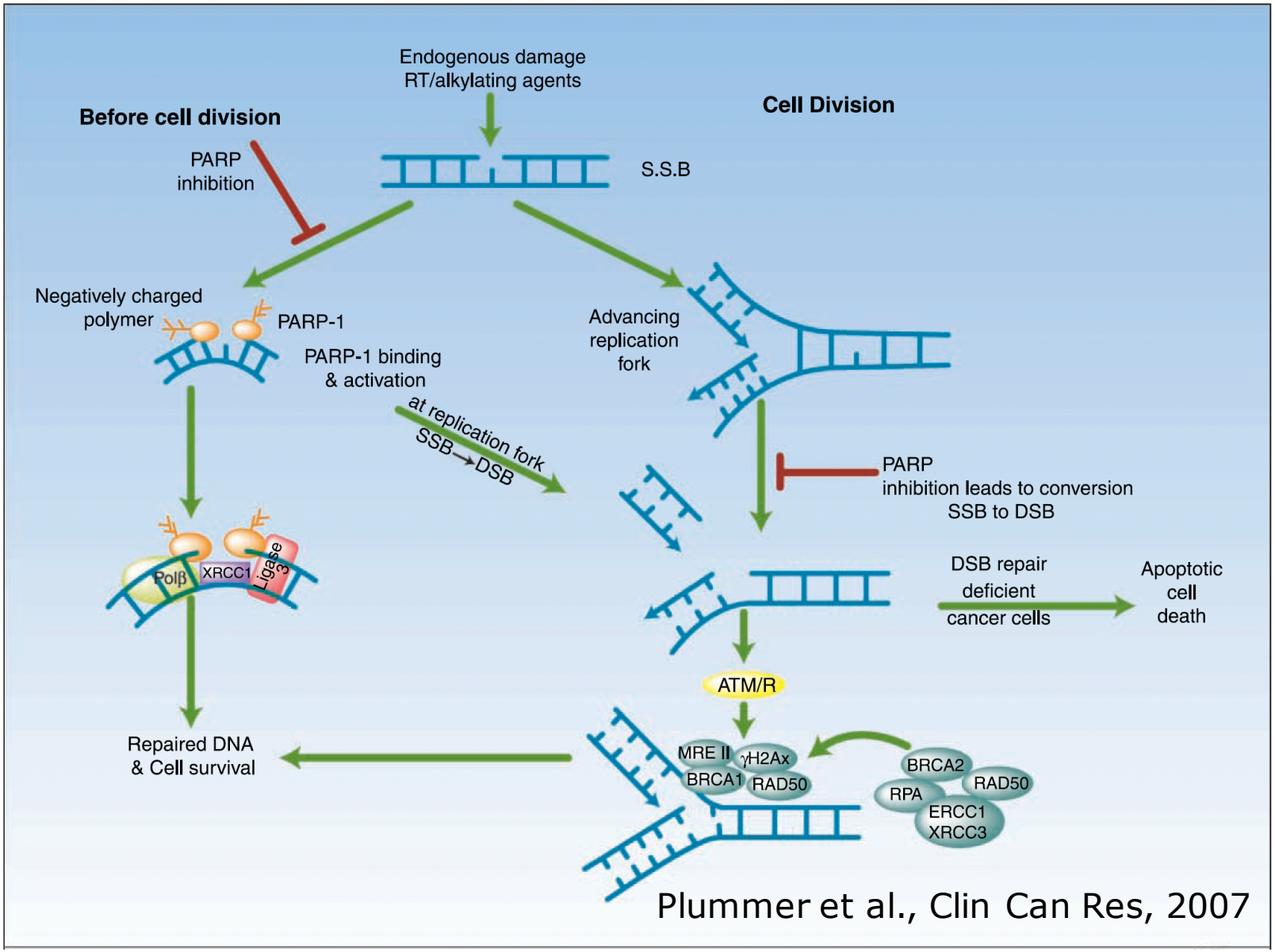

ERRB2
LGSC
cadherin
β-catenin
EMC
LGSC
CCC
LGSC
CCC
EMC
PPP2R1A
PI3K
KRAS
MC
cyclin E1
HGSC
PTEN
EMC
AKT
HGSC
BRAF
LGSC
BRCA1/2
TP53
Rb
HGSC
MEK
mTOR
CCC
EMC
CCC
ZNF217
β-catenin
LEF/TCF
cyclin D1
ERK
Chromosomal instability
EMC
CCC
ARID1A
cell cycle control
cell survival
DNA damage
Repair defect
Tumor initiation and progression

Base Excision Repair via PARP



Plummer et al., Clin Can Res, 2007

PARP Function in DNA Repair

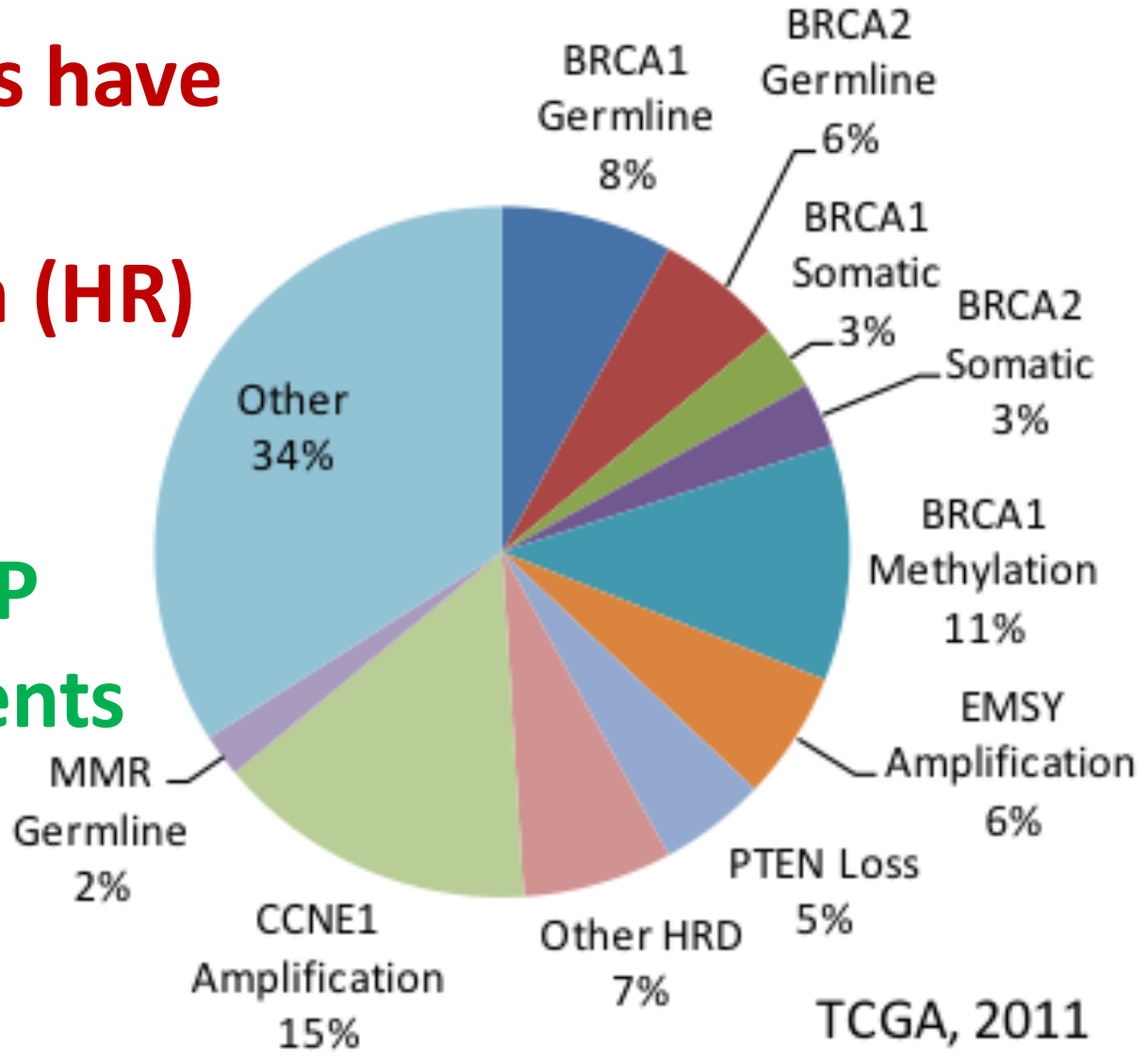


Plummer et al., Clin Can Res, 2007

The Era of PARP inhibitors

~40% of HGSCs have homologous recombination (HR) defect

Inhibiting PARP for those patients



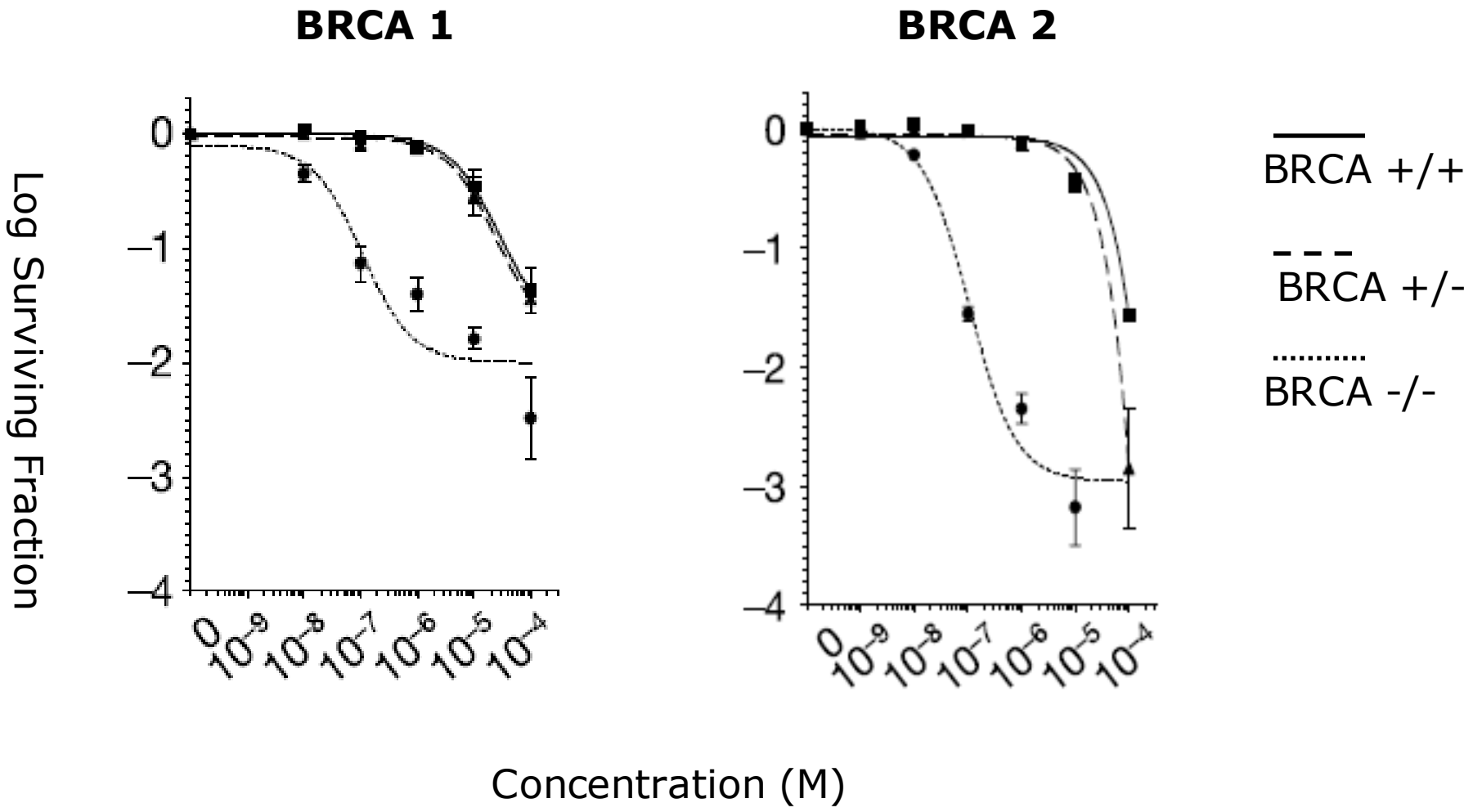
Rationale Behind PARP Inhibition

- BRCA Negative (and HR deficient) Tumors
  - Unable to repair double strand DNA breaks using homologous recombination
  - Rely upon PARP to repair single-strand breaks and replication fork stalls
- In Combination with Chemotherapy
  - Chemotherapies cause DNA single strand breaks
  - Inhibition of PARP will not allow single strand repair at these sites

Olaparib FDA Approval

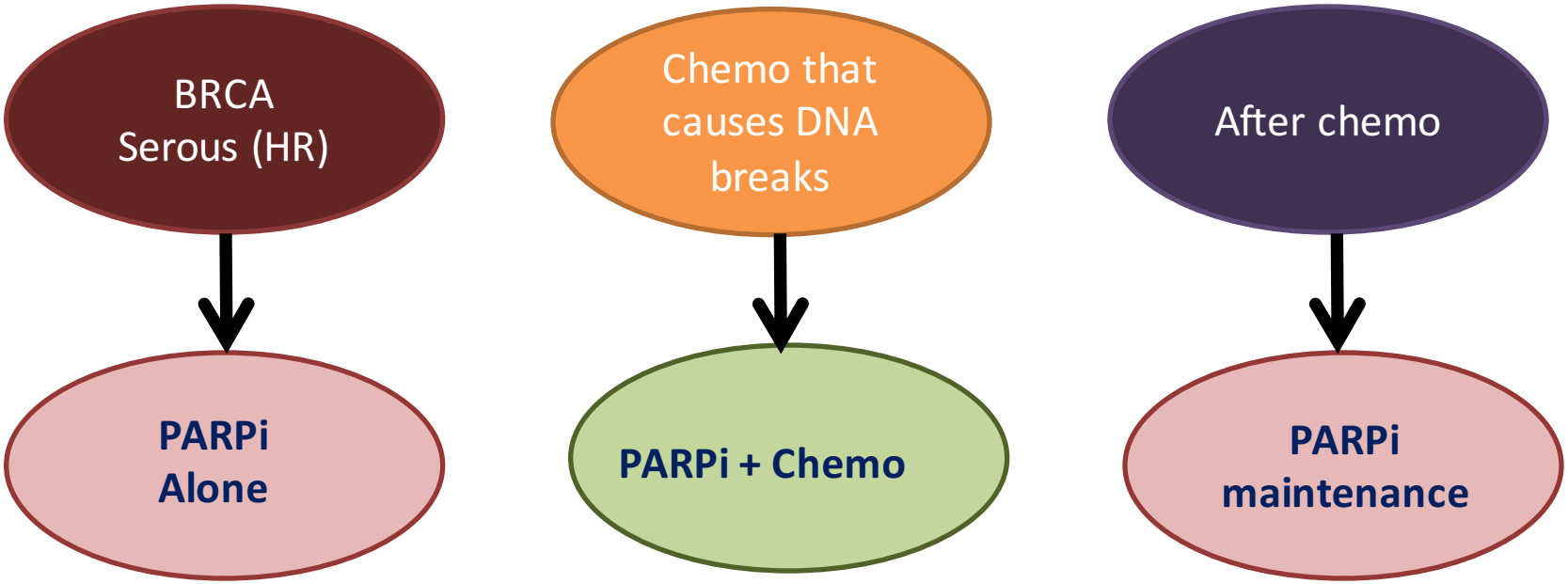
- December 2014
- Patients
  - Germline *BRCA 1/2* mutation
  - ≥ 3 prior lines of therapy
- Basis of Approval
  - 34% ORR in 137 patients
  - Duration of response 7.9 months
- **Is this advancing care or an option of care?**

PARP Inhibitors Selectively Kill BRCA Deficient Tumor Cells



Farmer et al., Nature 2005

CLINICAL TRIAL DESIGNS

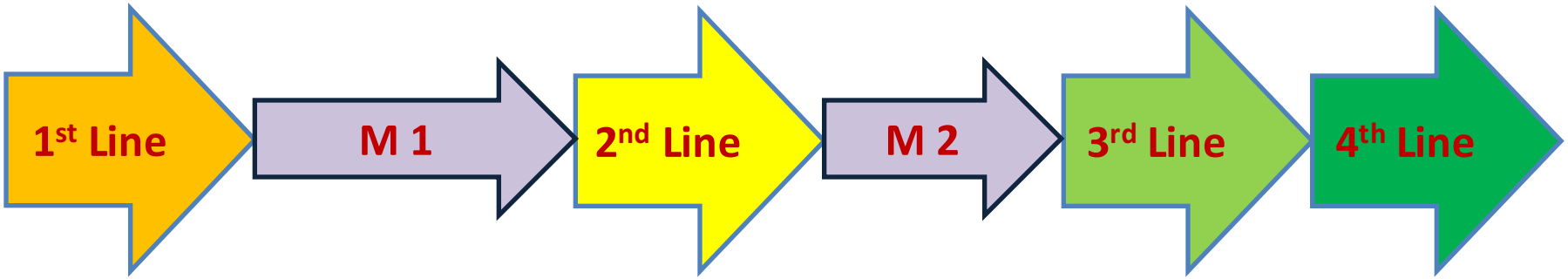


PARP Inhibitors in Clinical Trials with Registration Potential

Drug	Trial	Phase	Design
Olaparib (AZD2281)	SOLO 1	3	Maintenance – following front line treatment, germline and somatic BRCA
	SOLO 2	3	Maintenance – following platinum combination therapy for platinum sensitive recurrence, germline and somatic BRCA
	SOLO 3	3	Treatment – monotherapy/standard chemotherapy for platinum sensitive recurrence, germline BRCA
Niraparib (MK4827)	NOVA	3	Maintenance – following platinum combination therapy for platinum sensitive recurrence, germline BRCA or high grade serous
	QUADRA	2	Treatment – ≥ 3 priors, high grade serous
Rucaparib (CO-338)	ARIEL 3	3	Maintenance – following platinum combination therapy for platinum sensitive recurrence, high grade serous or endometrioid
	ARIEL 2	2	Treatment – 3/4 priors, high grade serous or endometrioid
Veliparib (ABT888)	GOG 3005	3	Treatment – first line with chemotherapy

https://clinicaltrials.gov

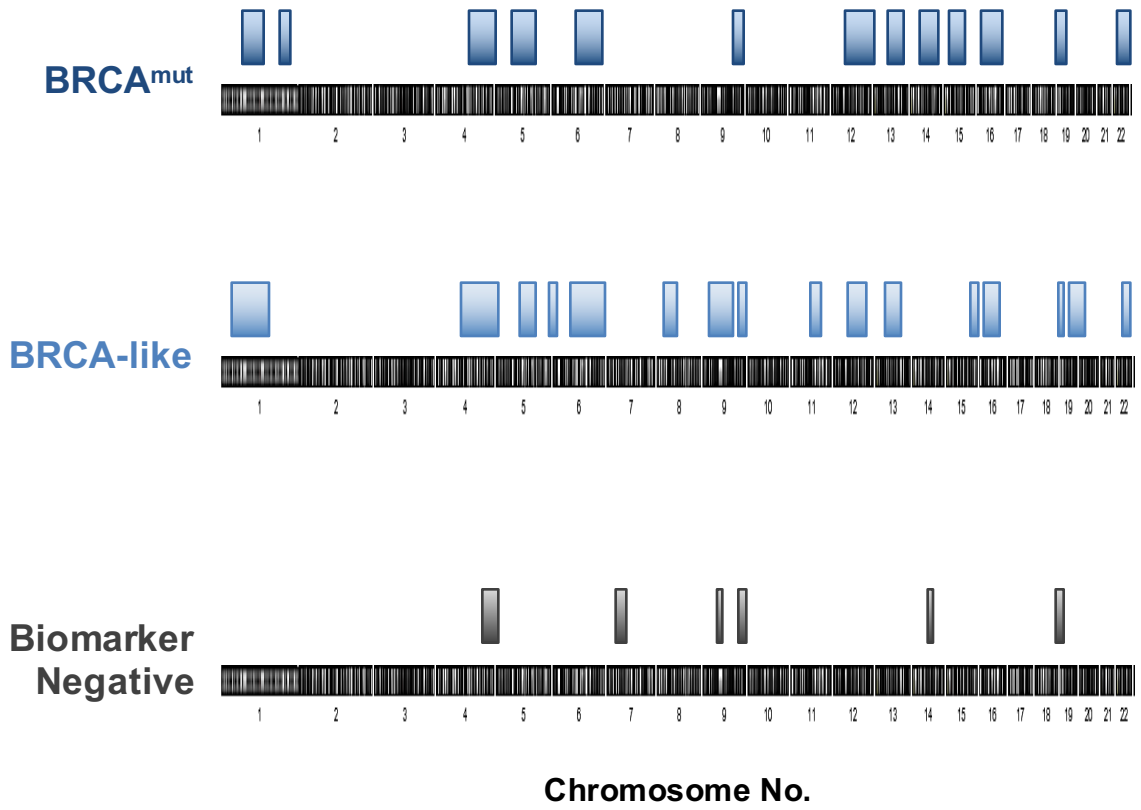
When to Use a PARP Inhibitor?



4th Line (or beyond?)

- ≥ 3 lines of chemotherapy = "unmet medical need" by FDA
- Response rate data led to olaparib accelerated approval in germline BRCA patients (December 2014).
- Niraparib and rucaparib phase 2 studies opened in January 2015
- Phase 2 study of liposomal doxorubicin vs. olaparib failed to show superiority of olaparib. Will SOLO 3 succeed?
- More work is needed to discern who will really benefit.

HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS



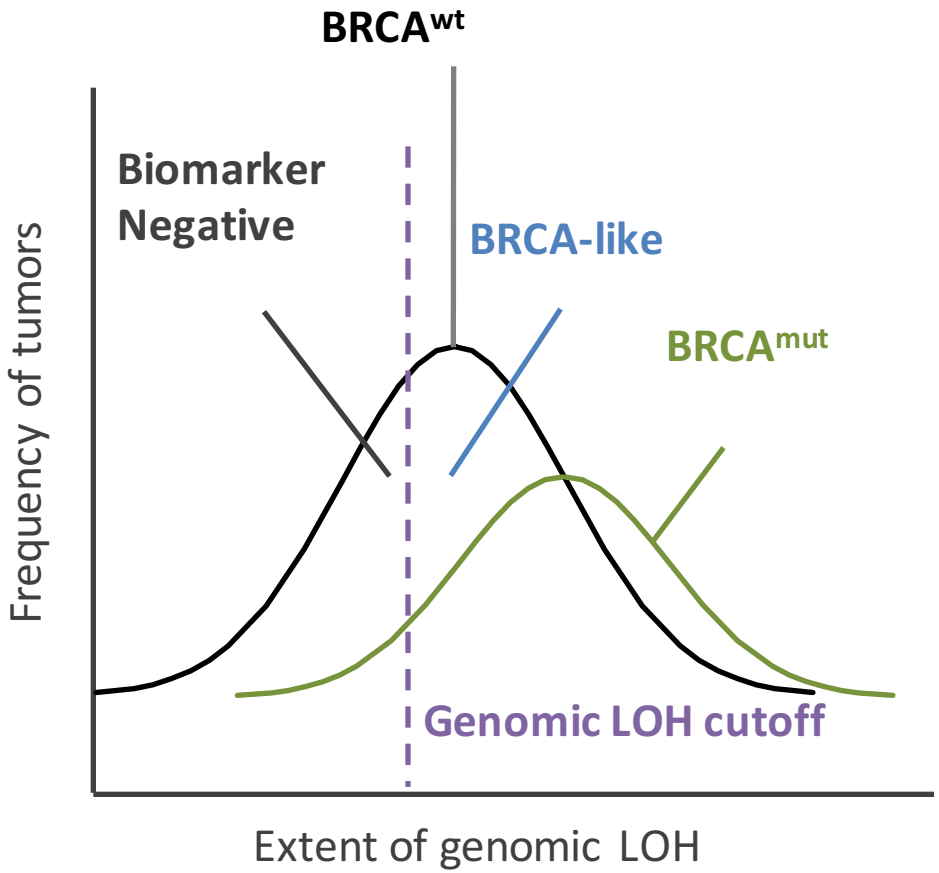
Hypothesis 1:
Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

Hypothesis 2:
Ovarian cancer patients who are "biomarker negative" (ie, with low genomic LOH) will not respond to PARPi.

NGS=next-generation sequencing; mut=mutation; wt=wild type.

McNeish et al., ASCO 2015

HGOC patients can be classified into three molecular subgroups: BRCA^{mut}, BRCA-like, Biomarker Negative



McNeish et al., ASCO 2015

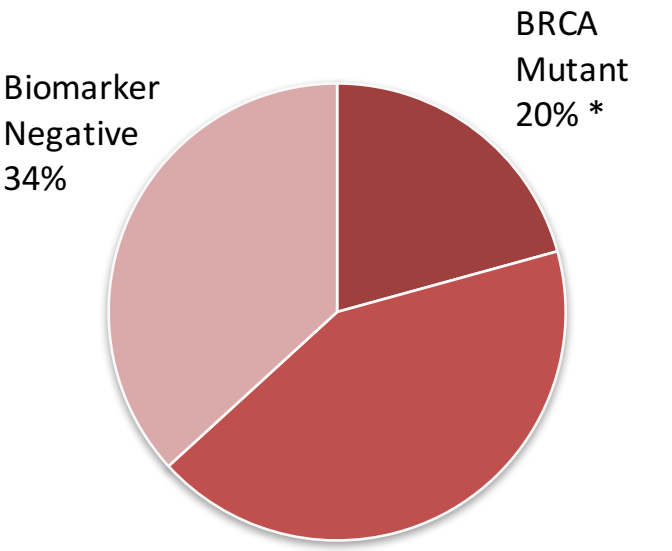
Patient characteristics

Parameter	Total (N=204)
Median age, years (range)	65 (31–86)
ECOG PS grade	
0 / 1 / Pending (%)	67 / 30 / 3
Diagnosis	
Epithelial ovarian cancer (%)	80
Primary peritoneal / fallopian tube cancer (%)	12 / 7 (1 UNK)
Histology	
Serous / endometrioid / mixed/ pending (%)	96 / 2 / 2 / 1
No. of prior treatment regimens	
Median no. of regimens (range)	1 (1–6)
1–2 (%)	81
>2 (%)	19
Median no. of plat-based regimens (range)	1 (1–5)
1–2 (%)	86%
>2 (%)	14

UNK – unknown

Data cut 01APR2015

Distribution of HRD molecular subgroups (N=191)



* Enrollment of known gBRCA patients was capped

McNeish et al., ASCO 2015

BRCA^{wt} patients can be split into 2 subgroups with enhanced benefit observed in BRCA-like tumors

HRD Subgroup	Median PFS (mo) [90% CI]	Overall Response Rate, % (N)	
		RECIST	RECIST + CA-125
BRCA^{mut}	9.4 [7.3, NR]	69 (27/39)	82 (32/39)
BRCA-like	7.1 [3.7, 10.8]	30 (22/74)	45 (33/74)
Biomarker negative	3.7 [3.5, 5.5]	13 (8/62)	21 (13/62)

NR – not reached

McNeish et al., ASCO 2015

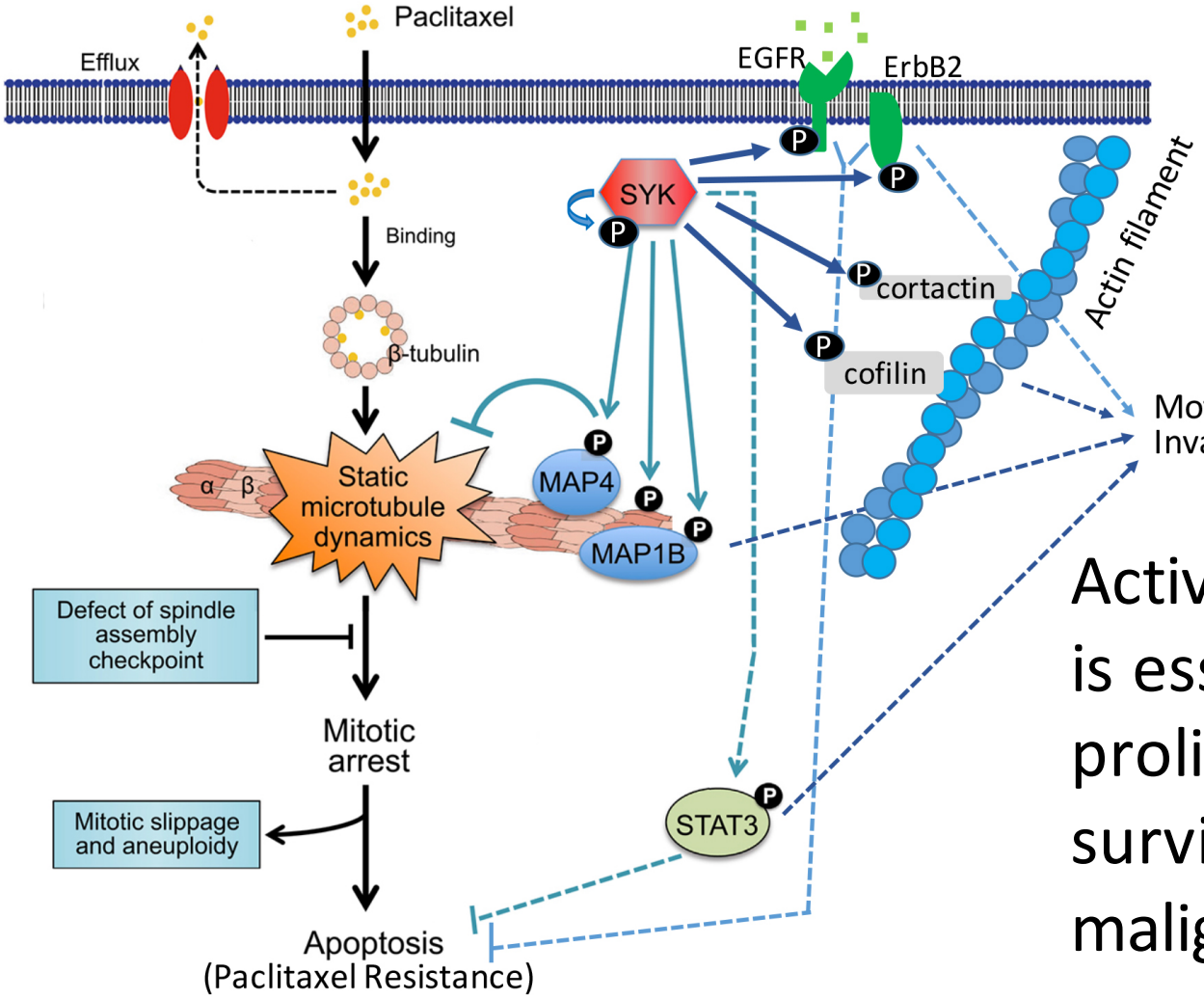
Emerging Pipeline

Targeted therapy and precision cancer medicine based on understanding tumor biology…

- Spleen Tyrosine Kinase (SYK) inhibitor
- Synthetic lethality- ARID1A tumor suppressor
- Immune checkpoint inhibitor
- Others

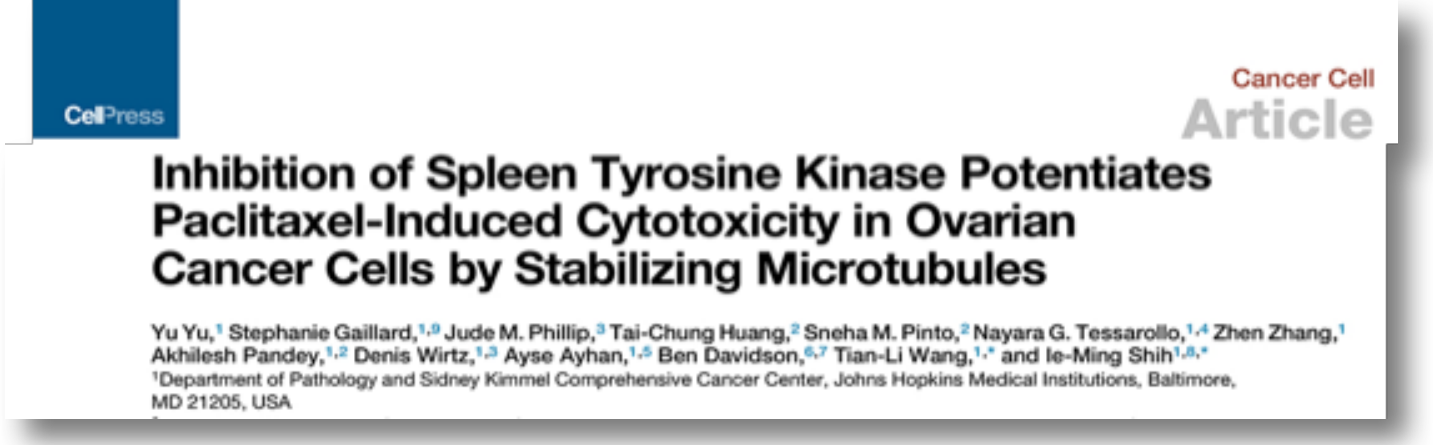
Spleen Tyrosine Kinase (SYK)

A non-receptor tyrosine kinase mediates signal transduction of transmembrane receptors.



The biological role of SYK in solid tumors remains largely elusive.

Activated SYK signaling is essential for proliferation and survival in B-cell malignancies.



CellPress

Cancer Cell
Article

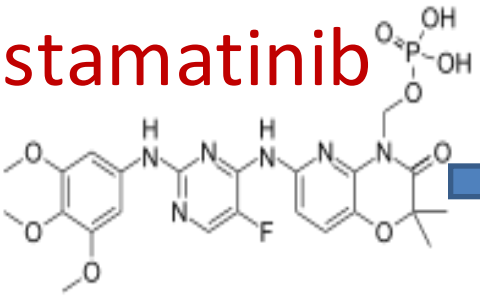
Inhibition of Spleen Tyrosine Kinase Potentiates Paclitaxel-Induced Cytotoxicity in Ovarian Cancer Cells by Stabilizing Microtubules

Yu Yu,[1] Stephanie Gaillard,[1,9] Jude M. Phillip,[3] Tai-Chung Huang,[2] Sneha M. Pinto,[2] Nayara G. Tessarollo,[1,4] Zhen Zhang,[1] Akhilesh Pandey,[1,2] Denis Wirtz,[1,3] Ayse Ayhan,[1,5] Ben Davidson,[6,7] Tian-Li Wang,[1,*] and Ie-Ming Shih[1,8,*]
[1]Department of Pathology and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD 21205, USA

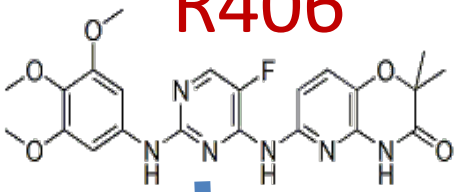
- Ovarian cancer cells surviving paclitaxel treatment have higher levels of activated SYK.
- Inhibition of SYK sensitizes ovarian cancer cells (especially TR) to paclitaxel via enhancing microtubule stability.
- This is made possible via altering phosphorylation of MAP1B and MAP4 and tubulins and microtubule-associated proteins.
- Microtubule-independent pathway may also exist.

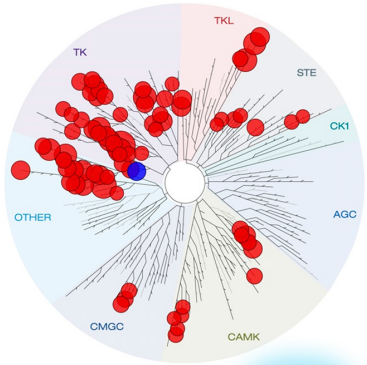
SYK inhibitors in clinical trials

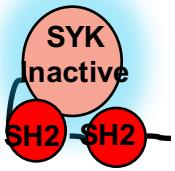
(1) Fostamatinib

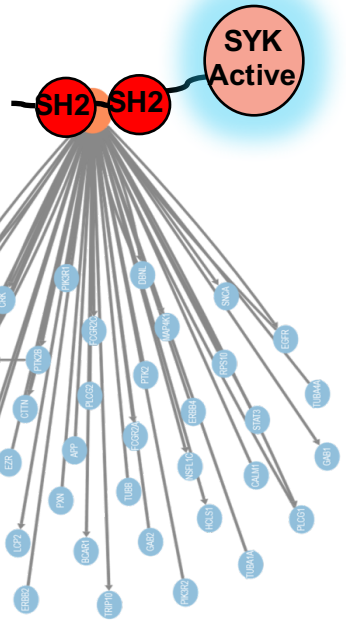


R406

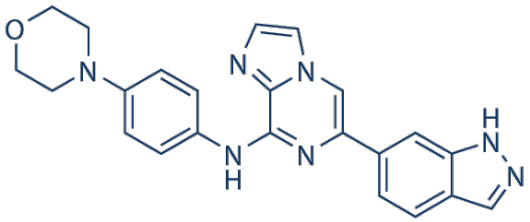


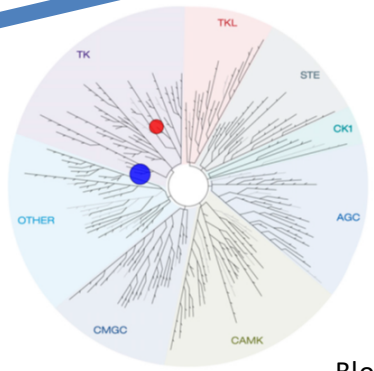






(2) Entospletinib





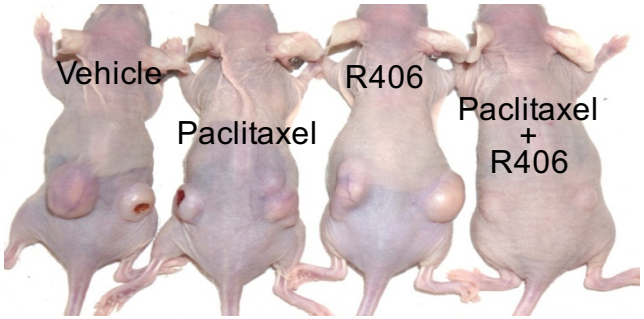
Blood, 2015. PMID: 25696919

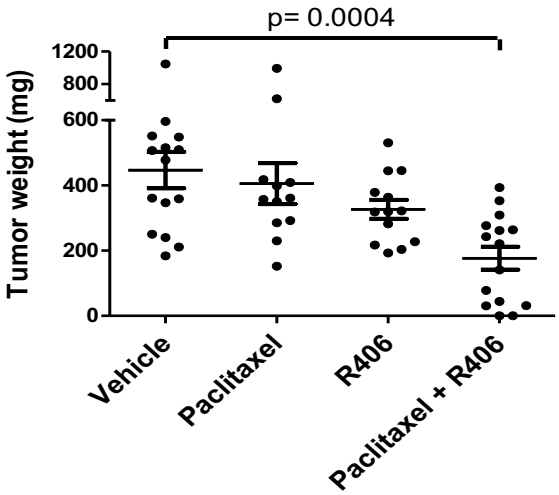
SYK inhibitors in clinical trials

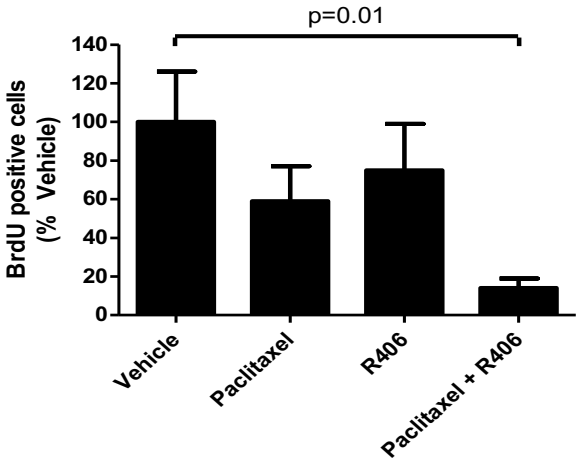
Study	pts (n)	Drug	Disease Studied	Phase
Weinblatt et al. (2008) [PMID: 18975322]	189	Fostamatinib	Rheumatoid arthritis	II
Weinblatt et al. (2010) [PMID: 20879879]	457	Fostamatinib	Rheumatoid arthritis	II
Friedberg et al. (2010) [PMID: 19965662]	68	Fostamatinib	NHL & CLL	I/II
Genovese et al. (2011) [PMID: 21279990]	219	Fostamatinib	Rheumatoid arthritis	II
Weinblatt et al. (2013) [PMID: 23378467]	457	Fostamatinib	Rheumatoid arthritis	II
Park et al. (2013) [PMID: 23404627]	37	Fostamatinib	CRC thyroid, NSLC, H&N, RCC	II
Genovese et al. (2013) [PMID: 25225285]	322	Fostamatinib	Rheumatoid arthritis	III
Weinblatt et al. (2014) [PMID: 25223724]	918	Fostamatinib	Rheumatoid arthritis	III
Sharman et al. (2015) [PMID: 25696919]	186	Entosplatinib	NHL & CLL	II

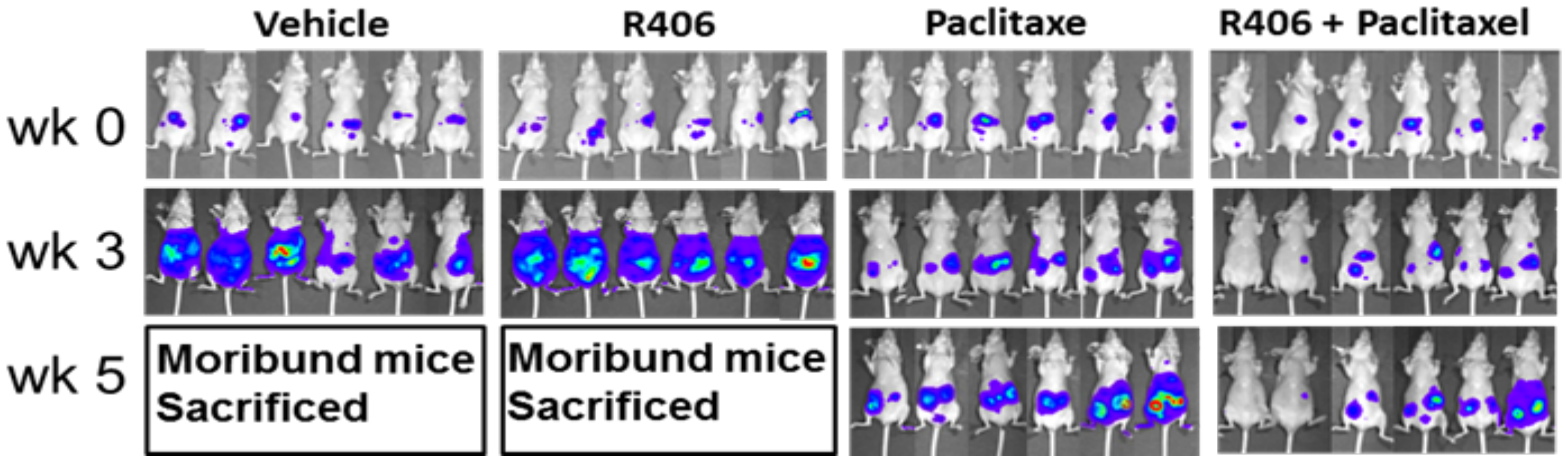
Acceptable toxicity: fatigue, neutropenia, anemia, nausea, diarrhea, URI-like

R406 significantly sensitizes paclitaxel cytotoxicity





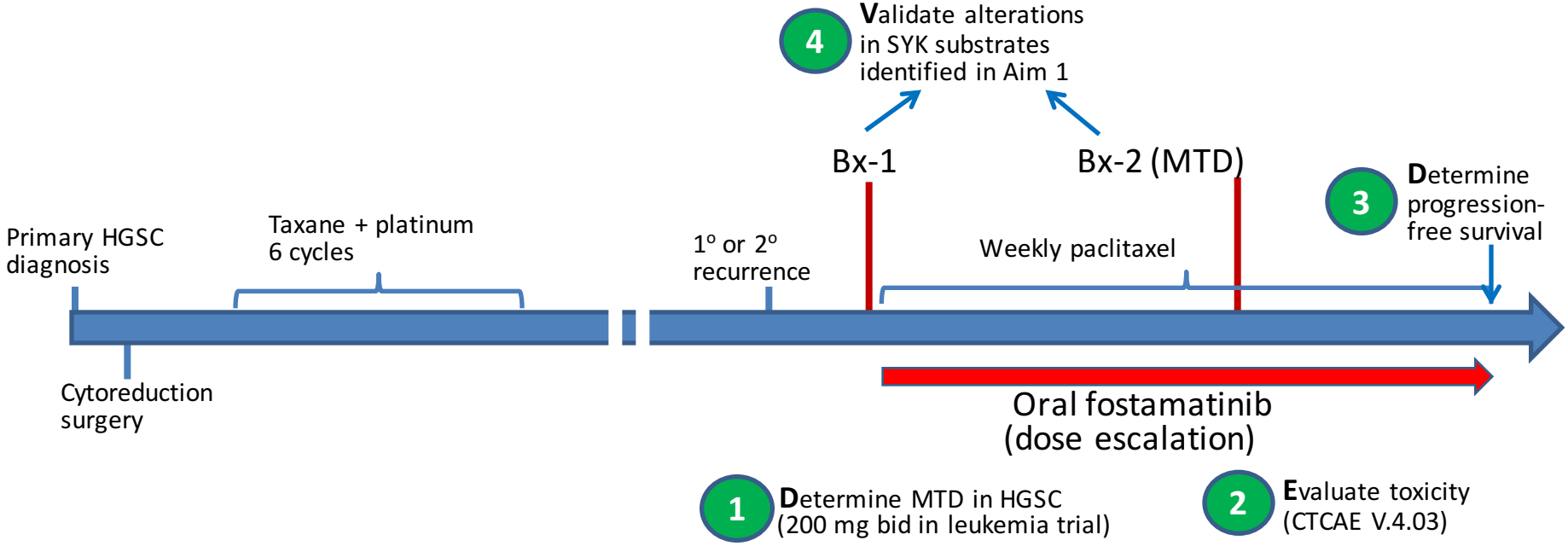




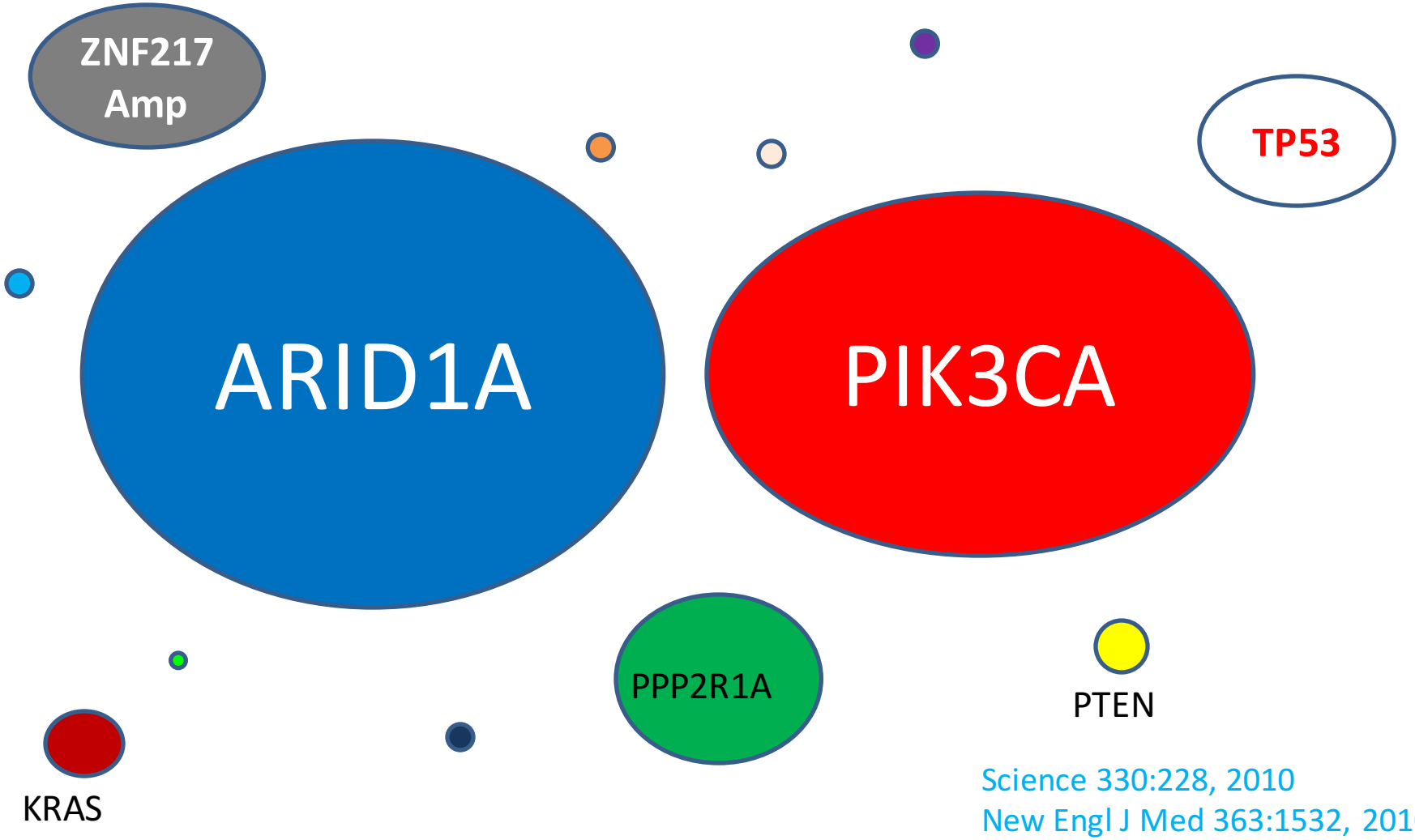
Phase I Clinical Trial

Phase I trial
24 patients

i) have recurrent ovarian/tubal/peritoneal HGSC
ii) have received initial or interval cytoreduction surgery and taxane-and platinum-based chemotherapy
iii) have RECIST measurable disease
iv) be a candidate for treatment with weekly paclitaxel



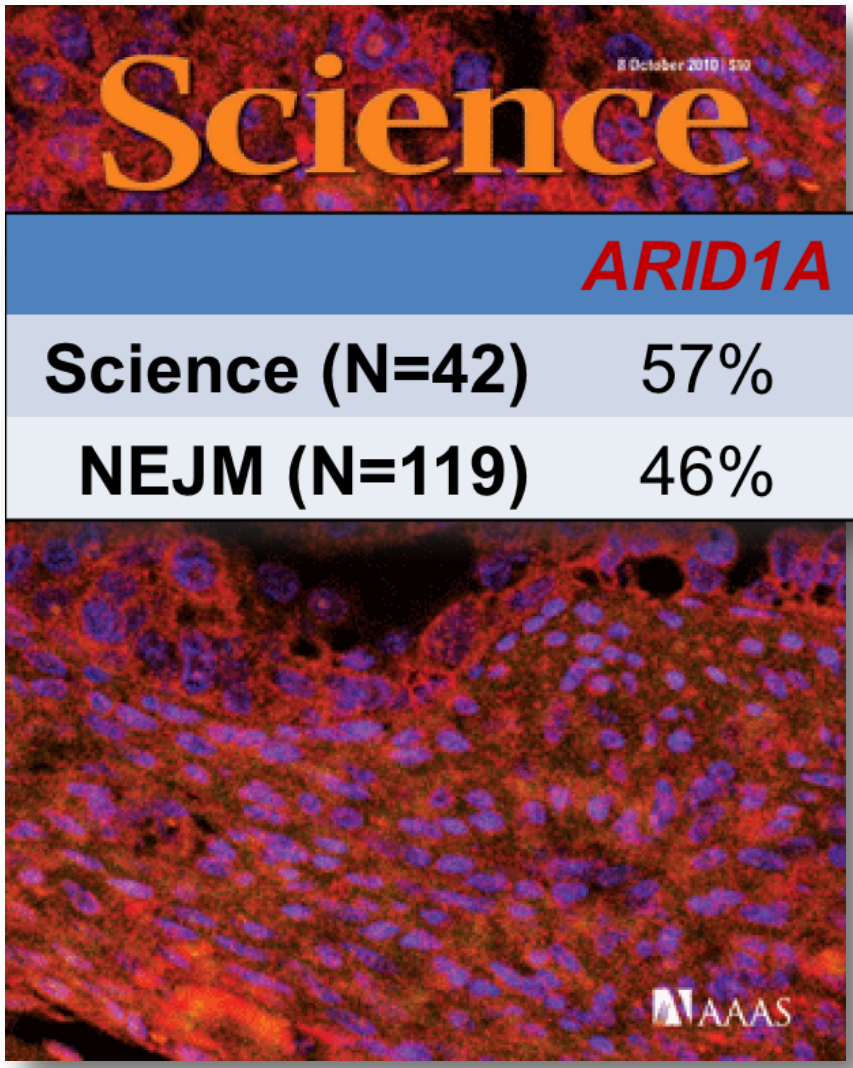
Genomic alterations in ovarian clear-cell carcinoma



Science 330:228, 2010
New Engl J Med 363:1532, 2010
Clin Cancer Res 16:1997, 2010

Somatic mutation of ARID1A

AT-rich interactive domain 1A (ARID1A)



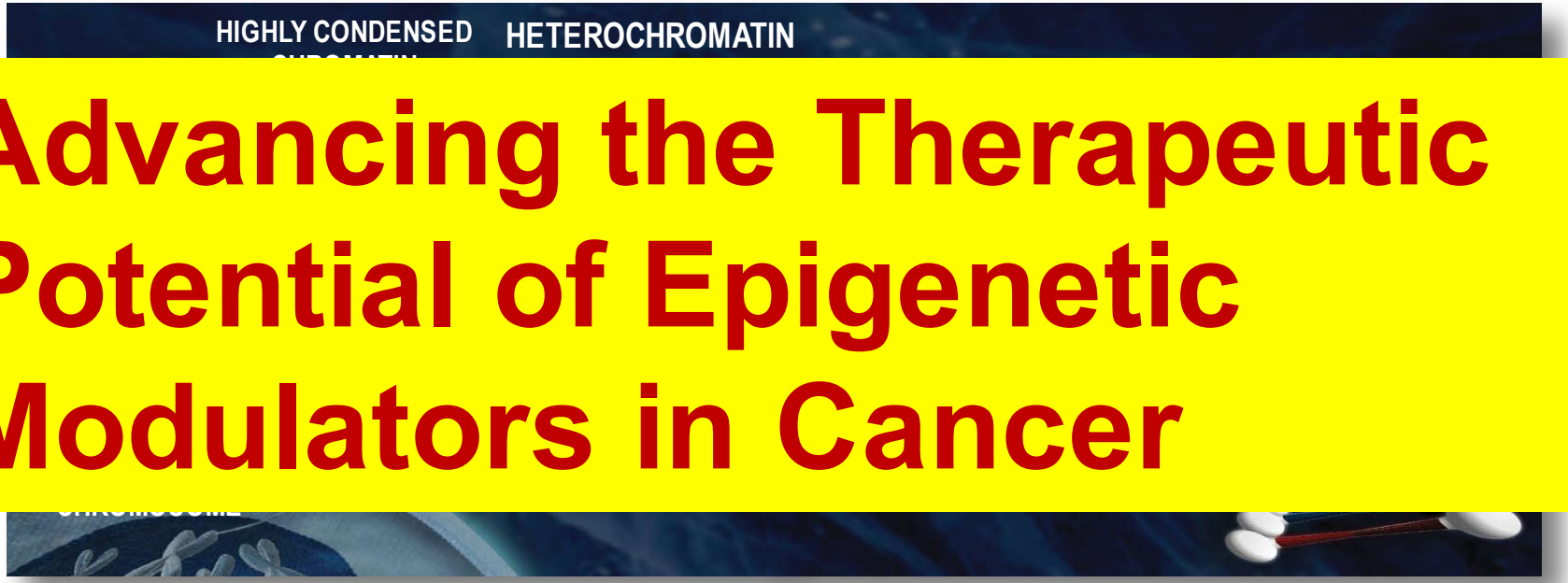
Frequent Mutations of Chromatin Remodeling Gene *ARID1A* in Ovarian Clear Cell Carcinoma

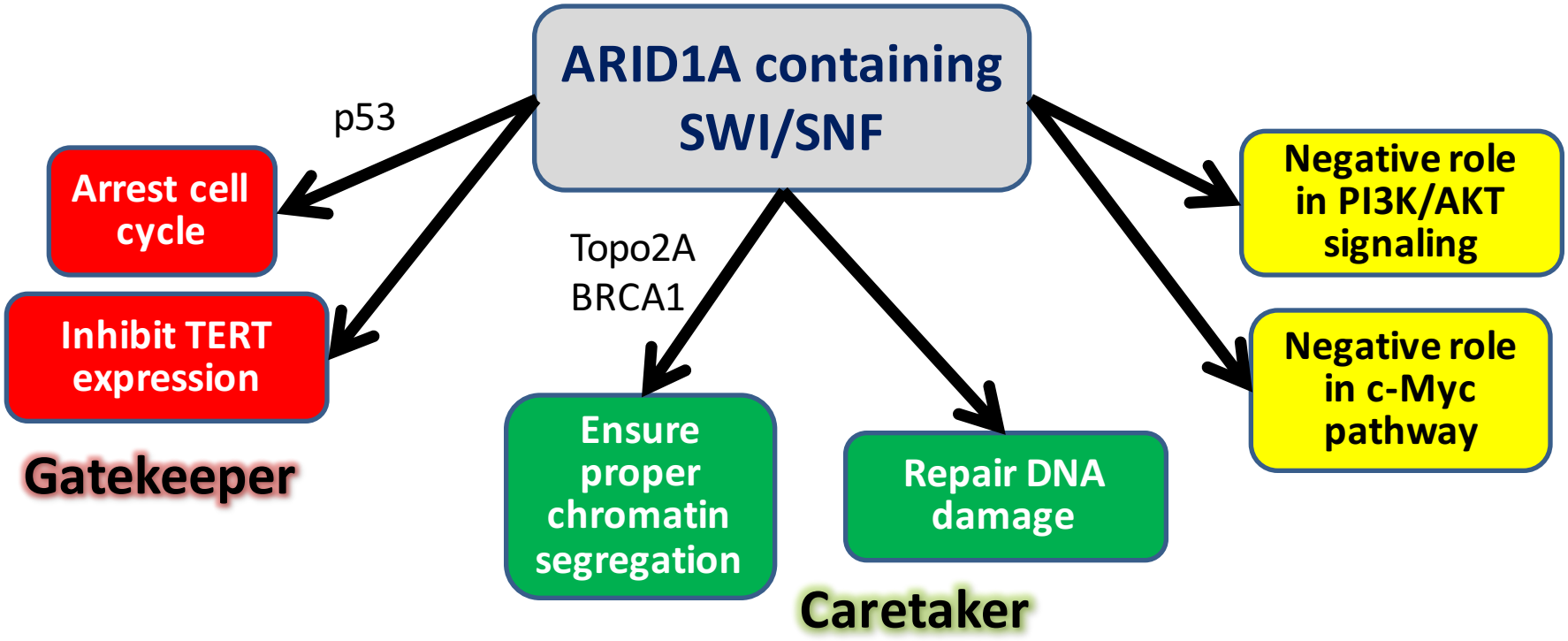
	ARID1A	*PIK3CA*	*PPP2R1A*	*KRAS*
Science (N=42)	57%	40%	7.1%	4.7%
NEJM (N=119)	46%	-	-	-

Associated Ovarian Carcinomas

Kimberly C. Wiegand, B.Sc., Sohrab P. Shah, Ph.D., Osama M. Al-Agha, M.D., Yongjun Zhao, D.V.M., Kane Tse, B.Sc., Thomas Zeng, M.Sc., Janine Senz, B.Sc., Melissa K. McConechy, B.Sc., Michael S. Anglesio, Ph.D., Steve E. Kalloger, B.Sc., Winnie Yang, B.Sc., Alireza Heravi-Moussavi, Ph.D., Ryan Giuliany, B.Sc., Christine Chow, B.M.L.Sc., John Fee, B.Sc., Abdalnasser Zayed, B.Sc., Leah Prentice, Ph.D., Nataliya Melnyk, B.Sc., Gulisa Turashvili, M.D., Ph.D., Allen D. Delaney, Ph.D., Jason Madore, M.Sc., Stephen Yip, M.D., Ph.D., Andrew W. McPherson, B.A.Sc., Gavin Ha, B.Sc., Lynda Bell, R.T., Sian Fereday, B.Sc., Angela Tam, B.Sc., Laura Galletta, B.Sc., Patricia N. Tonin, Ph.D., Diane Provencher, M.D., Dianne Miller, M.D., Steven J.M. Jones, Ph.D., Richard A. Moore, Ph.D., Gregg B. Morin, Ph.D., Arusha Oloumi, Ph.D., Niki Boyd, Ph.D., Samuel A. Aparicio, B.M., B.Ch., Ph.D., Ie-Ming Shih, M.D., Ph.D., Anne-Marie Mes-Masson, Ph.D., David D. Bowtell, Ph.D., Martin Hirst, Ph.D., Blake Gilks, M.D., Marco A. Marra, Ph.D., and David G. Huntsman, M.D.

Advancing the Therapeutic Potential of Epigenetic Modulators in Cancer





RESEARCH ARTICLE

Cancer Discovery

ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors

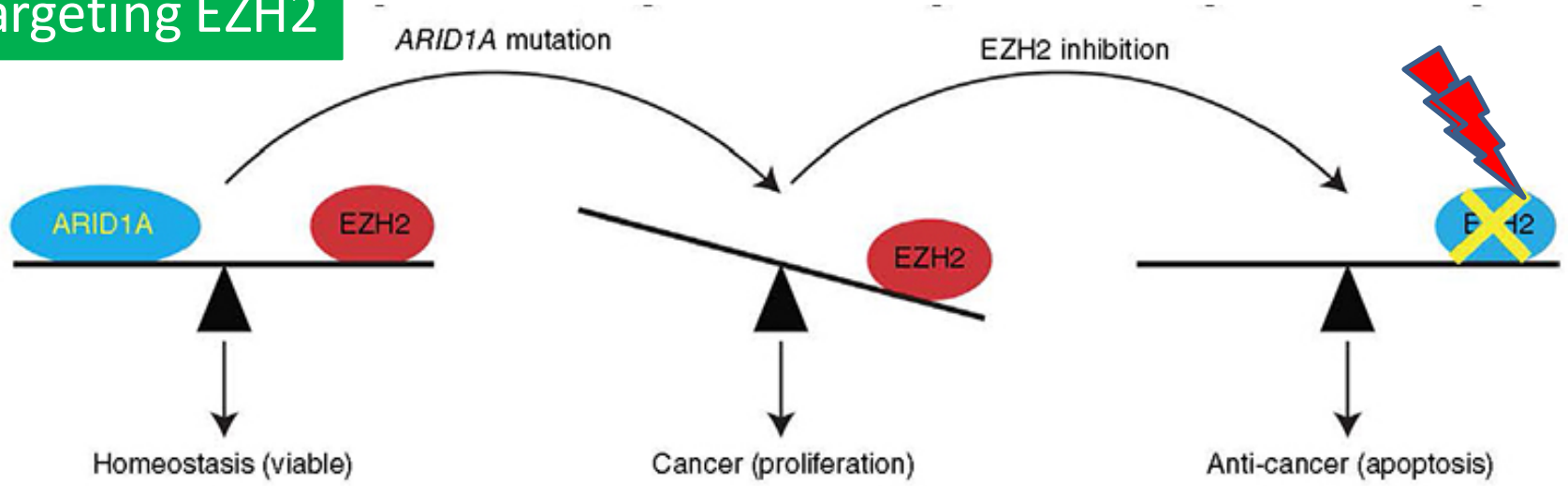
Jianfeng Shen[1], Yang Peng[2], Leizhen Wei[3,4], Wei Zhang[1], Lin Yang[1,5], Li Lan[3,4], Prabodh Kapoor[6], Zhenlin Ju[7], Qianxing Mo[8], Ie-Ming Shih[9], Ivan P. Uray[1], Xiangwei Wu[1], Powel H. Brown[1], Xuetong Shen[6], Gordon B. Mills[2], and Guang Peng[1,5]

nature medicine

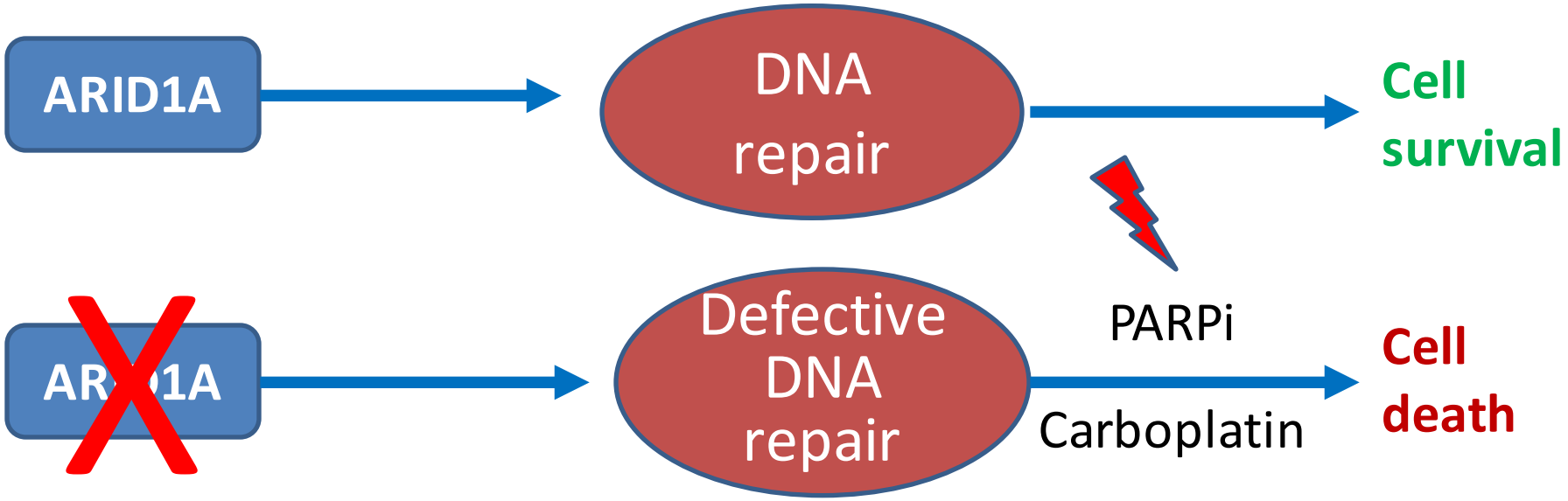
Synthetic lethality by targeting EZH2 methyltransferase activity in *ARID1A*-mutated cancers

Benjamin G Bitler[1], Katherine M Aird[1], Azat Garipov[1], Hua Li[1], Michael Amatangelo[1], Andrew V Kossenkov[2], David C Schultz[3], Qin Liu[4], Ie-Ming Shih[5], Jose R Conejo-Garcia[6], David W Speicher[2,4] & Rugang Zhang[1]

Targeting EZH2



Targeting DNA repair

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Gynecologic Oncology 141 (2016) 86–94

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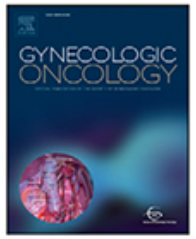


Leveraging immunotherapy for the treatment of gynecologic cancers in the era of precision medicine

Dmitriy Zamarin [a], Amir A. Jazaeri [b,*]

[a] Department of Medicine, Gynecologic Medical Oncology Service, Memorial Sloan Kettering Cancer Center, United States
[b] Department of Gynecologic Oncology and Reproductive Medicine, University of Texas, MD Anderson Cancer Center, United States

Through biomarker-guided clinical trials, we'll be able to better understand the mechanisms of response and resistance to immunotherapy and develop treatment strategies that will extend the benefit from immunotherapy to a broader range of patients and tumor types.

Cancer Science 2010;101:2658-63 The official journal of the Japanese Cancer Association JCA

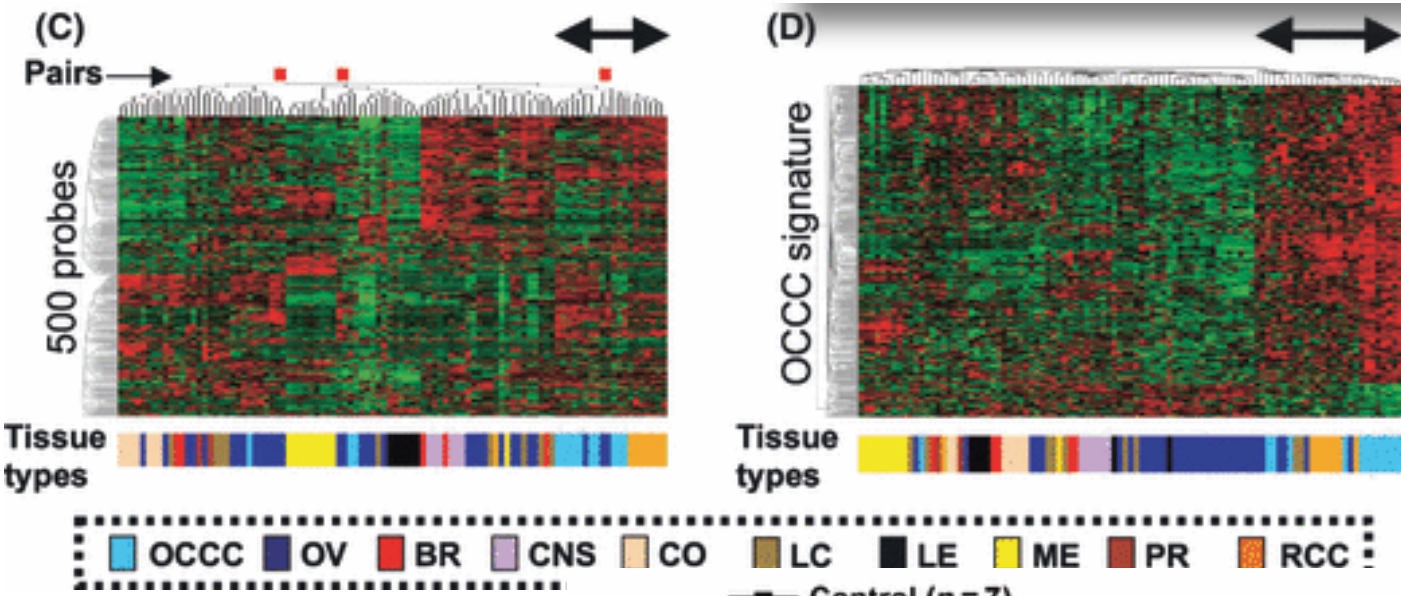
Sorafenib efficacy in ovarian clear cell carcinoma revealed by transcriptome profiling

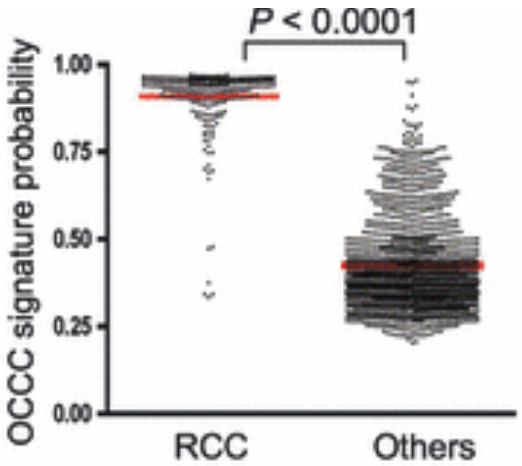
Noriomi Matsumura,[1] Masaki Mandai,[1,6] Takako Okamoto,[1] Ken Yamaguchi,[1,2] Shogo Yamamura
Tsukasa Baba,[1] Junzo Hamanishi,[1] Hyun S. Kang,[1] Shigeyuki Matsui,[4] Seiichi Mori,[5] Susan K. Mu
Ikuo Konishi[1]

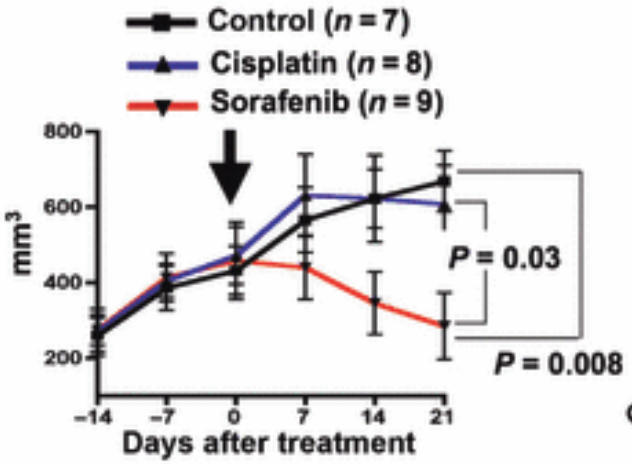
Cancer Biology & Therapy 15:1, 22–25; January 2014; © 2014 Landes Bioscience

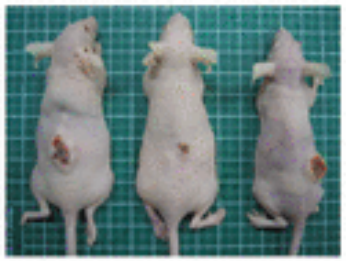
Two cases of recurrent ovarian clear cell carcinoma treated with sorafenib

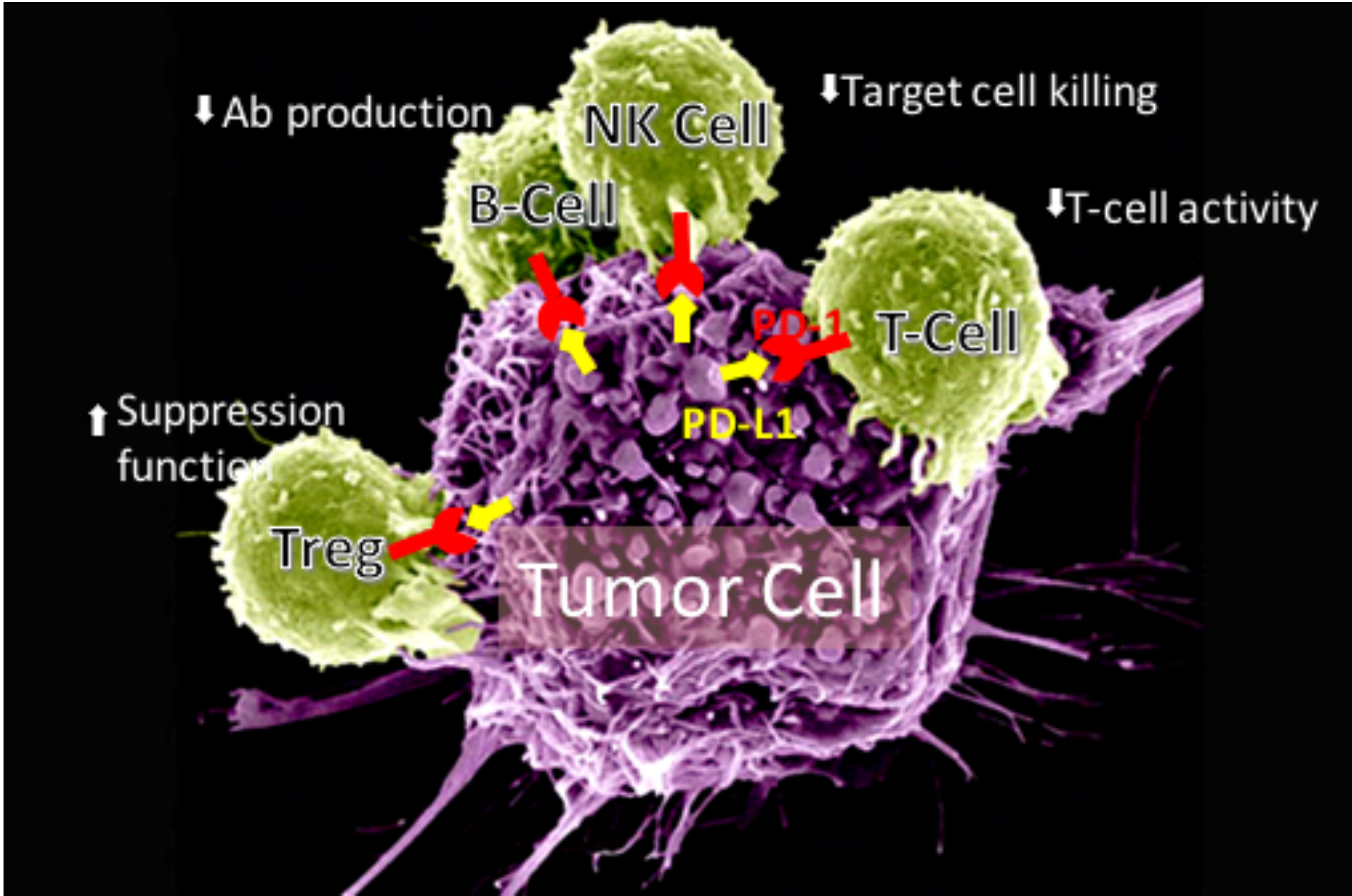
Masafumi Koshiyama, Noriomi Matsumura*, Tsukasa Baba, Ken Yamaguchi, Yumiko Yoshioka, and Ikuo Konishi









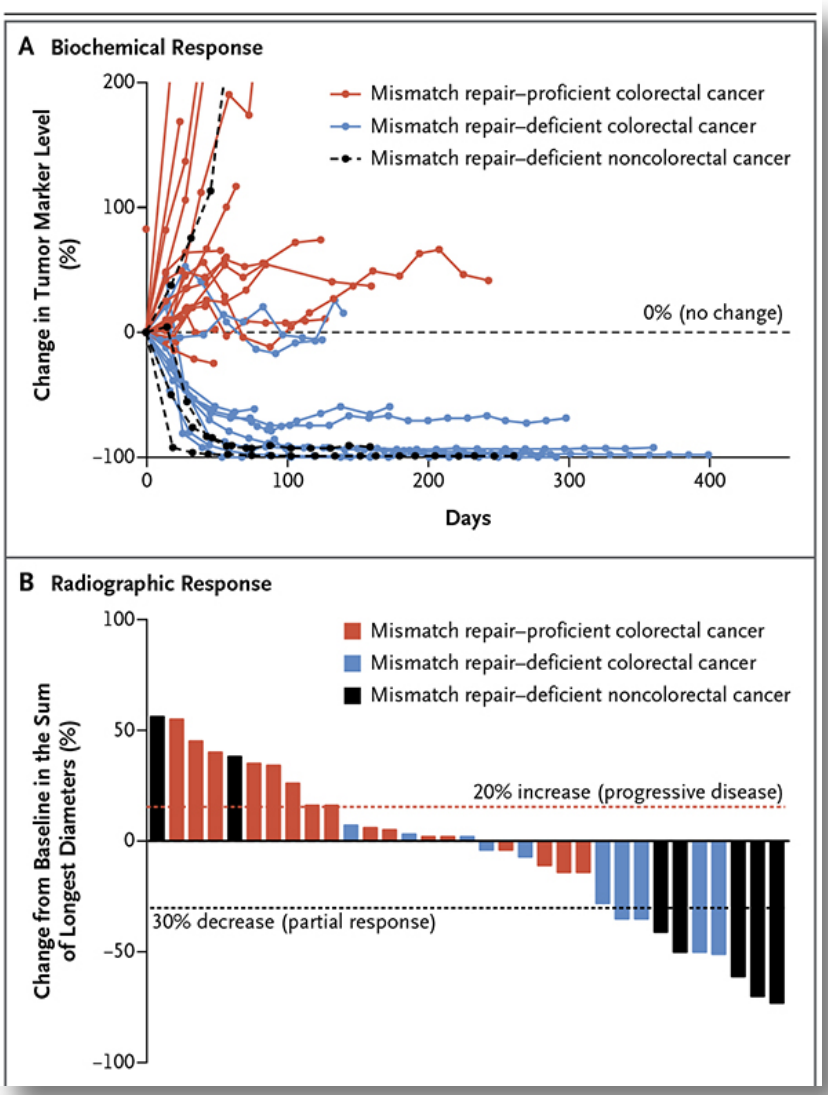

⬇Ab production
NK Cell
⬇Target cell killing
B-Cell
⬇T-cell activity
PD-1
T-Cell
PD-L1
⬆Suppression
Treg
Tumor Cell

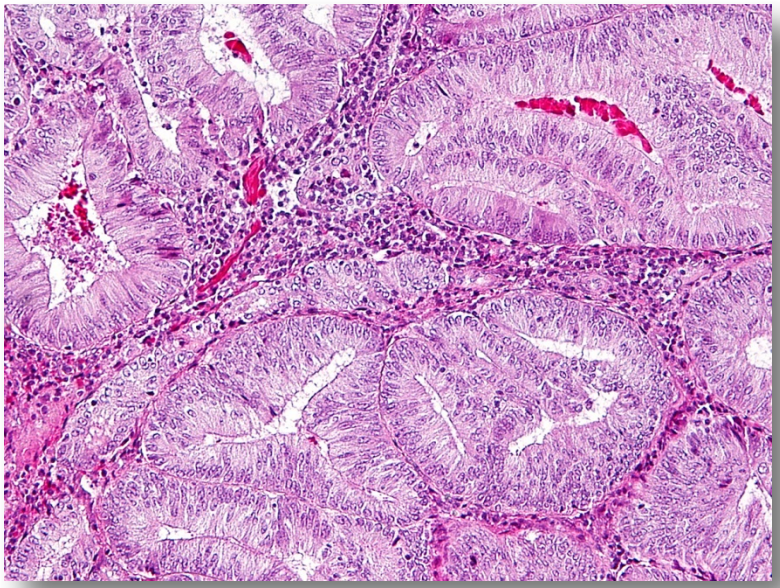
The NEW ENGLAND JOURNAL of MEDICINE

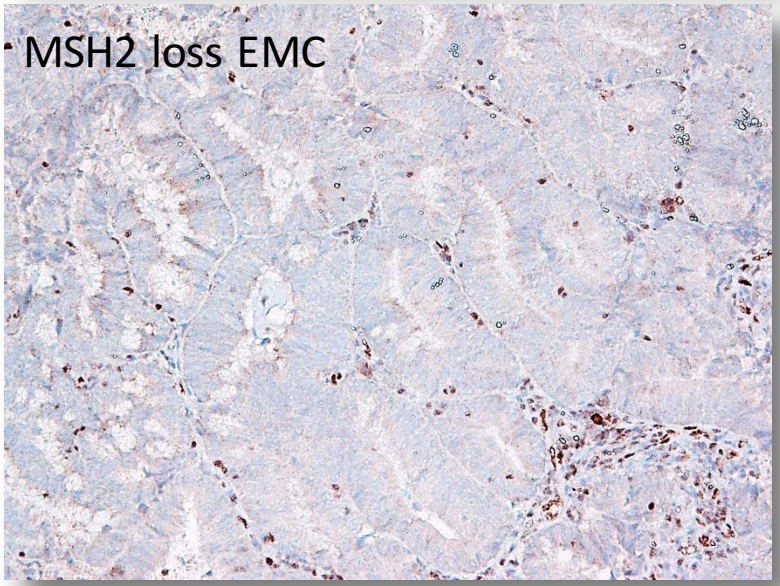
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Pembrolizumab NCT01876511

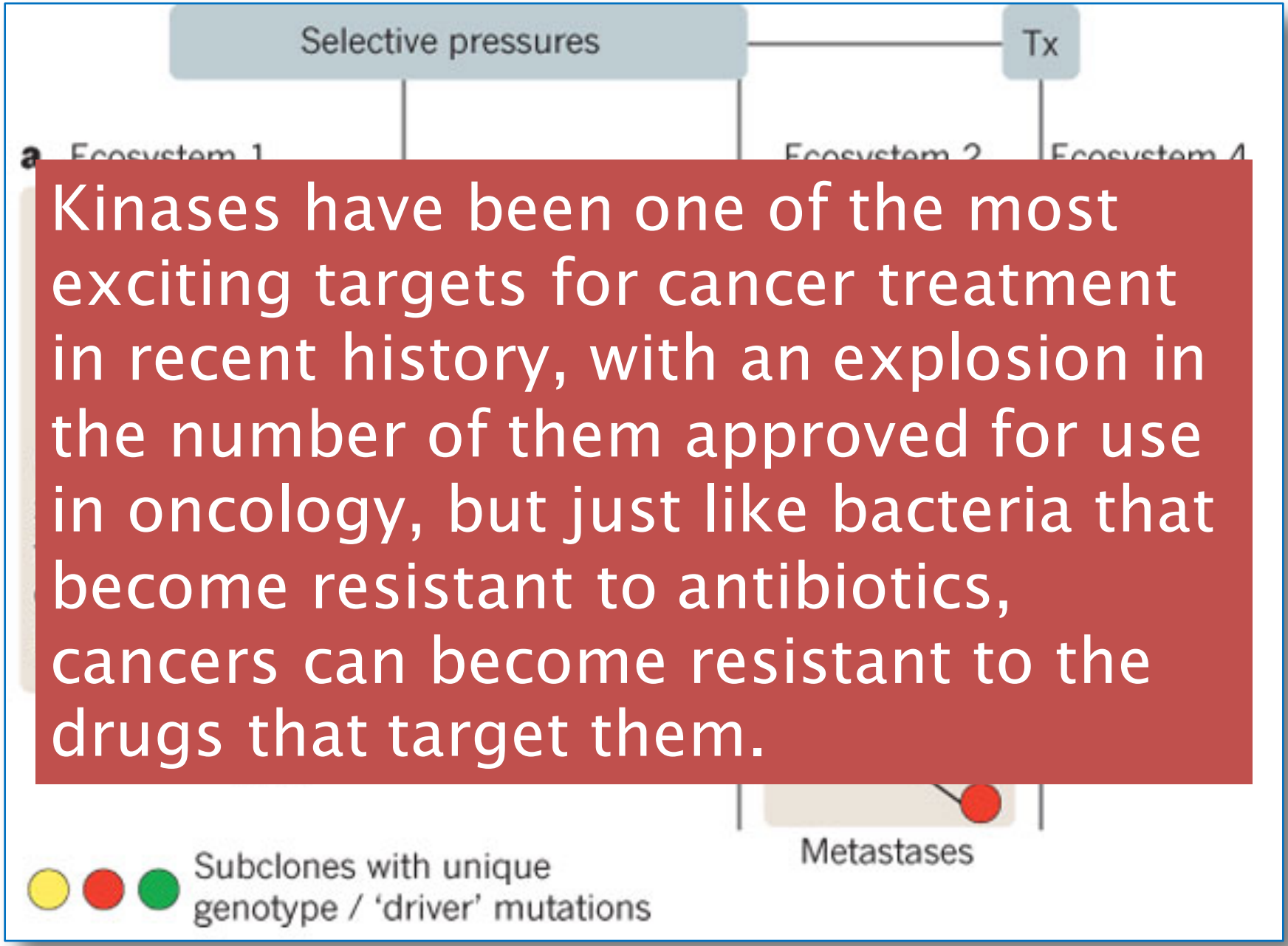






Challenges

- Resistance: Intra-tumoral heterogeneity (tumor evolution driven by Darwinian selection)
- A lot of potential targets but few effective and safe drugs (inhibitors)
- Predictive biomarkers/signatures
- Tumor micro- and macro-environment
- When and how to use?



Kinases have been one of the most exciting targets for cancer treatment in recent history, with an explosion in the number of them approved for use in oncology, but just like bacteria that become resistant to antibiotics, cancers can become resistant to the drugs that target them.

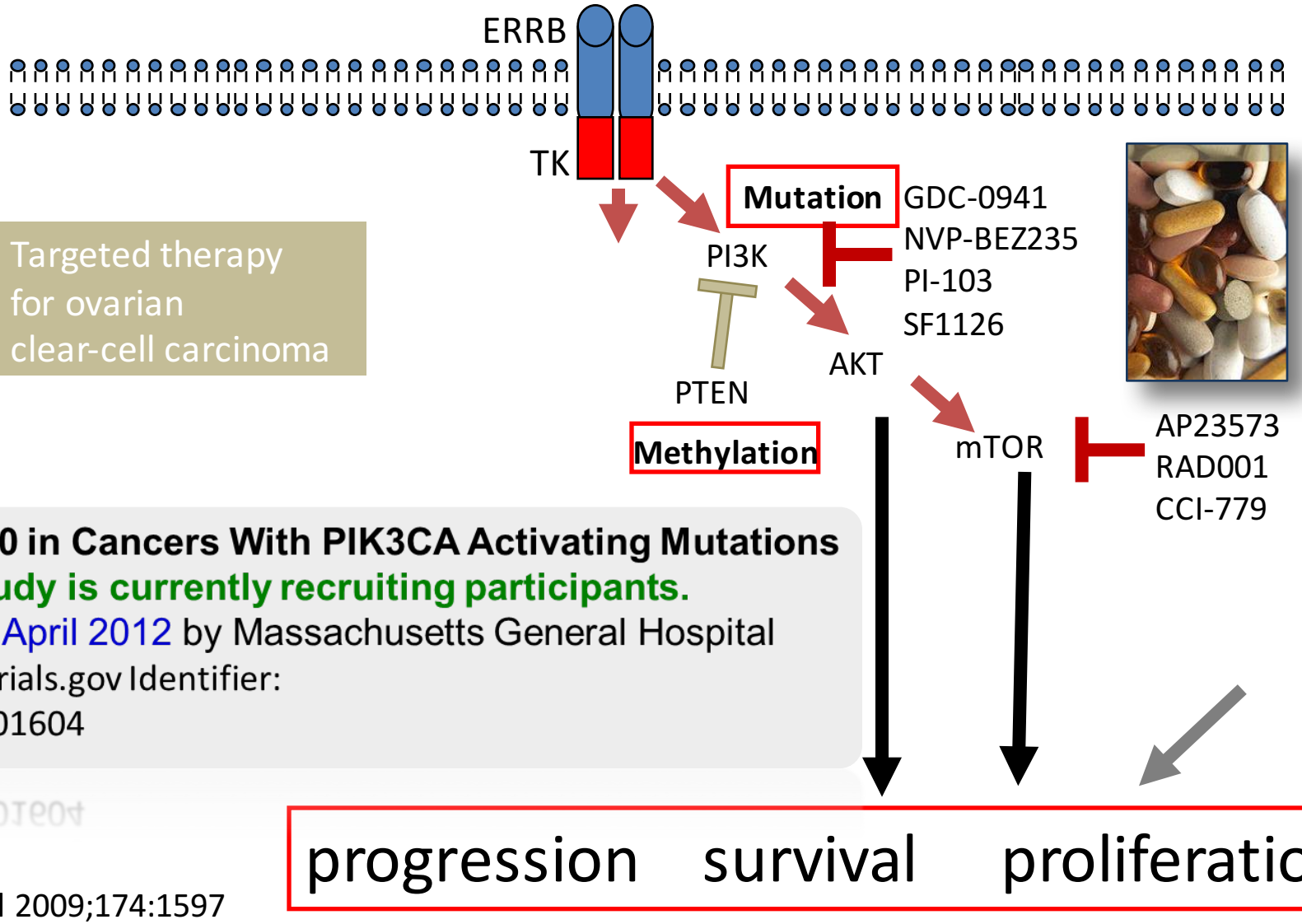
Nature 481:306, 2012

nature medicine

- Intratumoral heterogeneity as a source of therapeutic resistance.
- Majority of resistant clones were part of small, pre-existing subpopulations that selectively escaped under therapeutic challenge.
- Up-front therapeutic combinations that target non-overlapping resistance is a preferred approach?

de novo alterations, in part because of the resolution limits of next-generation sequencing. To address this, we developed a high-complexity barcode library, ClonTracer, which enables the high-resolution tracking of more than 1 million cancer cells under drug treatment. In two clinically relevant models, ClonTracer studies showed that the majority of resistant clones were part of small, pre-existing subpopulations that selectively escaped under therapeutic challenge. Moreover, the ClonTracer approach enabled quantitative assessment of the ability of combination treatments to suppress resistant clones. These findings suggest that resistant clones are present before treatment, which would make up-front therapeutic combinations that target non-overlapping resistance a preferred approach. Thus, ClonTracer barcoding may be a valuable tool for optimizing therapeutic regimens with the goal of curative combination therapies for cancer.

Targeting PI3K in ovarian clear cell carcinoma



Targeted therapy for ovarian clear-cell carcinoma

BKM120 in Cancers With PIK3CA Activating Mutations
This study is currently recruiting participants.
Verified April 2012 by Massachusetts General Hospital
ClinicalTrials.gov Identifier:
NCT01501604

Am J Pathol 2009;174:1597

Determining appropriate use of biomarker status in treatment of metastatic colorectal cancer

KRAS/NRAS wild-type

- Eligible for an anti-VEGF or anti-EGFR regimen in a given line of therapy

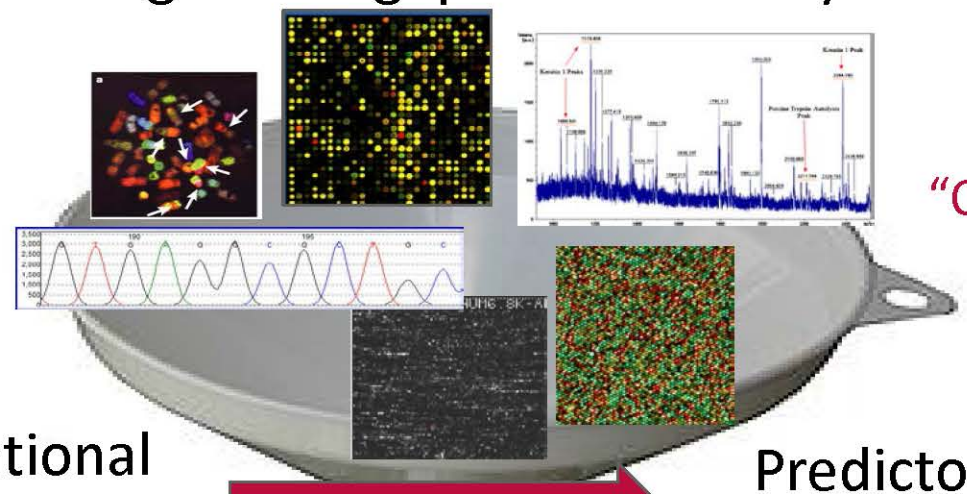
KRAS/NRAS mutated

- Eligible for an anti-VEGF regimen
- Ineligible for an anti-EGFR regimen

Translation from omics discoveries to clinically useful omics-based tests

Discovery

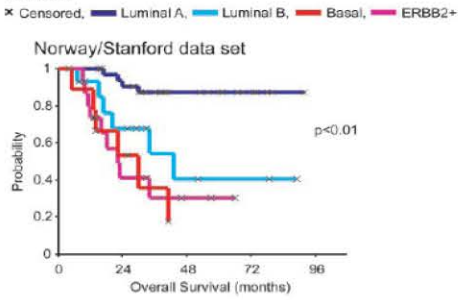
High-throughput omics assays

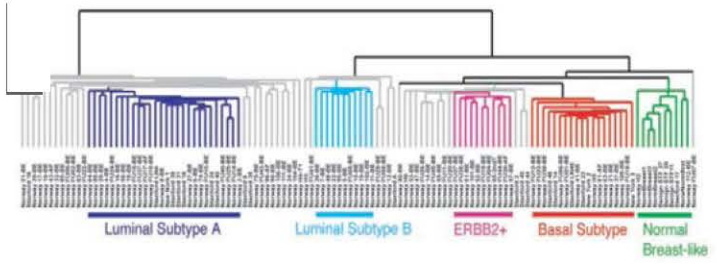


"Omics predictor"

Computational models

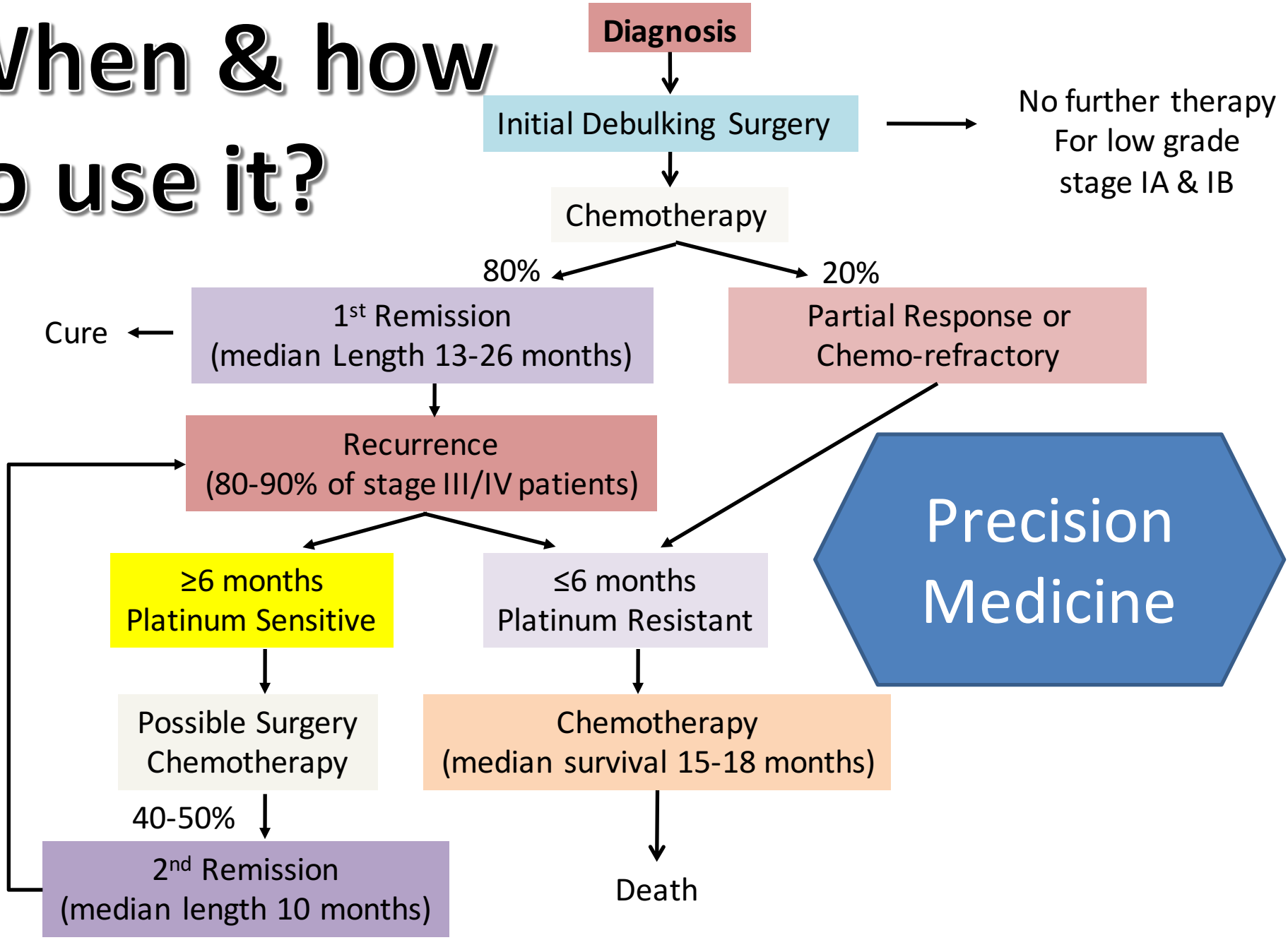
Predictors, classifiers, risk scores





Clinical Utility?

When & how to use it?



"Cancer is no more of a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal combustion engine would not help anyone to understand our traffic problems. The causes of congestion can be many. A traffic jam is due to failure of the normal relationship between driven cars and their environment can occur

whether they themselves

are running normally or not."

D.W. Smithers, Lancet, March 1962

Summary- choose your poison

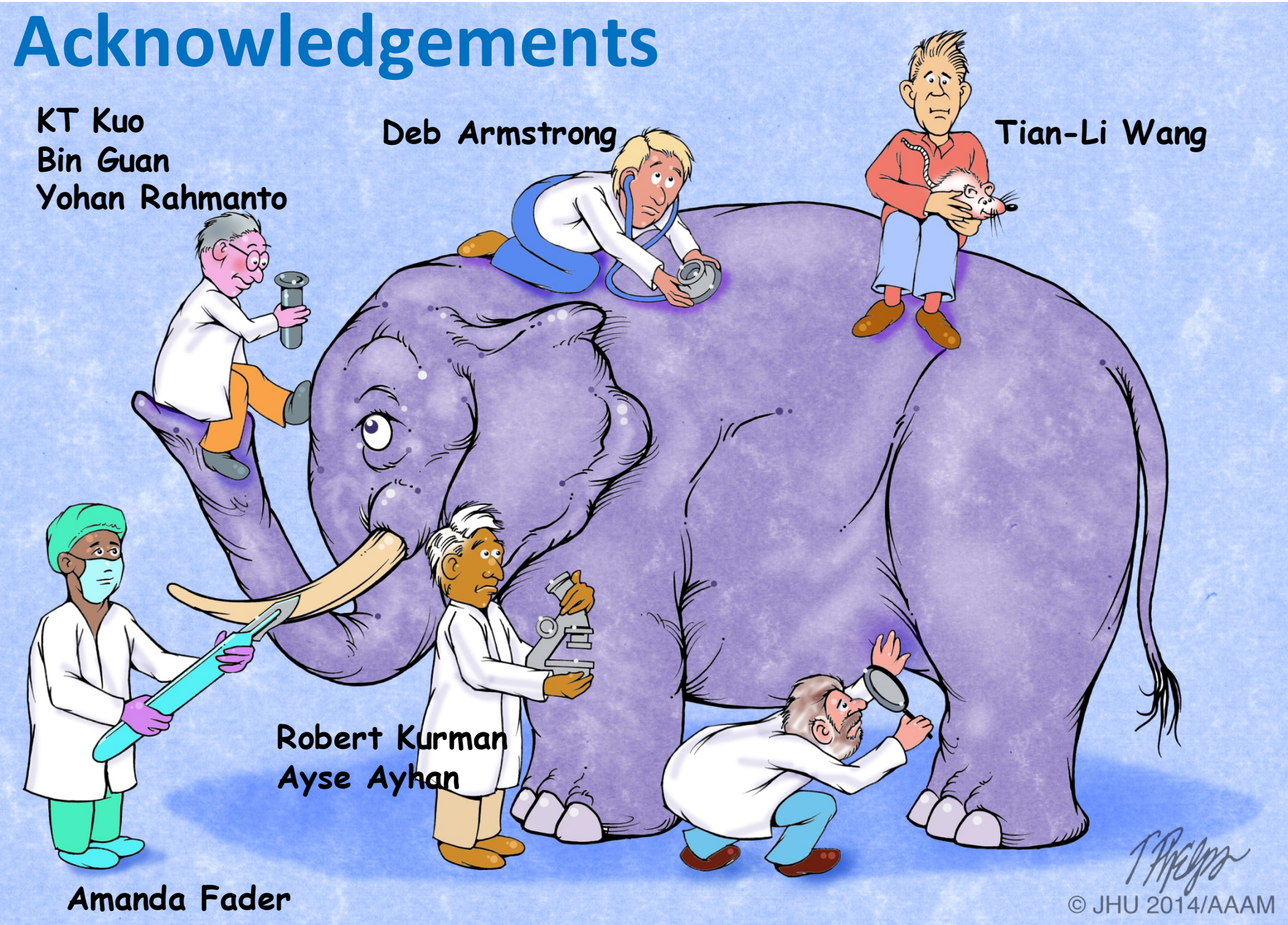
We are not there yet but making progress

Targeted therapy and precision cancer medicine based on understanding tumor biology

Sensitization of chemotherapy and radiotherapy

Revisit personalized primary prevention and early detection

Acknowledgements



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