Ovarian cancer

Ovarian Cancer in the 'Omics Era

TRACO lecture

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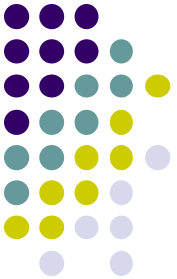
Ovarian Cancer



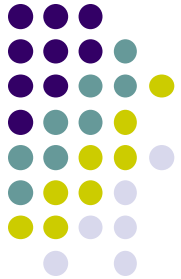
- Most lethal gynecologic malignancy in the US
  - >16,000 deaths/yr
  - 5th most common cancer death for women
- 70% diagnosed with advanced disease
- < 35% of advanced stage patients alive at 5y

Ovarian Cancer Stages

Ovarian Cancer

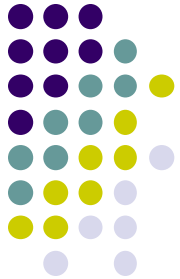
Stage	Description	Incidence	Survival
I	Confined to ovaries	20%	90%
II	Confined to pelvis	5%	65%
III	Spread IP or nodes	58%	45%
IV	Distant metastases	17%	<5%

Treatment for Newly Diagnosed Ovarian Cancer



- Complete surgical staging
- Optimal reductive surgery
- Chemotherapy
- *Clinical Trials*

The State of Treatment for Newly Diagnosed Ovarian Cancer

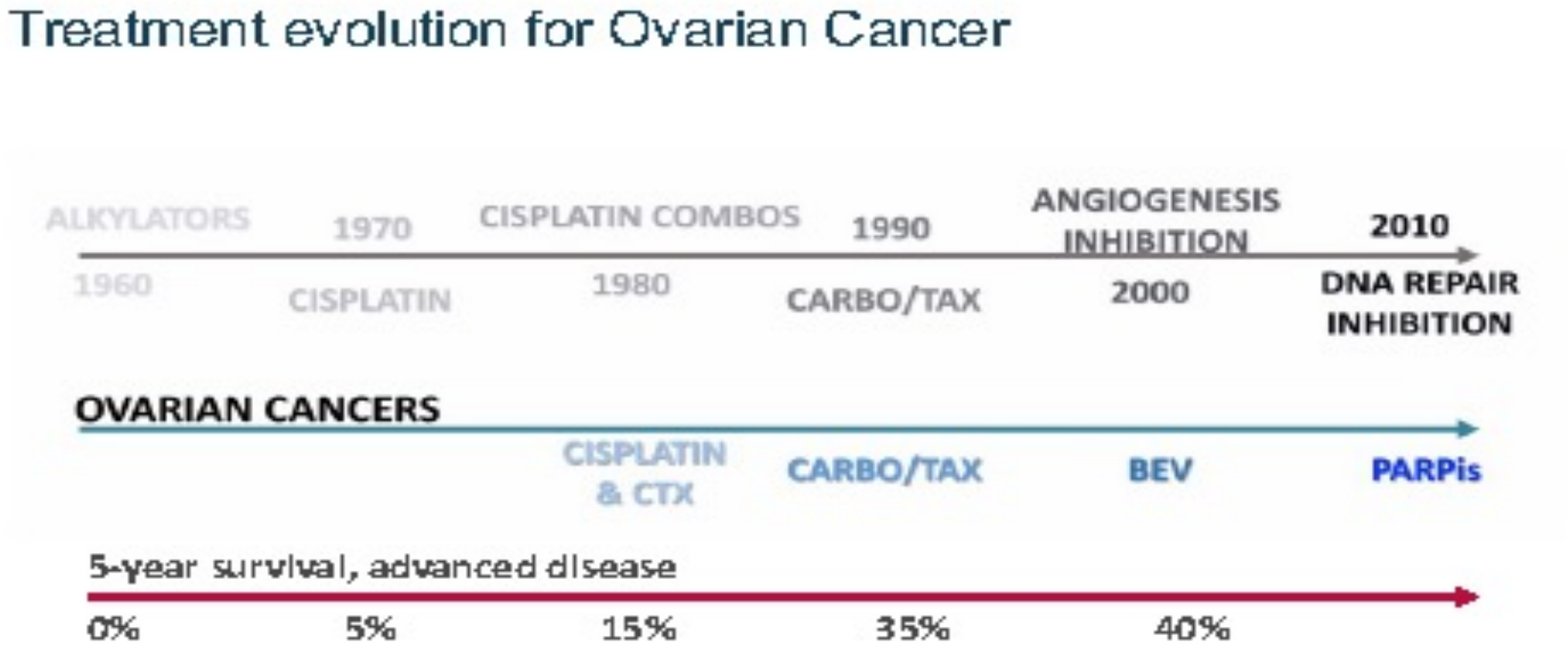


- Complete surgical staging
- Optimal reductive surgery
- **Chemotherapy**
  - Platinum = cisplatin or carboplatin

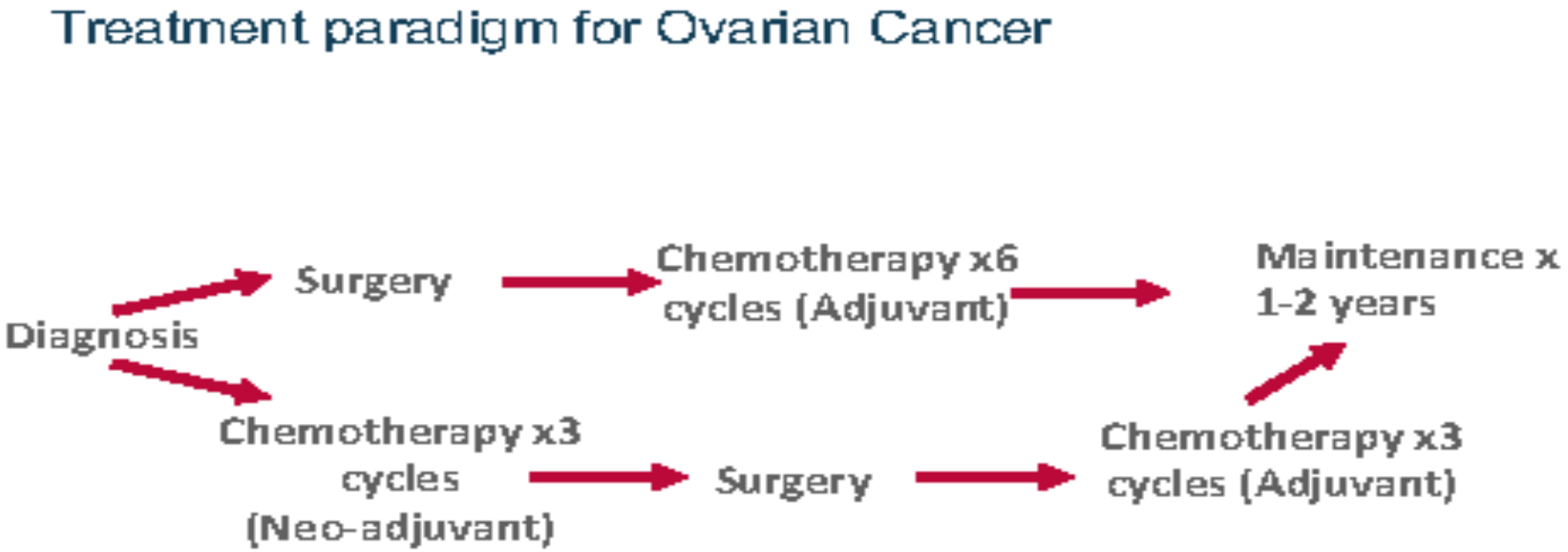
    AND
  - Taxane = paclitaxel or docetaxel
  - *Intraperitoneal if Stage III, optimal reduction*

- *Clinical Trials*

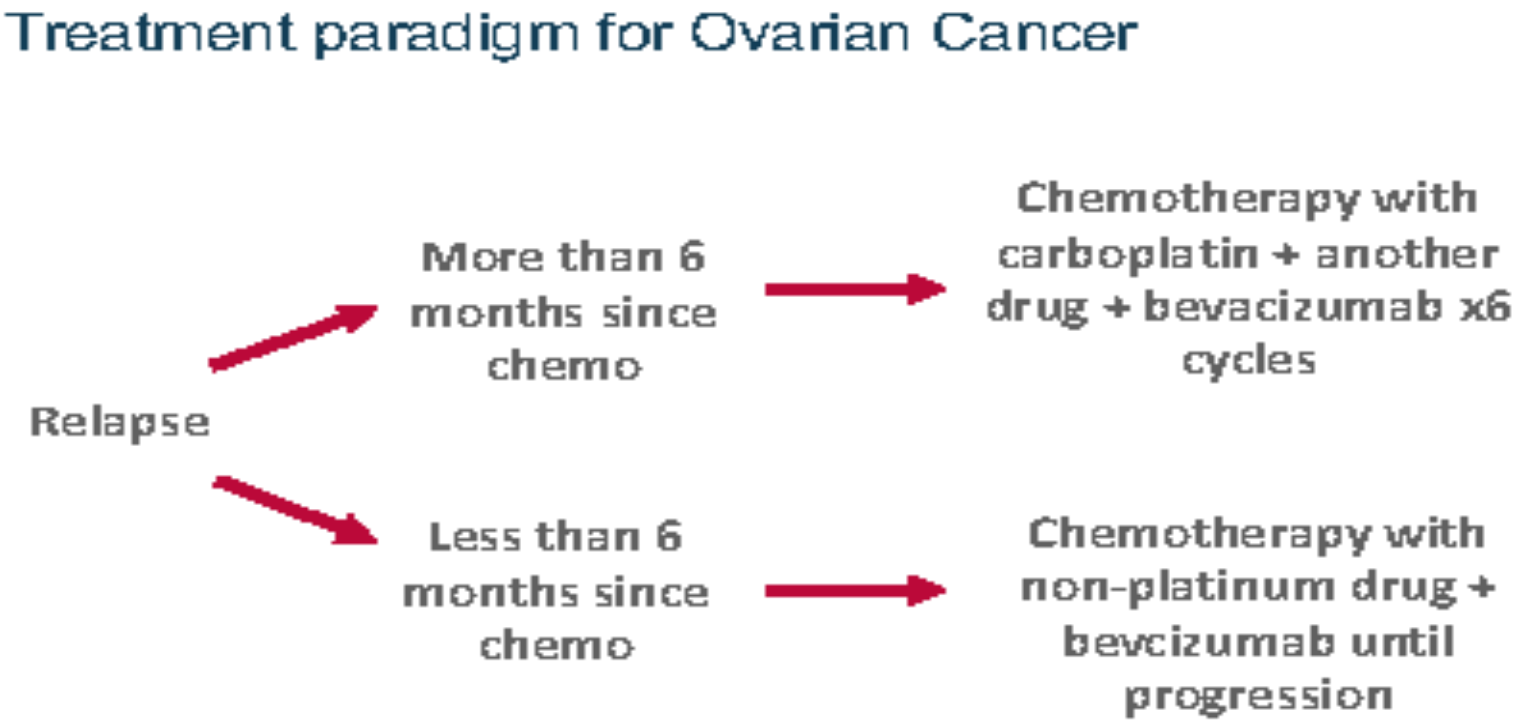
Ovarian cancer treatment



Treatment paradigm



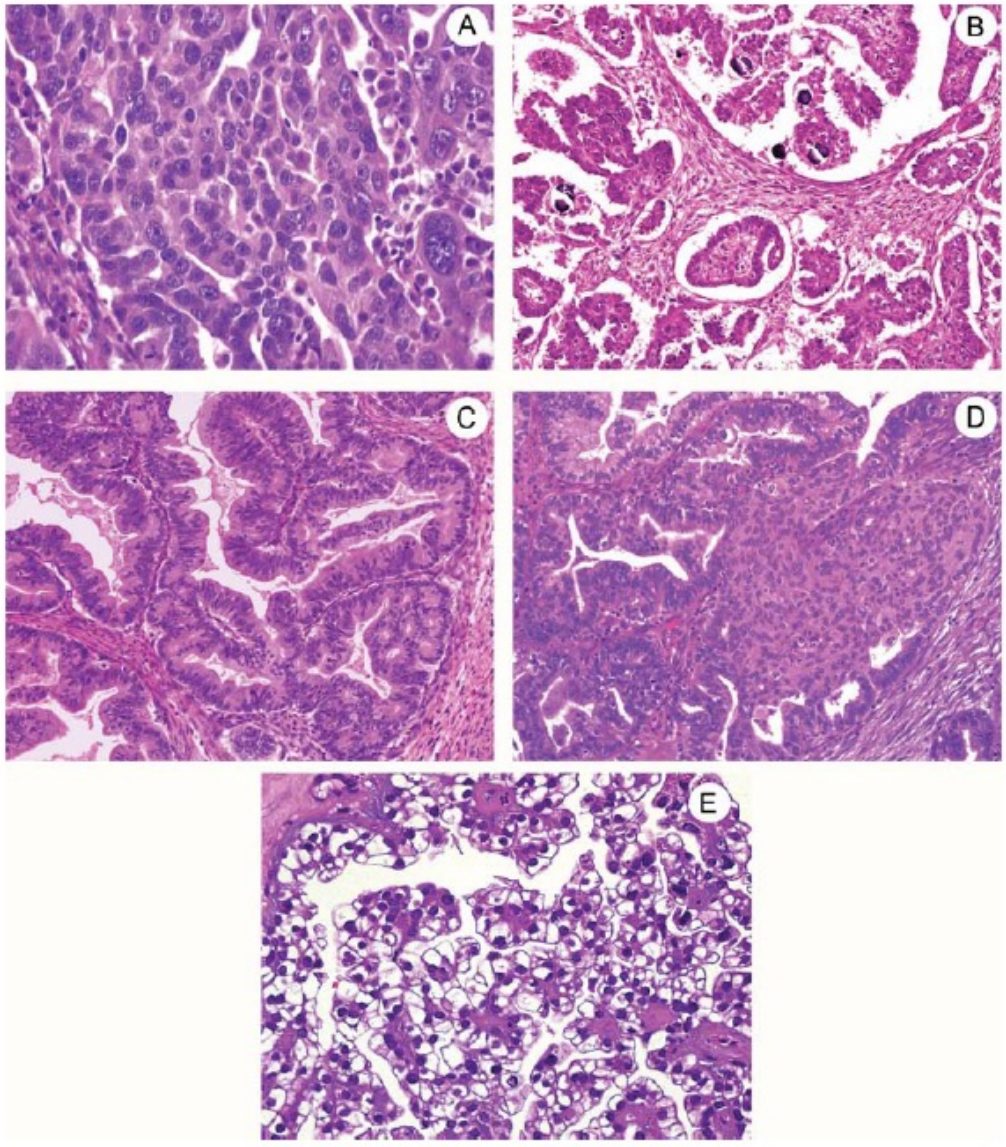
Treatment paradigm



Ovarian Cancer

Prevalence

- Serous – 80%
- Endometrioid – 10%
- Clear cell – 5%
- Mucinous – 3%
- Other – 2%



Ovarian Cancer

Ovarian Cancer

Prevalence

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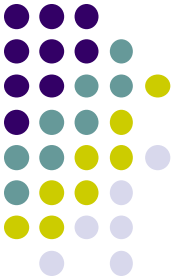
- Mucinous – 3%
- Other – 2%

Tissue of origin

- Fallopian tube?
  - Serous
- Endometriosis?
  - Endometrioid and clear cell
- Mullerian epithelium
  - Extra-uterine

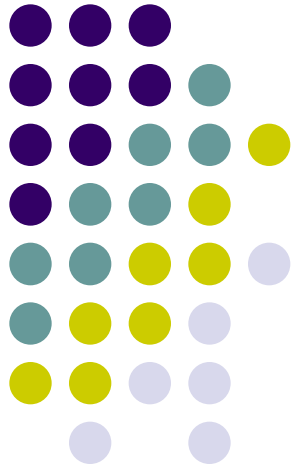
Ovarian Cancer



- Increasing our understanding about the biological and biochemical events underlying ovarian cancer progression will create avenues for new treatments

- Can we use Genomics?

Clear cell, Endometrioid



Clear Cell cancers

- 5-10% of all cases (serous = 70%)
- Worse response to standard chemotherapy
- Associated with endometriosis (up to 40%)

Clear cell ovarian cancer

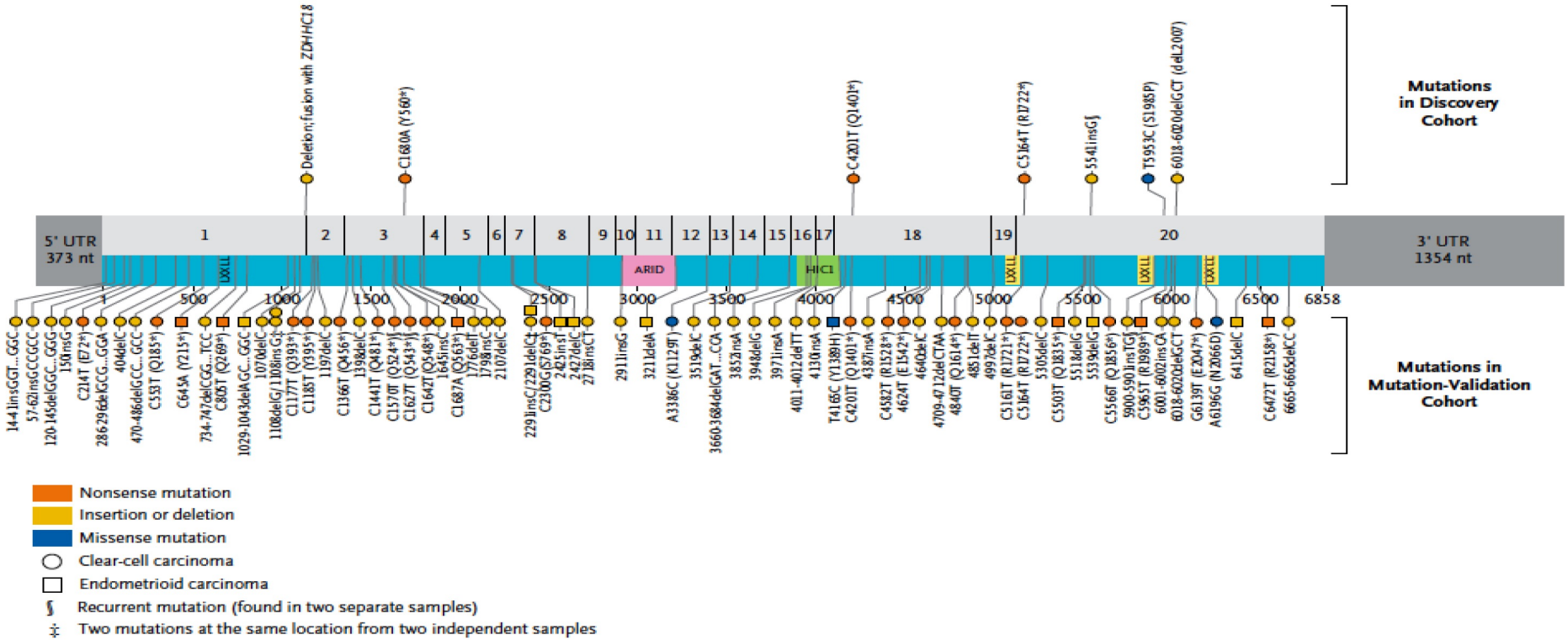
Clear cell OC – genomics

- Sequenced RNA from 18 clear cell ovarian cancers, and one cell line (discovery)
- Sequenced DNA exons from 210 samples
  - 101 more clear cell, 33 endometrioid, 76 serous, 1 more clear cell line (validation)
- Immunostain 455 more samples
  - 132 clear cell, 125 endometrioid, 198 serous

Weigand, *NEJM* 2010

ARID1A mutations in clear cell

ARID1A mutations in clear cell

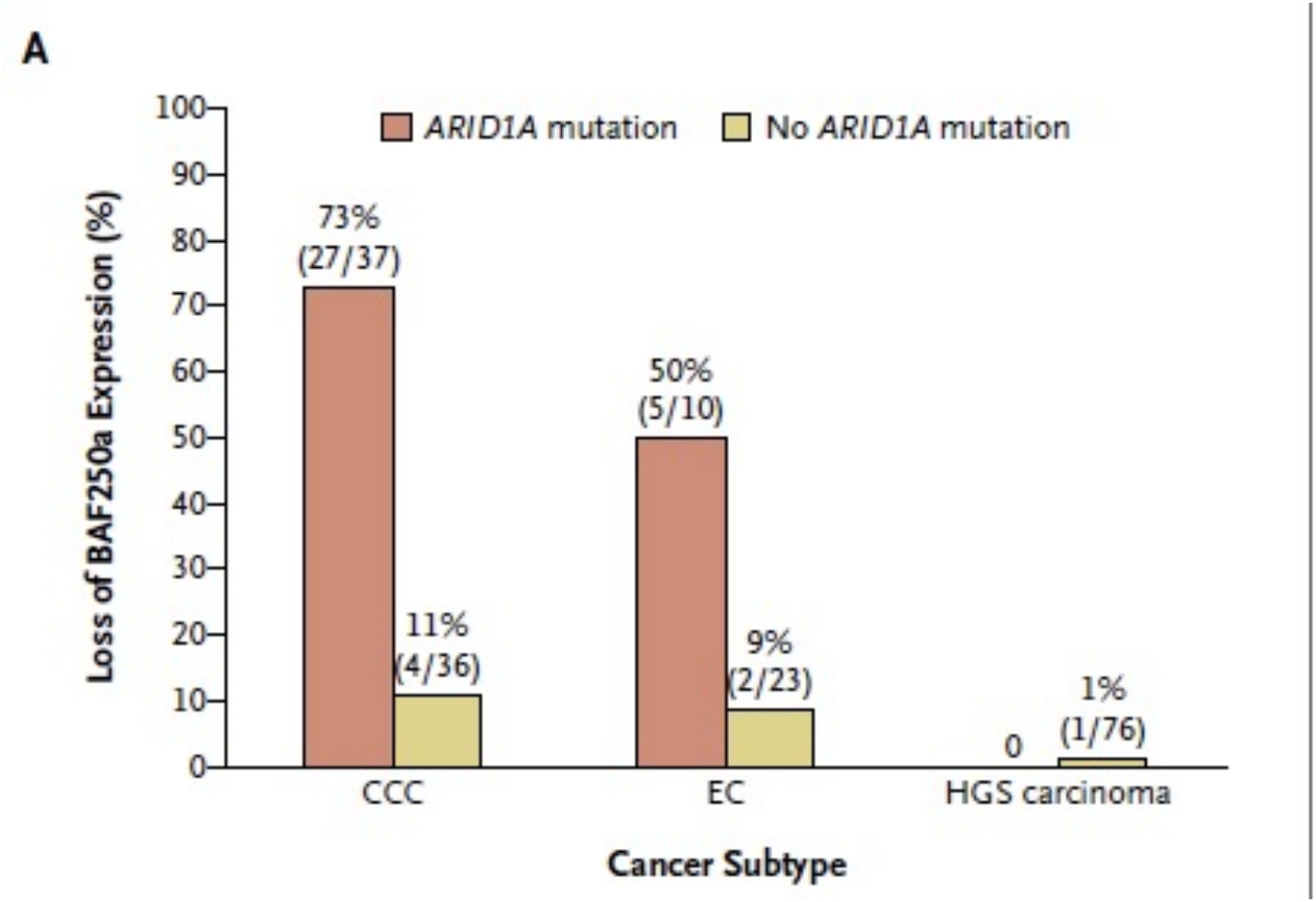


Weigand, *NEJM* 2010

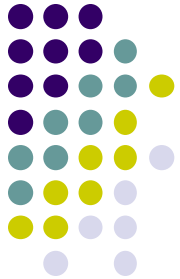
ARID1A

- SWI-SNF chromatin remodeling complex
- Mutated in breast cancer, lung cancer
- 1p36: deleted 6% of all cancers
- Tumor suppressor gene?

ARID1A mutations

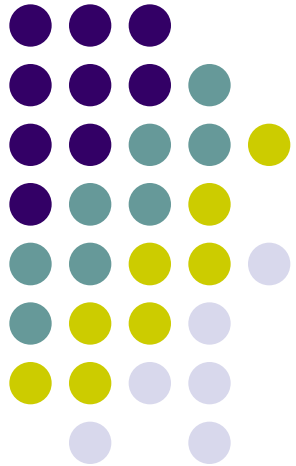


Clear cell and endometrioid cancer

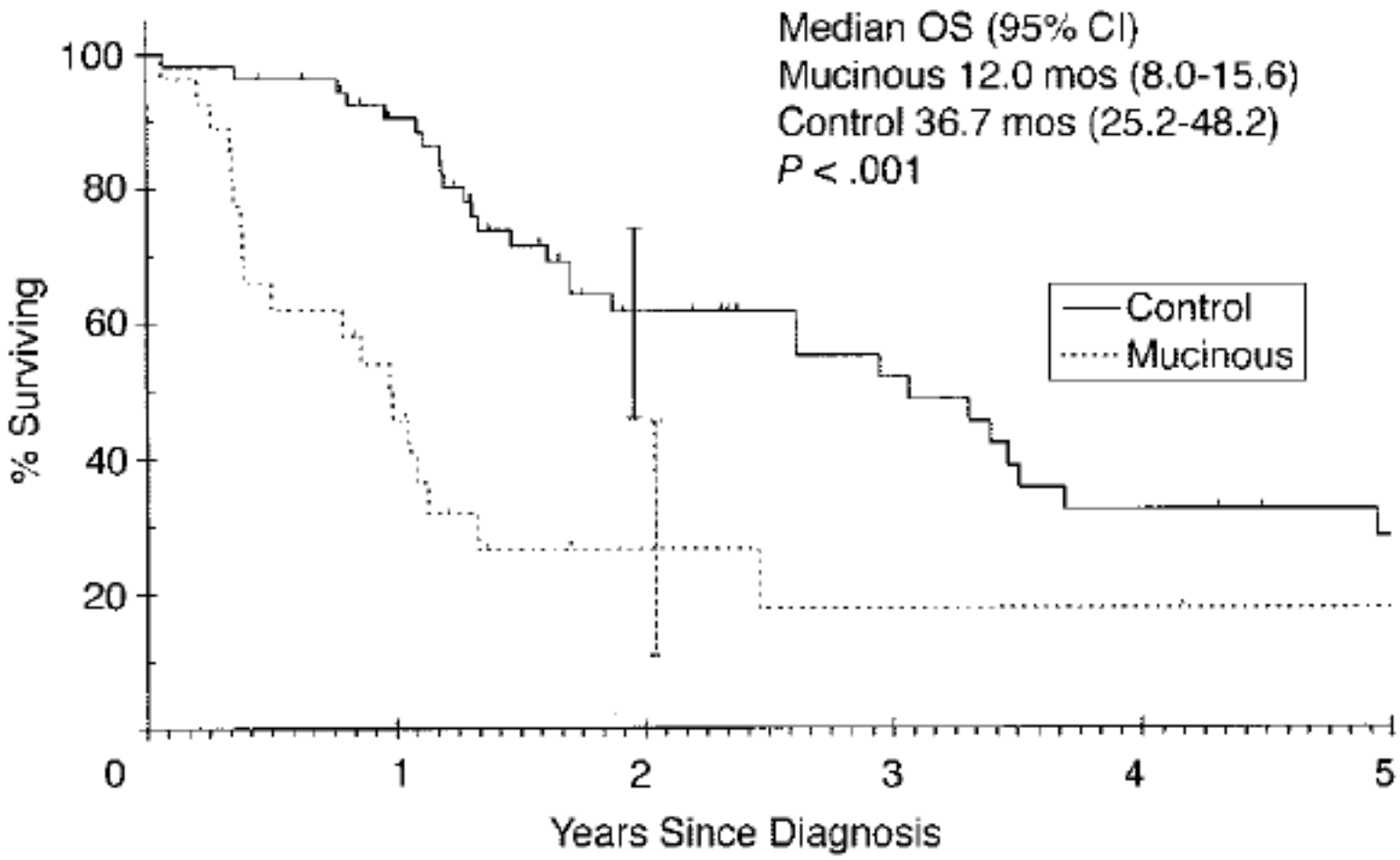


- ARID1A mutated or lost in
  - Over 40% clear cell
  - 30% endometrioid
  - Less than 1% serous
- Unknown oncogenic mechanism
  - No indication of which resulting pathways affected
  - Unclear therapeutic utility
- Diagnostic utility?
  - Not a ‘functional’ experiment

Mucinous

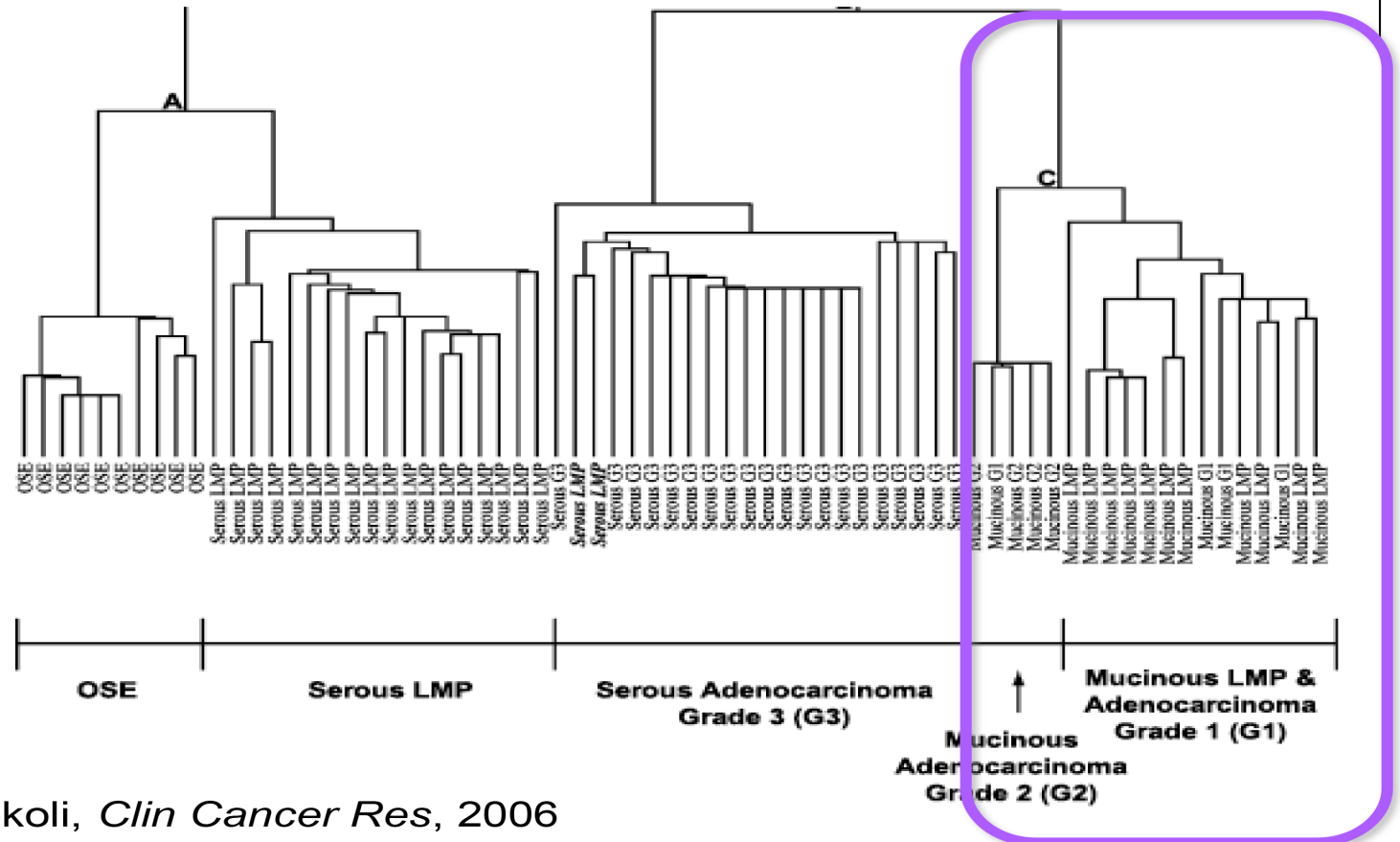


Mucinous ovarian cancer



Gene expression

Gene expression – mucinous versus serous



Wamunyokoli, *Clin Cancer Res*, 2006

K-ras mutations

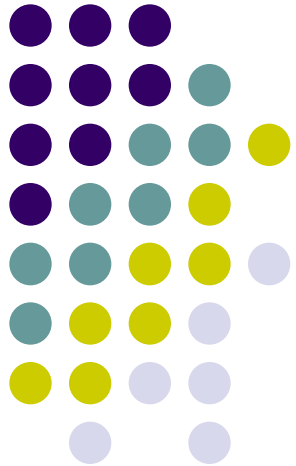
KRAS mutations - mucinous

Table 2: KRAS mutation frequencies observed in borderline malignancies

	borderline		
histotype	**n**	**mutated**	**% mutated**
serous	20	7	35.00
endometroid	1	0	0.00
mucinous	6	3	50.00
unknown	2	0	0.00
total	29	10	34.48

Auner, *BMC Cancer* 2009

Low grade serous



KRAS and BRAF mutations

KRAS and BRAF mutations

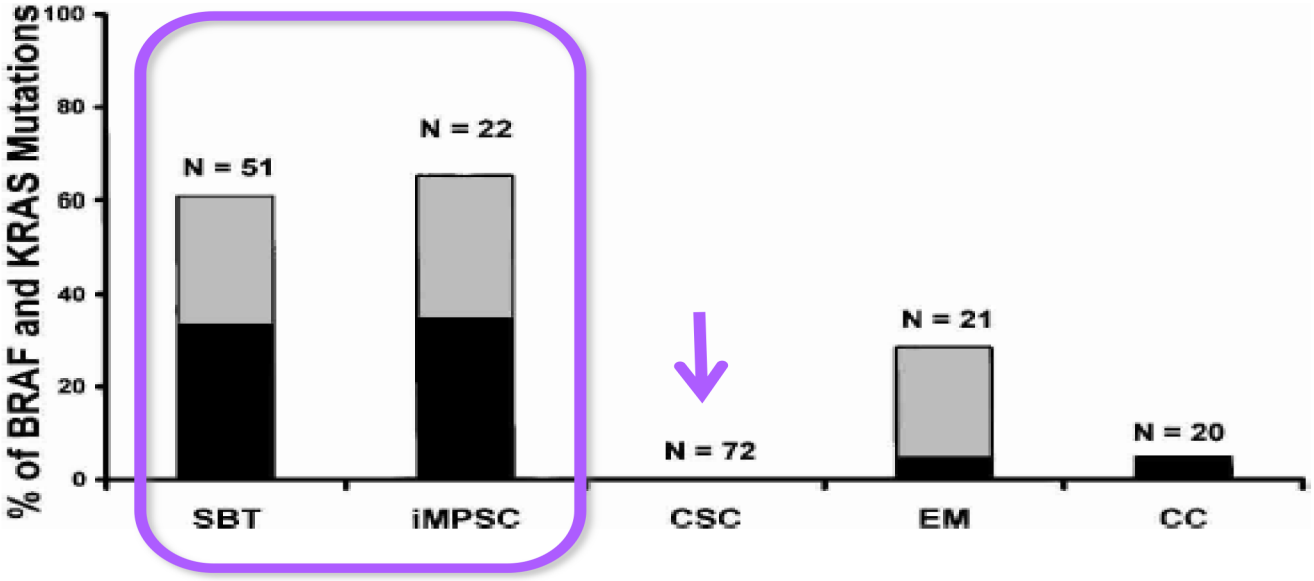
- BRAF codon 599
- KRAS codon 12 or 13

- 15 of 22 (68%) of low grade serous cancers
- 31 of 51 (61%) precursor lesions (SBT)
- None of 72 high grade serous cancers

Singer, *JNCI* 2003

KRAS and BRAF

KRAS and BRAF mutations



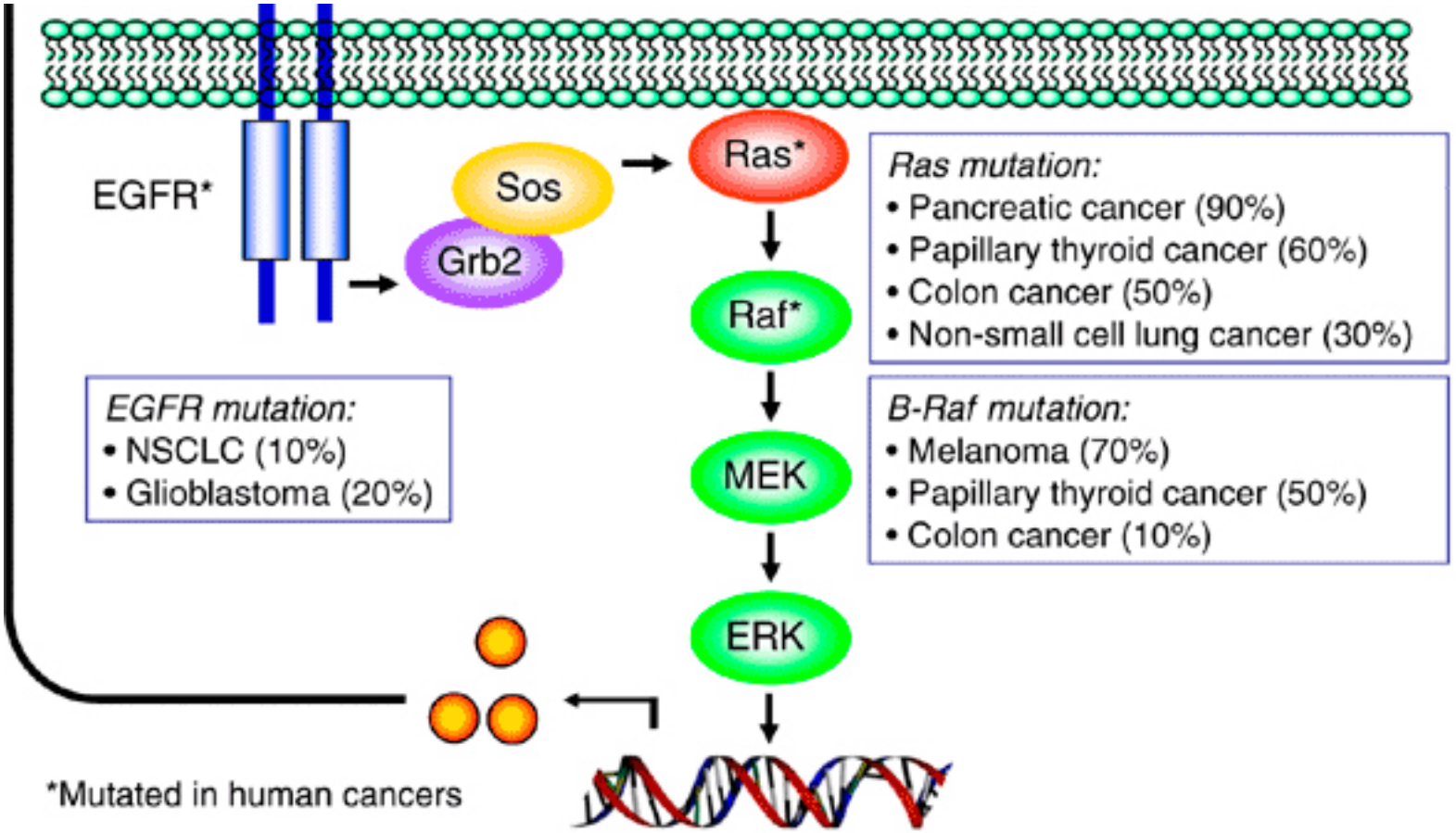
Serous borderline tumors

Invasive low grade serous cancers

High grade serous cancers

Singer, *JNCI* 2003

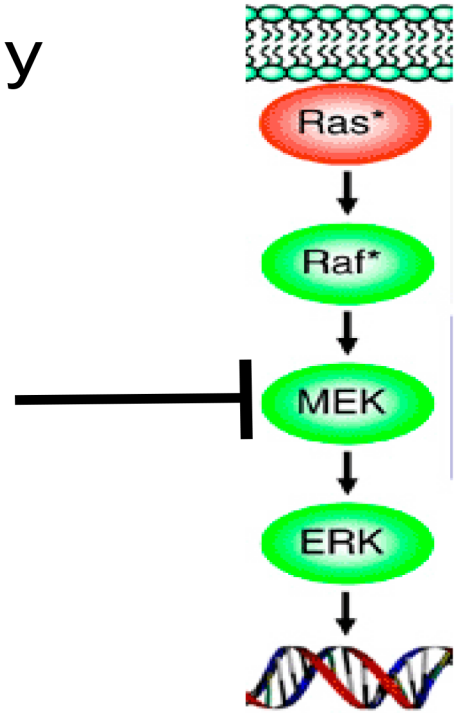
RAS signaling pathway
- a potential driver?



MEK inhibitor

Clinical trial: MEK inhibitor

- Recurrent Low Grade Serous ovarian cancer
- Selumetinib 50 mg twice daily
- 52 patients
  - 8 responses
  - 34 stable disease >4mo



Farley, *Lancet Oncol* 2013

Selumetinib responses

	Number	No tumour response	Tumour response	p value*
Total	34	27 (79%)	7 (21%)	
BRAF mutation				
No	32	25 (78%)	7 (22%)	1·000
Yes	2	2 (100%)	0	
KRAS mutation				
No	20	15 (75%)	5 (25%)	0·672
Yes	14	12 (86%)	2 (14%)	
BRAF or *KRAS* mutation				
No	18	13 (72%)	5 (28%)	0·405
Yes	16	14 (88%)	2 (13%)	

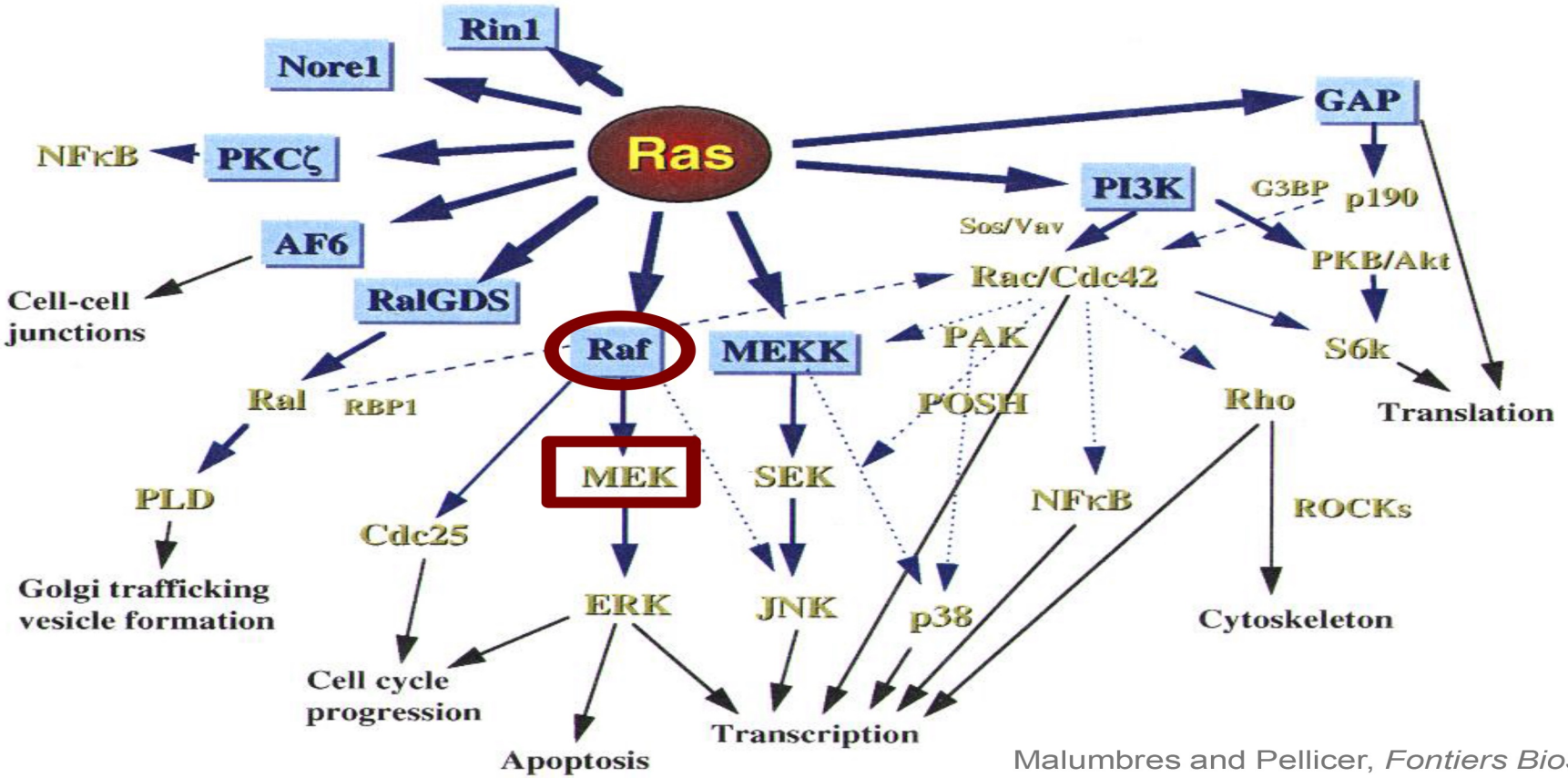
Data are number (%), unless otherwise indicated. *Fisher's exact test.

Table 8: **Tumour response (complete or partial) by *BRAF* and *KRAS* mutations**

Farley, *Lancet Oncol* 2013

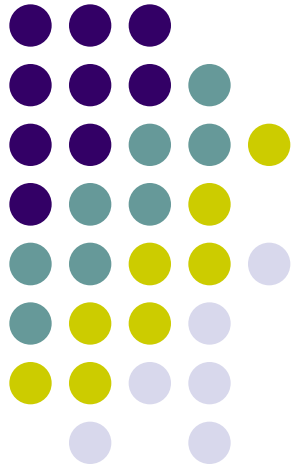
RAS signaling

RAS signaling



Malumbres and Pellicer, *Fontiers Biosci* 1998

High grade serous



High grade serous cancers

High grade serous cancers

- **The Cancer Genome Atlas (TCGA)**
  - Clinically annotated HGS-OvCa samples
  - Identify molecular abnormalities that
    - influence pathophysiology,
    - affect outcome and
    - constitute therapeutic targets.
  - Microarray analyses: 489 HGS-OvCa tumours,
    - mRNA expression,
    - microRNA (miRNA) expression,
    - DNA copy number and
    - DNA promoter methylation for and
  - Whole exome DNA sequence: 316 samples.

The Cancer Genome Atlas, *Nature* 2011

High grade serous cancers

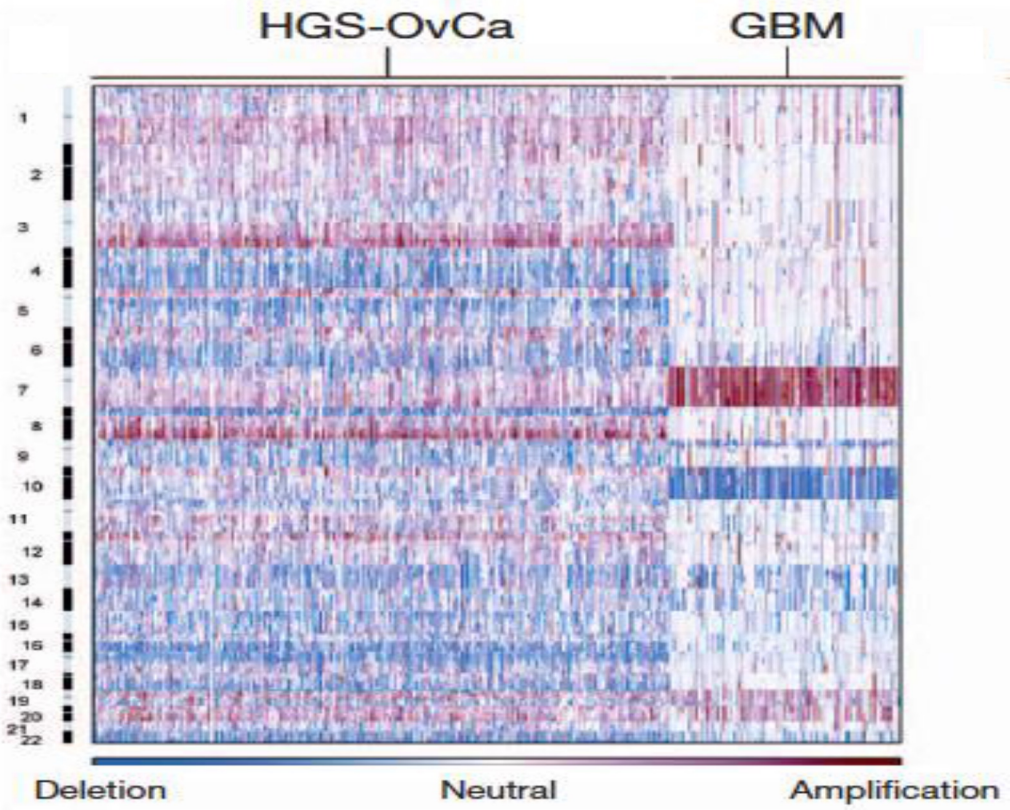
- **Sample inclusion criteria**
  - Newly diagnosed patients
  - ovarian serous adenocarcinoma
  - no prior treatment
  - companion normal tissue specimen
    - adjacent normal tissue,
    - peripheral lymphocytes,
    - or previously extracted germline DNA

Genome copy number

Genome copy number abnormality

Copy number profiles of 489 HGS-OvCa, compared with profiles of 197 glioblastoma multiforme (GBM) tumours.

Copy number increases (red) and decreases (blue) are plotted as a function of distance along the normal genome (vertical axis, divided into chromosomes).



Mutated genes

Table 2 | Significantly mutated genes in HGS-OvCa

Gene	No. of mutations	No. validated	No. unvalidated
TP53	302	294	8
BRCA1	11	10	1
CSMD3	19	19	0
NF1	13	13	0
CDK12	9	9	0
FAT3	19	18	1
GABRA6	6	6	0
BRCA2	10	10	0
RB1	6	6	0

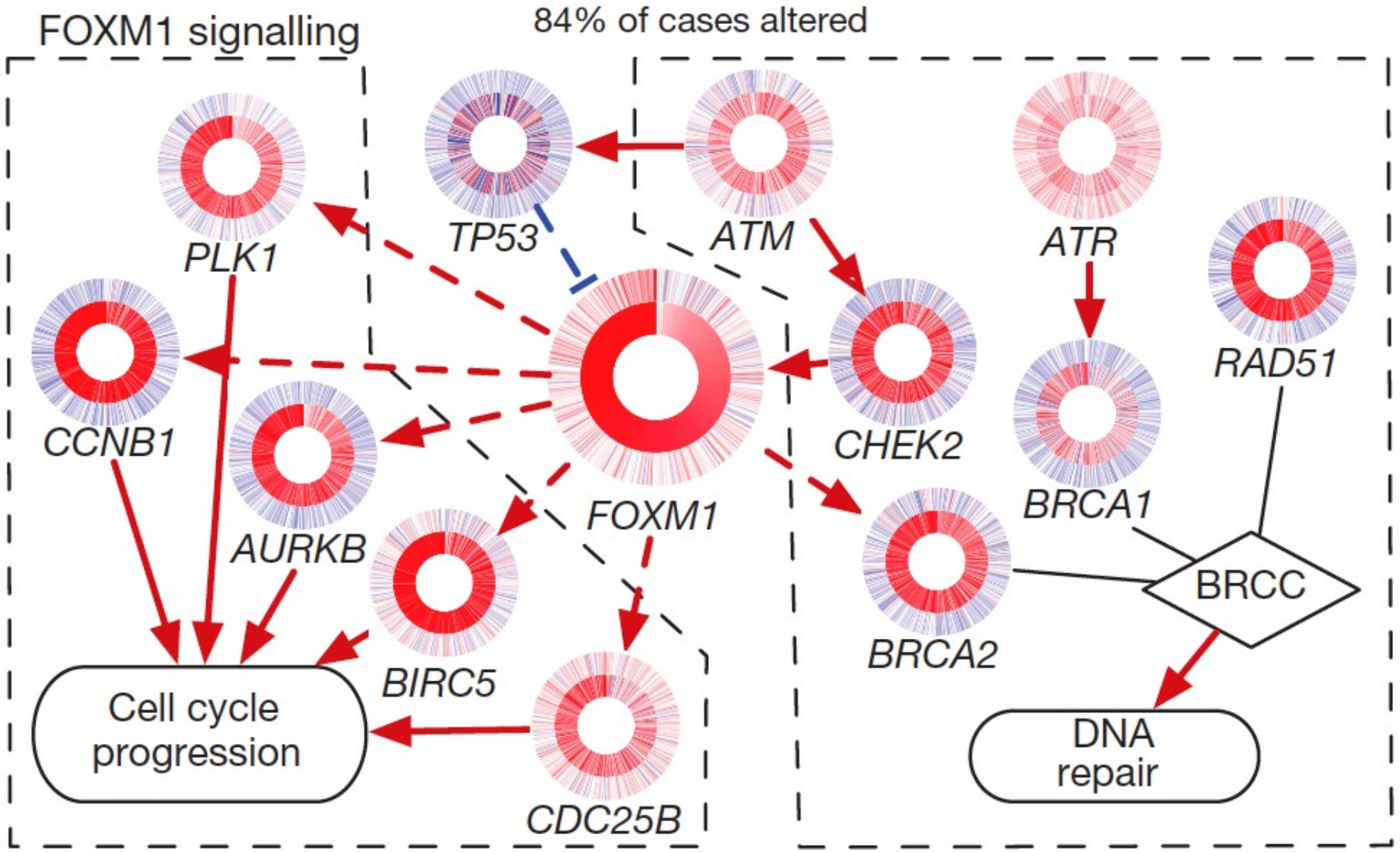
Validated mutations are those that have been confirmed with an independent assay. Most of them are validated using a second independent whole-genome-amplification sample from the same tumour. Unvalidated mutations have not been independently confirmed but have a high likelihood to be true mutations. An extra 25 mutations in *TP53* were observed by hand curation.

The Cancer Genome Atlas, *Nature* 2011

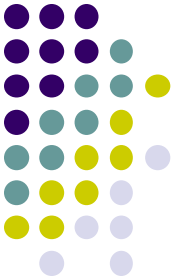
Altered pathways

Altered pathways in HGS-OvCa

Altered pathways in HGS-OvCa



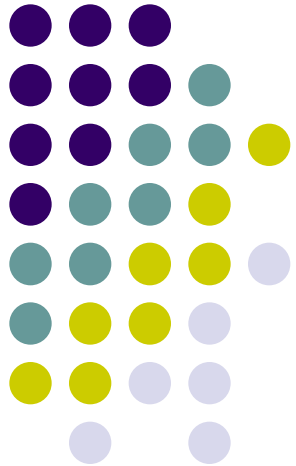
TCGA – what next?



- New **therapeutic** approaches?
  - 50% with HR defects : **PARP inhibitors**
  - commonly deregulated pathways: RB, RAS/PI3K, FOXM1, NOTCH, provide opportunities for therapeutic treatment
  - Inhibitors exist for 22 genes in regions of recurrent amplification
- aberrant genes or **networks**: targeted therapies selected to be effective ...

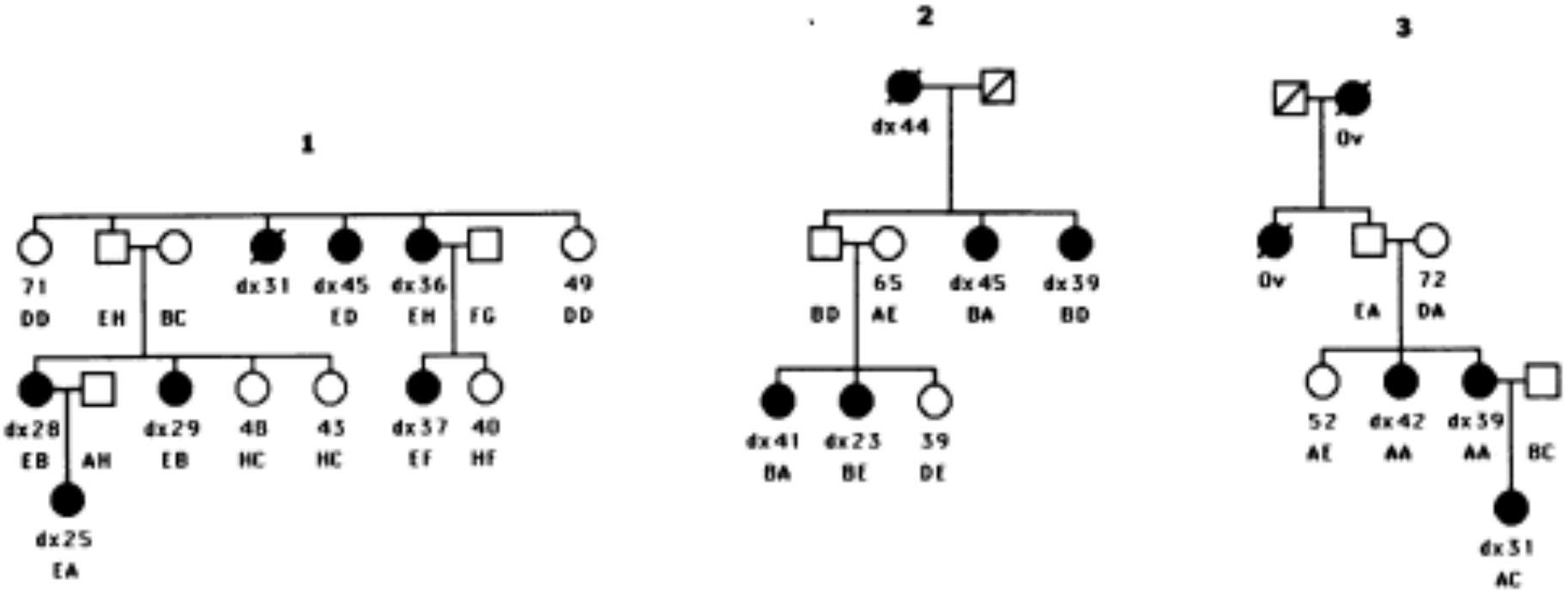
Targeting deficient Homologous Recombination

PARP inhibitors



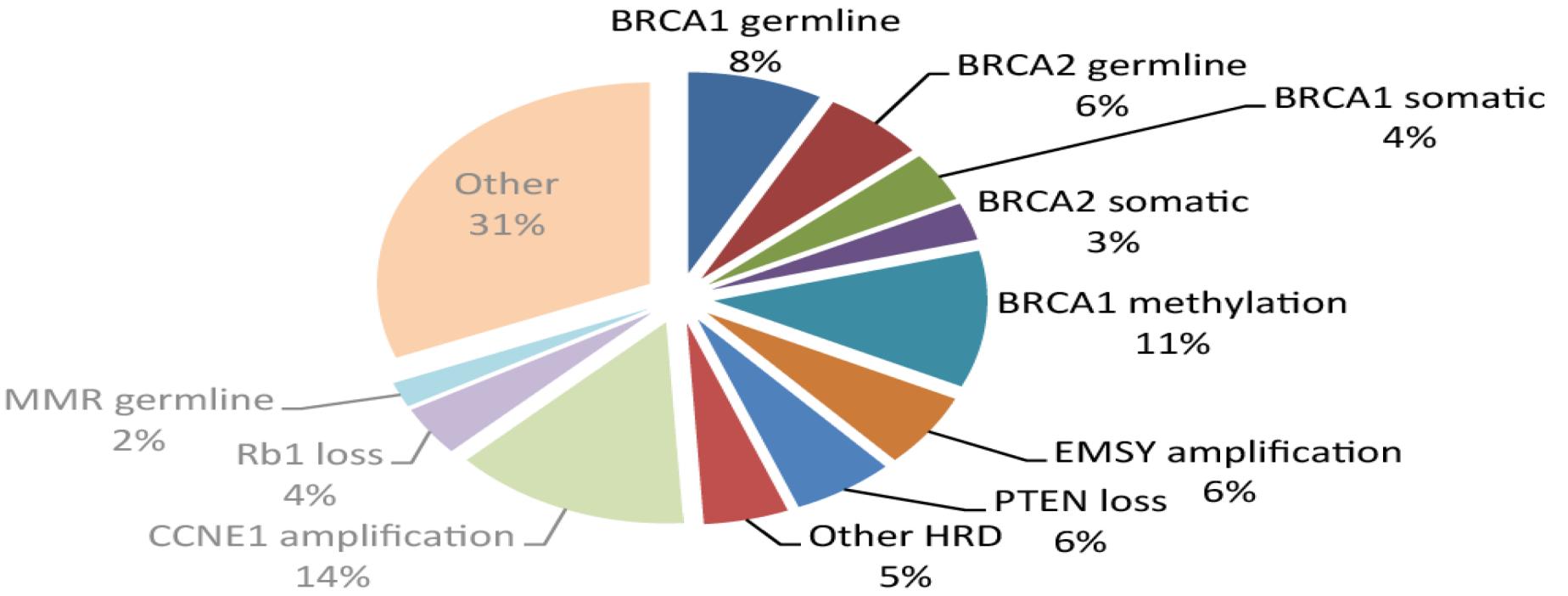
BRCA mutations

- Hall…King, *Science*, 1990



High grade serous cancers

High grade serous cancers



* HRD, homologous recombination defect

DNA repair

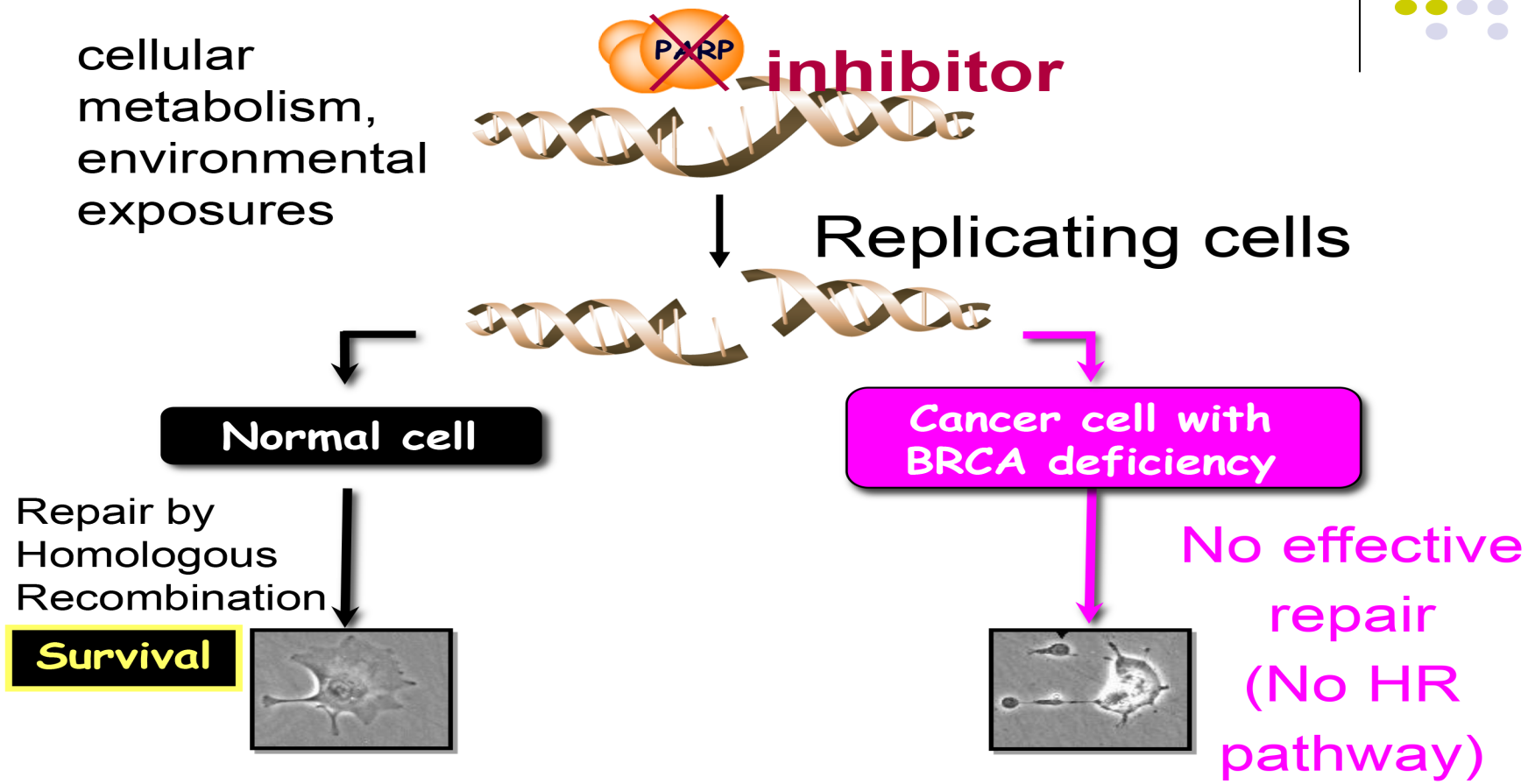
How is DNA repaired?

- Homologous recombination **(HR)**
- Undamaged DNA is the guide
- Replaces damaged part with the "correct" code
- **Uses BRCA**

- Base excision repair **(BER)**
- Cuts out damaged DNA
- Joins cut end with another piece
- **Uses PARP**

PARP inhibition

PARP inhibition: BRCA-mutant cancers



PARP inhibitors

PARP inhibitors

- Olaparib (Lynparza)
- Rucaparib (Rubraca)
- Niraparib (Zejula)

PARP inhibitors and clinical trials

PARP inhibitors clinical trials

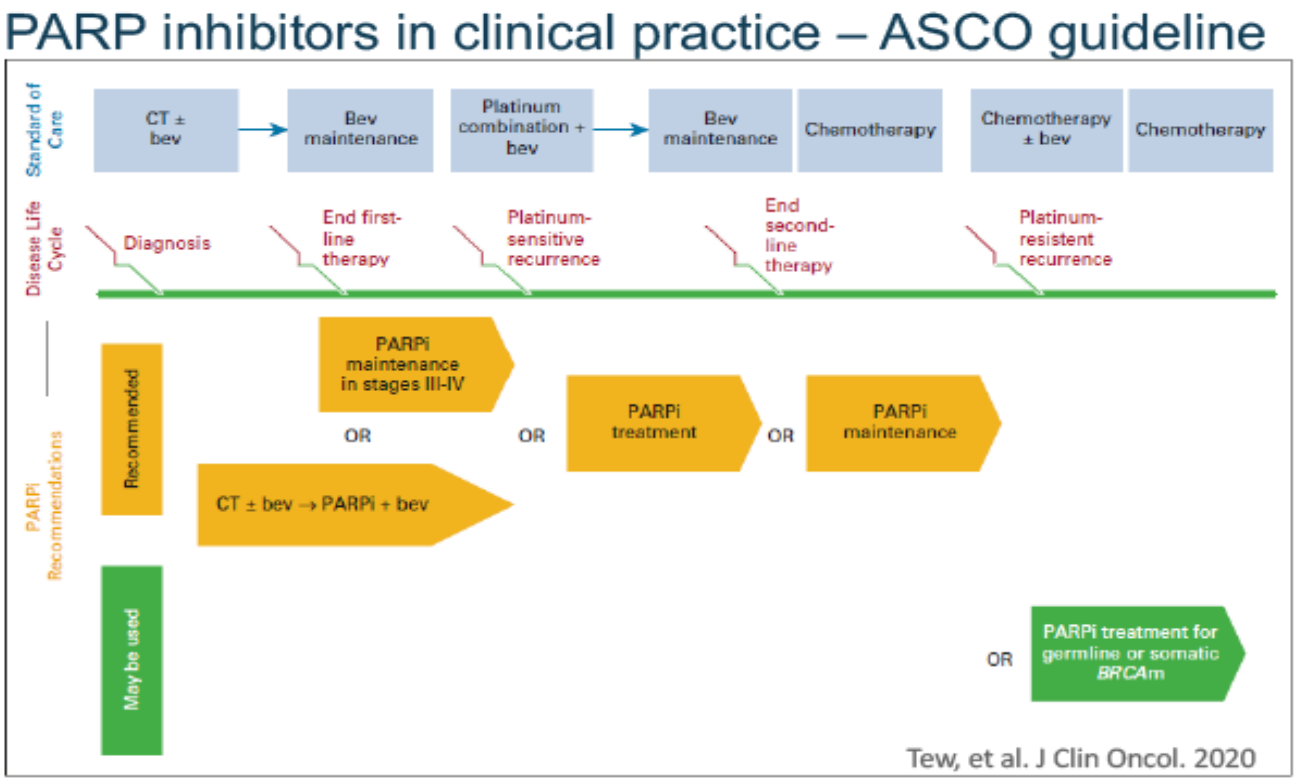
- Initial treatment
  - VELIA – veliparib with carboplatin + paclitaxel
- Maintenance treatment
  - First line
    - SOLO1 – olaparib in women with BRCA mutation
    - PRIMA – niraparib in women with high risk cancer
  - After platinum-sensitive relapse
    - SOLO2 – olaparib after response to 2nd line platinum
    - ARIEL – rucaparib in women with HR deficiency
- Relapsed ovarian cancer
  - Not currently recommended

PARP inhibitors use

PARP inhibitors – when to use

- First-line maintenance
  - BRCA mutation – germline (hereditary) or somatic (tumor only)
  - HR deficient – mutations in particular genes or changes in DNA
- Second-line maintenance
  - Response to second round of carboplatin/cisplatin
  - If no prior PARP inhibitor…
- Treatment
  - Not currently recommended

ASCO guideline



HR deficiency testing

HR deficiency testing

- Molecular testing
- Ex: MyRisk panel
  - **Germline** 36 genes with evidence for hereditary cancer
- Tumor testing
  - **Somatic** BRCA mutations

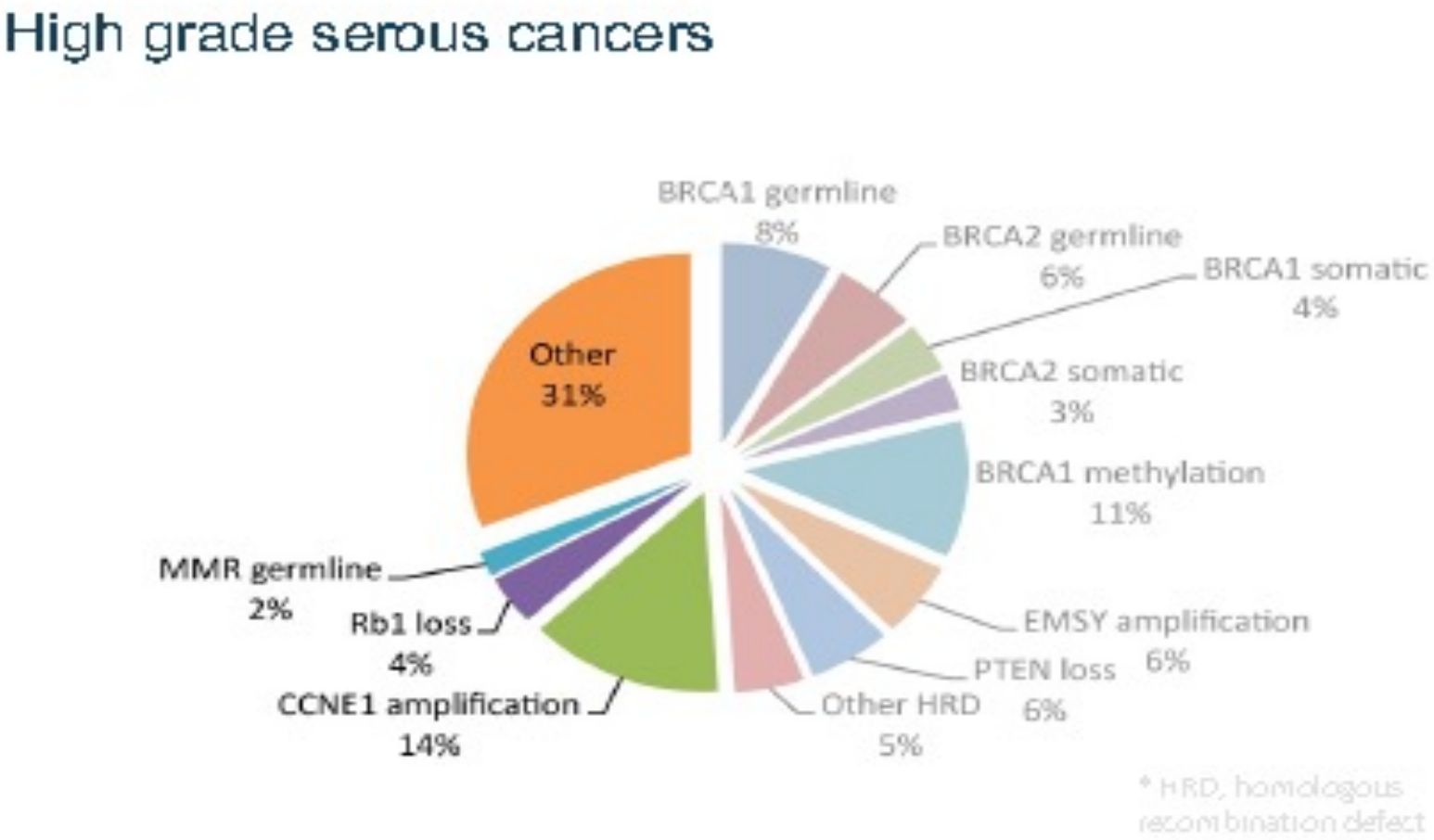
	ASSOCIATED GENES		ASSOCIATED SYNDROMES	
Genes	**Breast**	**Ovarian**	**Colorectal**	**Endometrial**
BRCA1	●	●		
BRCA2	●	●		
MLH1		●	●	●
MSH2		●	●	●
MSH6		●	●	●
PMS2		●	●	●
EPCAM		●	●	●
APC			●	
MUTYH Monoallelic			●	
MUTYH Biallelic			●	

ASCO guideline:
Konstantinopoulous, et al. J Clin Oncol. 2020

Exploration of new targets

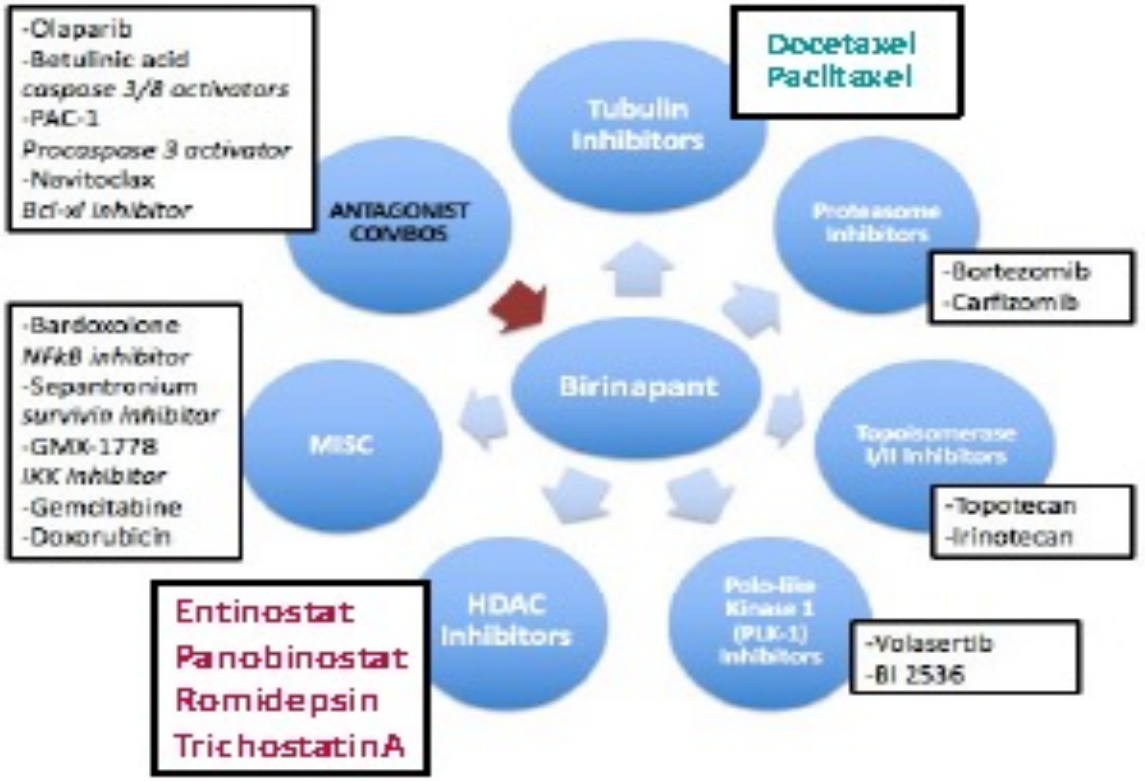
- Functional analysis

High grade serous cancers



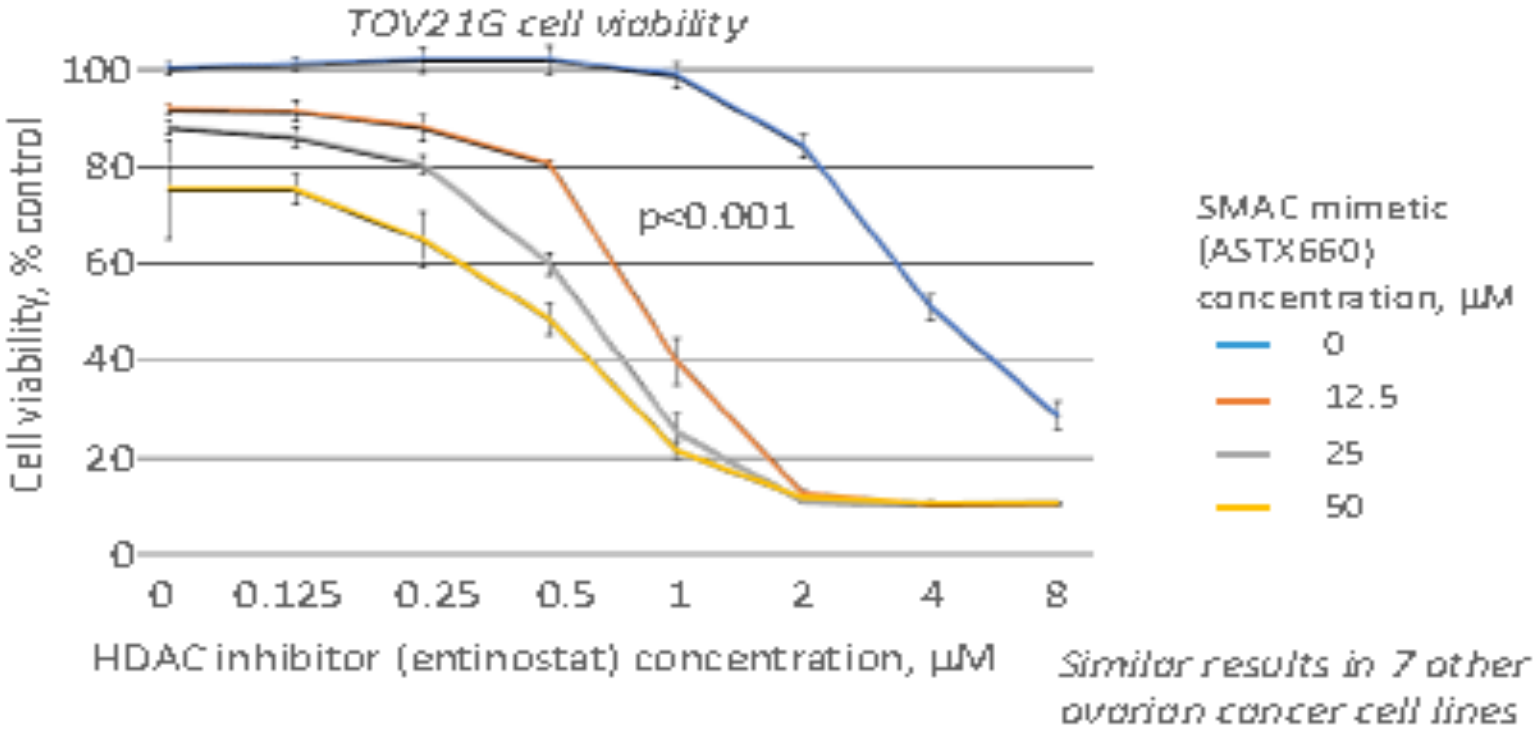
New targets

High throughput drug screen for new targets in ovarian cancer



SMAC mimetic and HDAC inhibitor

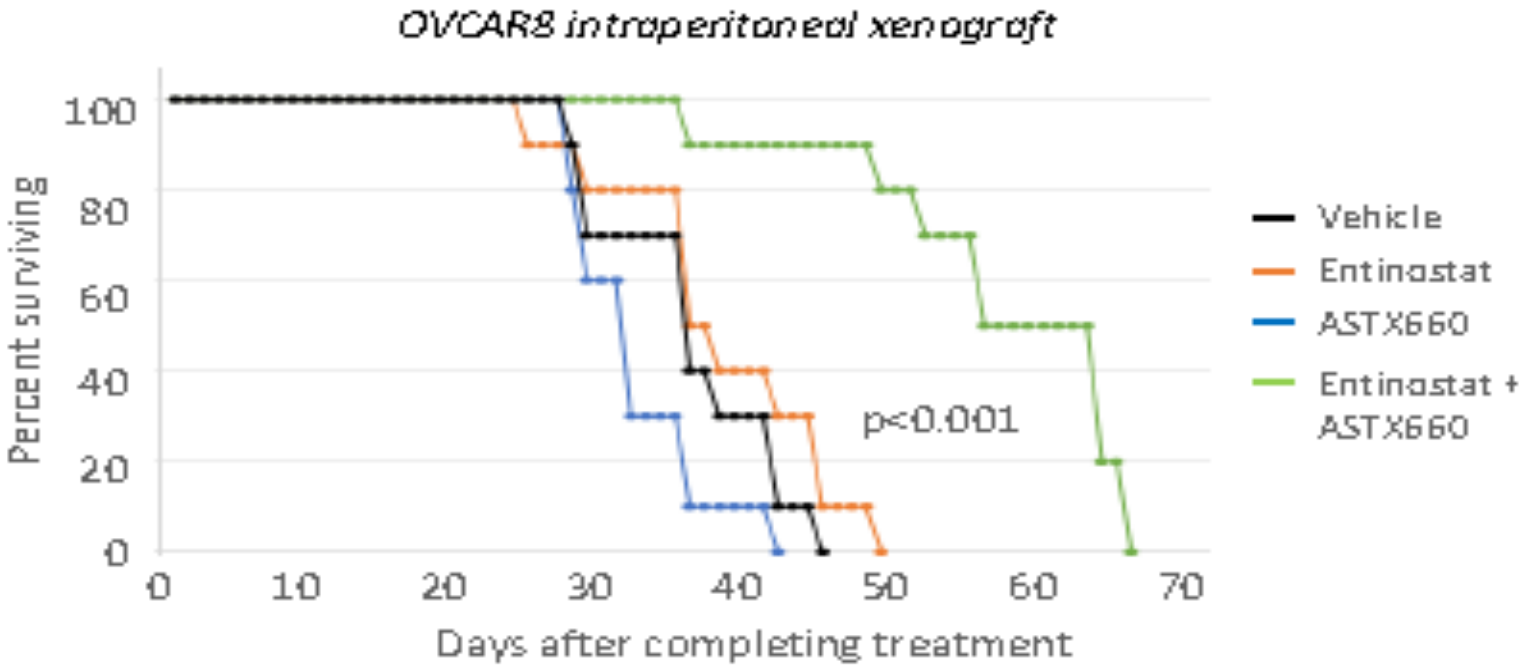
SMAC mimetic and HDAC inhibitor are highly synergistic *in vitro*



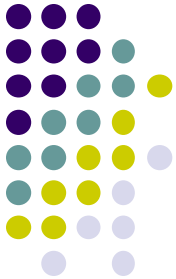
Similar results in 7 other ovarian cancer cell lines

Survival curve

SMAC mimetic + HDAC inhibitor prolongs survival in mice



Mechanism of synergy



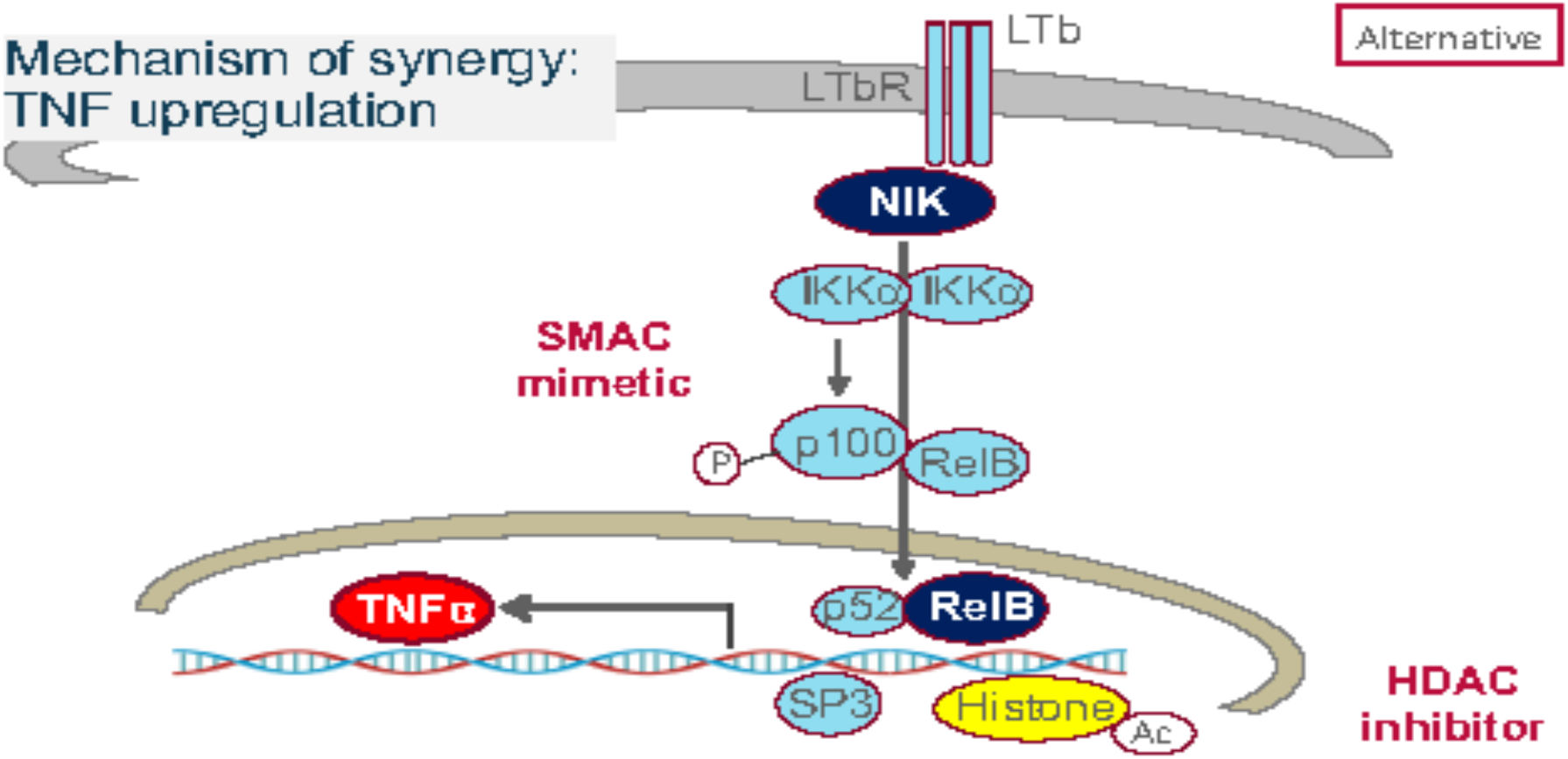
Mechanism of synergy

- Differential regulation of NF-κB classical and alternative pathways
- Pleotropic effects of TNFα

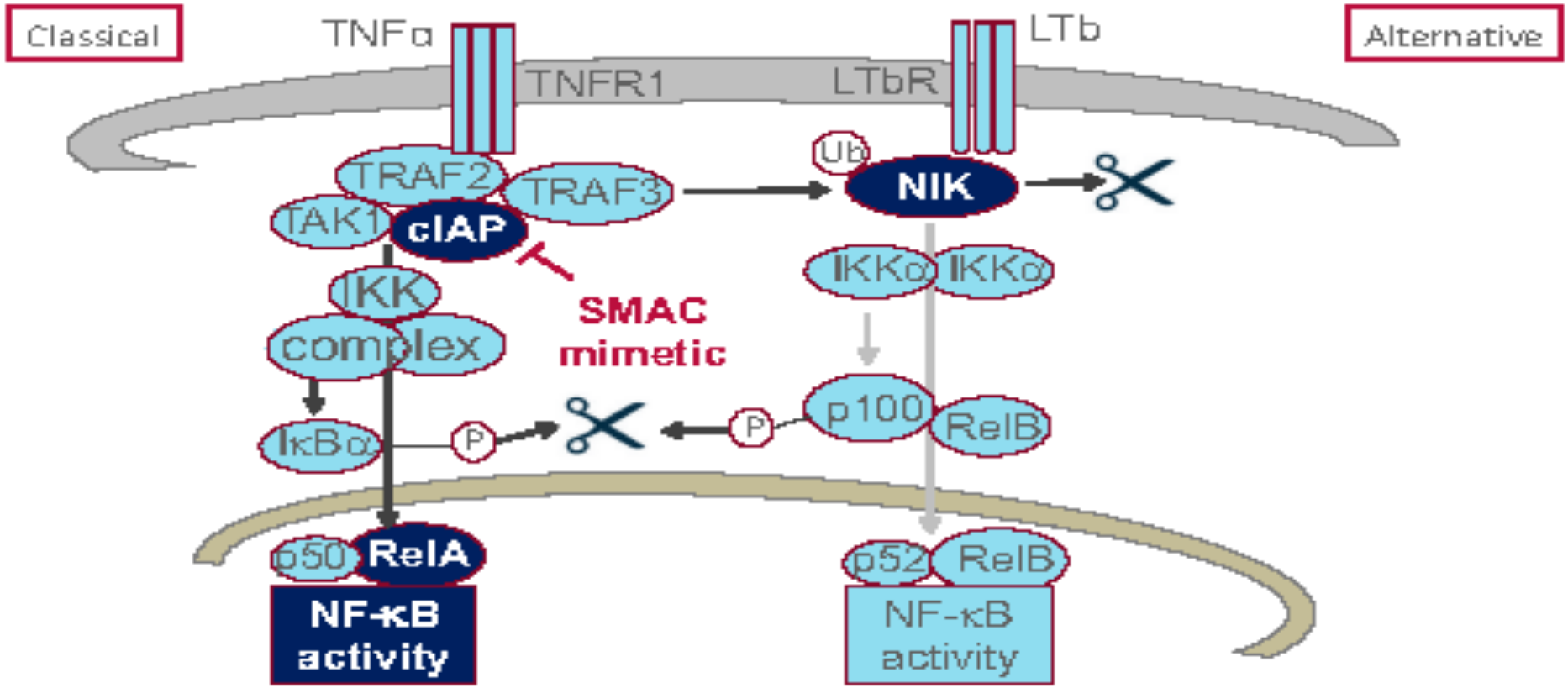
- Shifting balance between survival and apoptosis

TNF upregulation

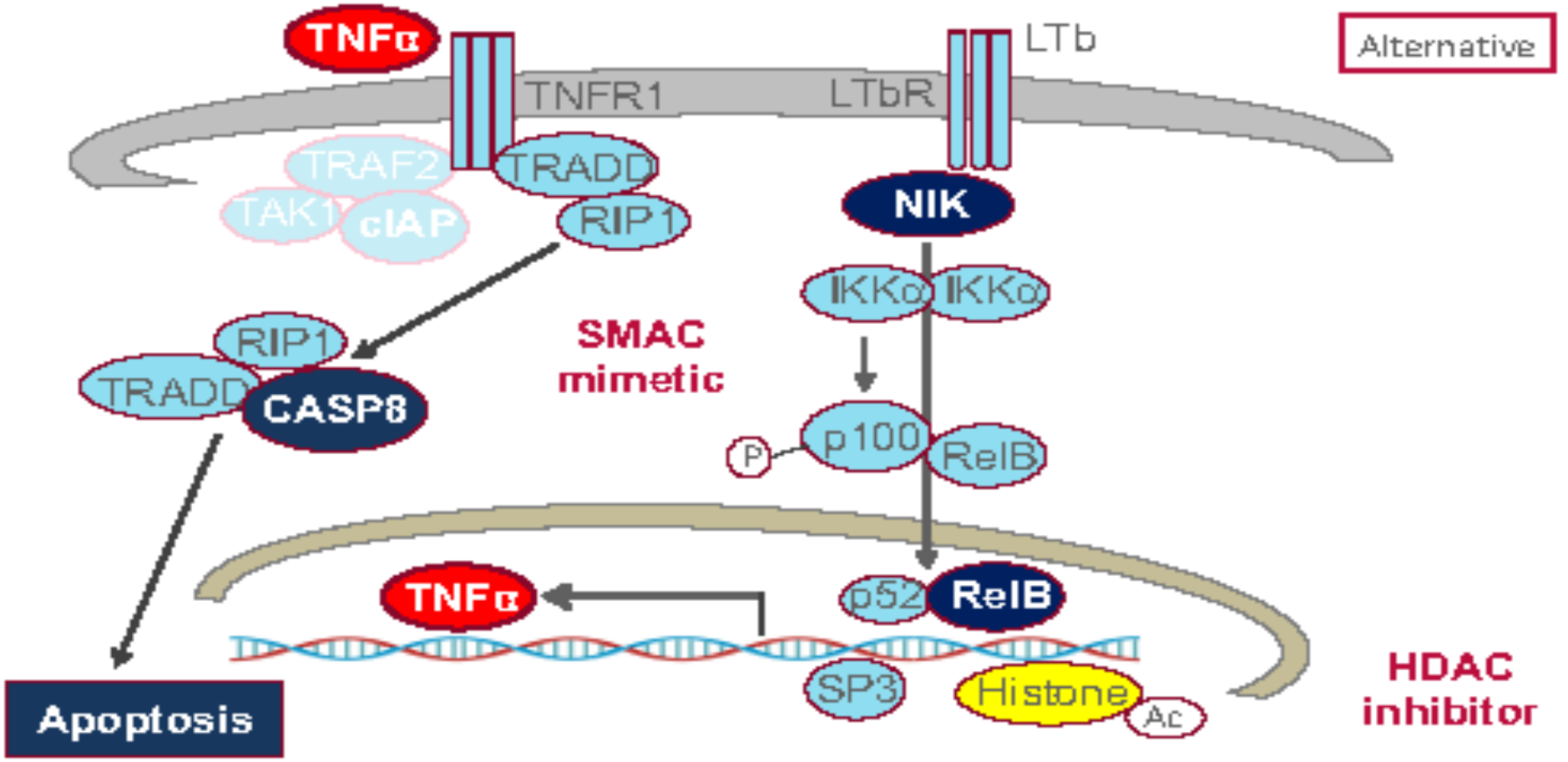
Alternative



NF-KB activity



TNF and SMAC mimetic



Phase 1 trial

SMACm + HDACi – phase 1 clinical trial under development

Oral Agents:

ASTX660 (SMAC mimetic, Astex)

Entinostat (HDAC inhibitor, Syndax)

- Clinical visit and labs weekly
- Restaging scans q8 weeks
- Expansion cohort at MTD

Dose Level	Entinostat (mg, orally)	ASTX660 (mg, orally)	Subjects (n)
-1	3, every other week	90 once daily	3-6
1	3, once weekly	90 once daily	3-6
2	5, once weekly	90 once daily	3-6
3	5, once weekly	120 once daily	3-6
4	5, once weekly	150, once daily	3-6
MTD	MTD, once weekly	MTD, once daily	15

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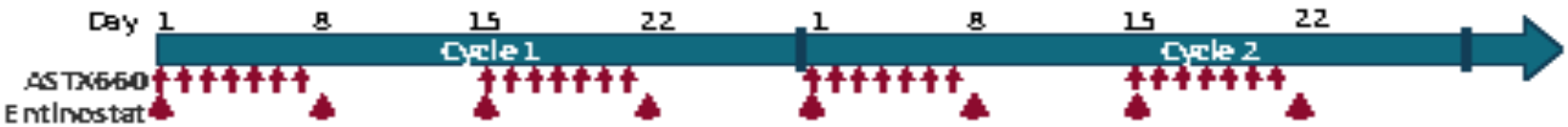
- Restaging scans q8 weeks
- Expansion cohort at MTD

Dose Level	Entinostat (mg, orally)	ASTX660 (mg, orally)	Subjects (n)
-1	3, every other week	90 once daily	3-6
1	3, once weekly	90 once daily	3-6
2	5, once weekly	90 once daily	3-6
3	5, once weekly	120 once daily	3-6
4	5, once weekly	150, once daily	3-6
MTD	MTD, once weekly	MTD, once daily	15



Phase 1 trial

SMACm + HDACi – phase 1 clinical trial under development

Oral Agents:

ASTX660 (SMAC mimetic, Astex)

Entinostat (HDAC inhibitor, Syndax)

- Clinical visit and labs weekly
- Restaging scans q8 weeks
- Expansion cohort at MTD

Dose Level	Entinostat (mg, orally)	ASTX660 (mg, orally)	Subjects (n)
-1	3, every other week	90 once daily	3-6
1	3, once weekly	90 once daily	3-6
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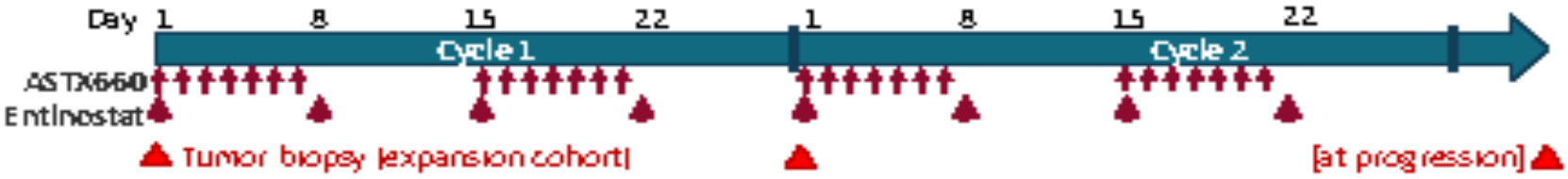
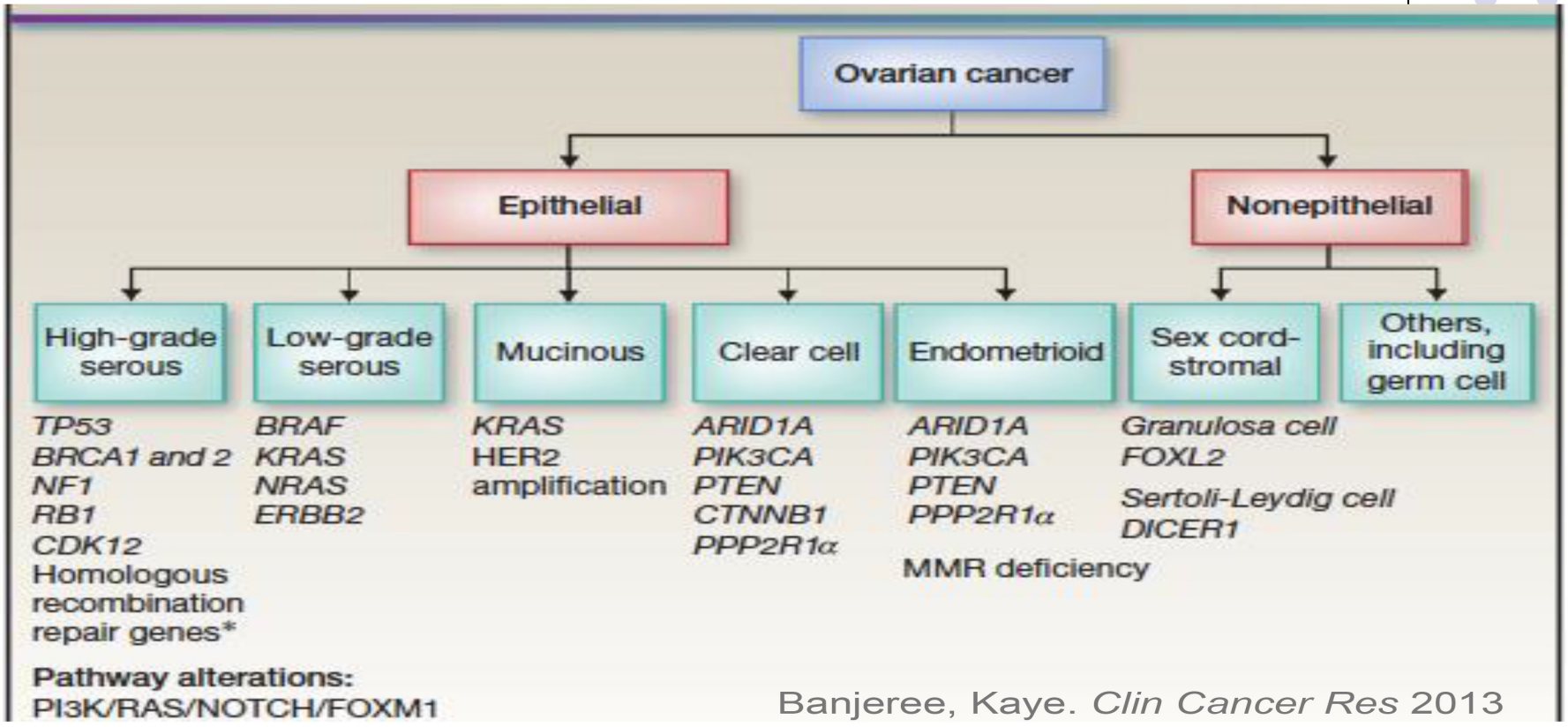


Studies for exploratory aims (expansion cohort): TNF upregulation, Target inhibition (cIAP level, H3 histone acetylation), CODEX immune cell assay

Ovarian cancer genomicsAcknowledgements

Ovarian cancer genomics



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