Emerging Opportunities in Rare Gynecologic Cancers

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Disclosure

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- Research funding: M-Trap
- Stockholder: Bio Path

Overview

- Rare cancers
- Molecular characteristics
- Therapeutic opportunities and trial development

What are rare cancers?

- NCI: <15 per 100,000 people per year
- ESMO: <6 per 100,000 people per year

Common cancers

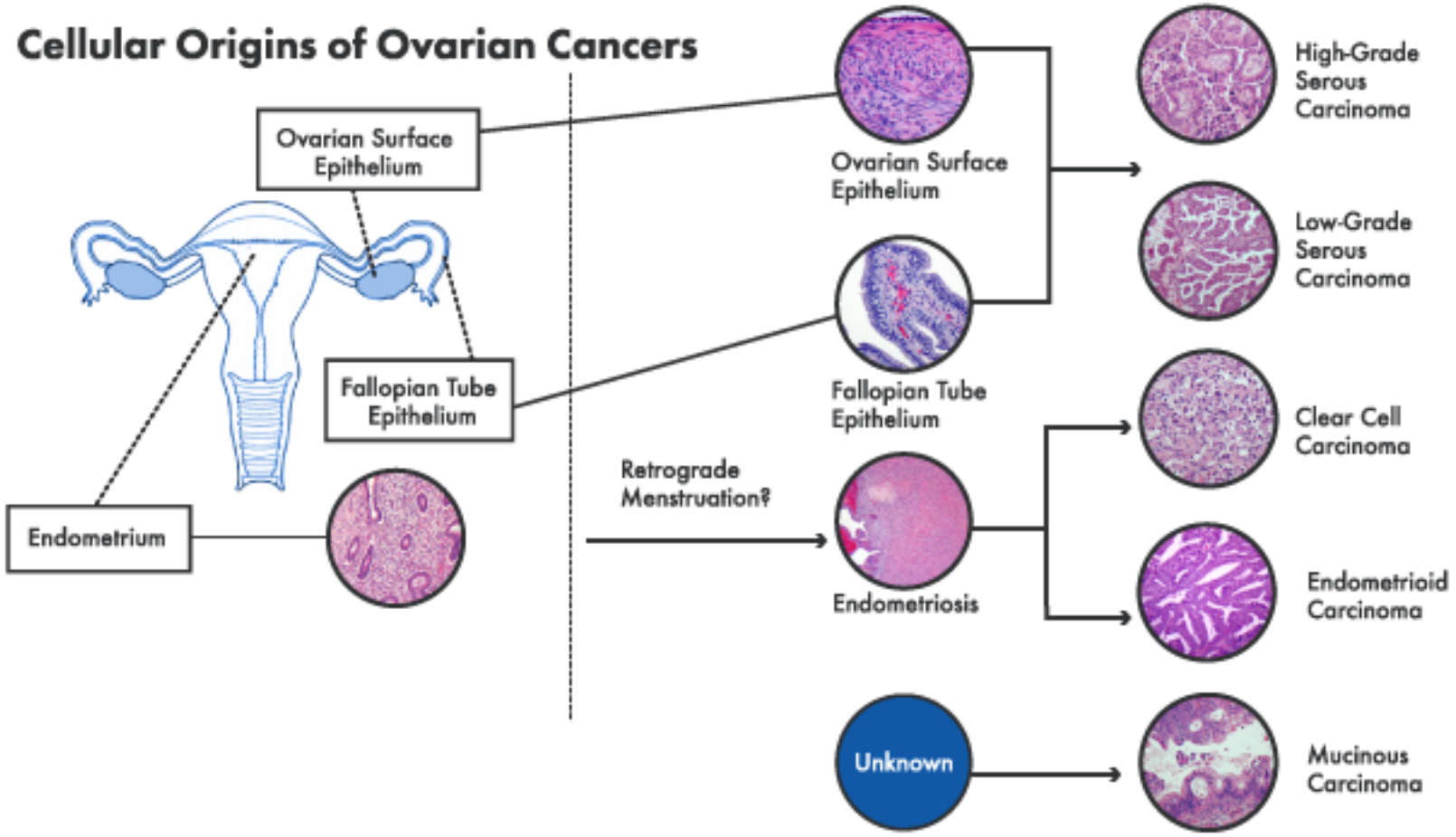
- By NCI definition, only 11 cancer types are classified as common in US adults:
  - Prostate
  - Breast
  - Lung
  - Colon
  - Uterus (endometrial)
  - Bladder
  - Melanoma
  - Rectum
  - Ovary
  - Non-Hodgkin lymphoma
  - Kidney or renal pelvis

Classification of “common cancers”

	Pathognomonic mutation	Post-genomics classification
Endometrial cancer	*POLE*	Molecularly defined subtype of common cancer
Breast cancer	*ERBB2* amplification	Molecularly defined subtype of common cancer
High-grade serous ovarian cancer	*BRCA1, BRCA2*	Molecularly defined subtype of common cancer
Non-small-cell lung cancers	*EML4–ALK* fusion	Molecularly defined subtype of common cancer
Prostate cancer	*TMPRSS2–ERG* fusion	Common cancer (prostate cancer)*
High-grade serous ovarian cancer	*TP53*	Common cancer (high-grade serous ovarian cancer)*

Boyd et al., Lancet Oncol, 2016

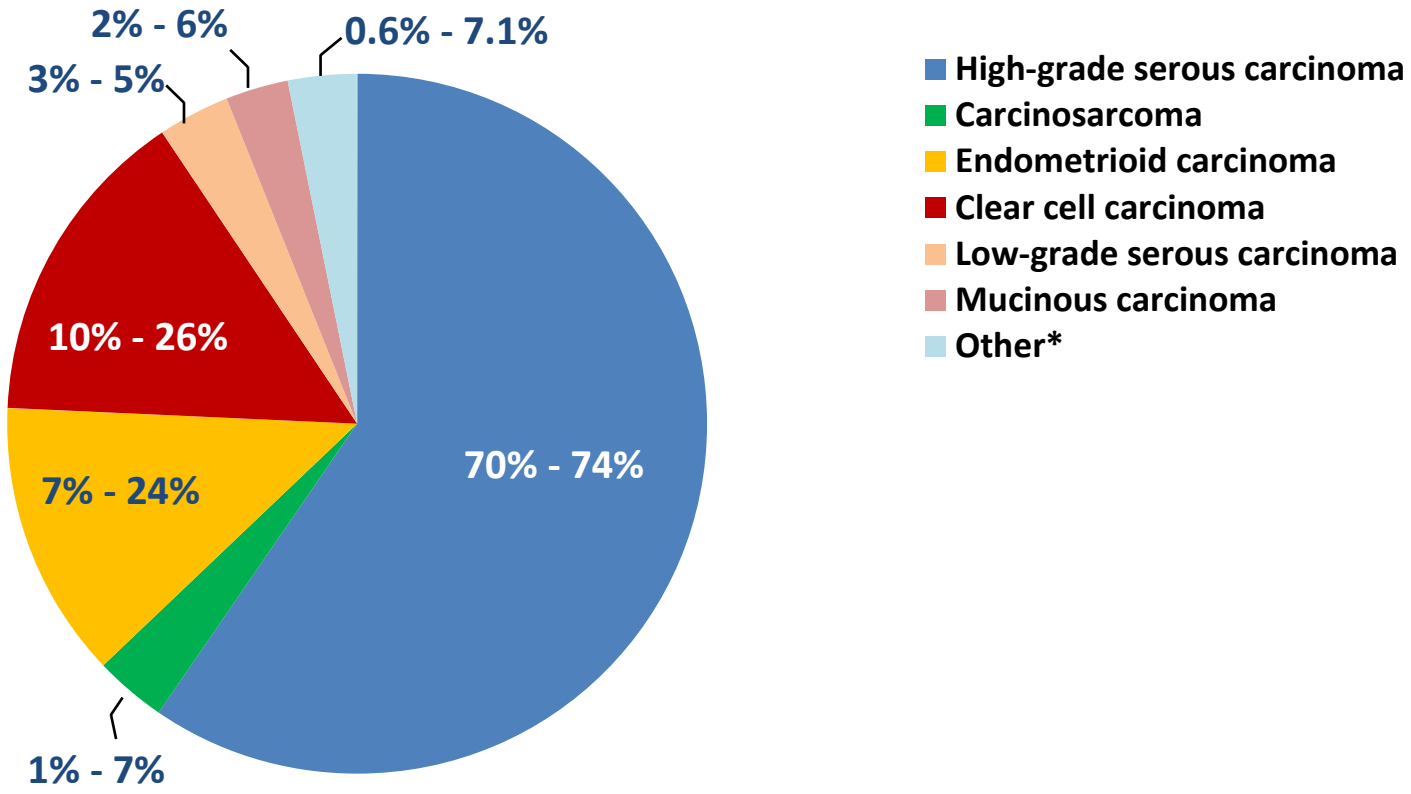
Ovarian Carcinomas – Origins



www.nas.edu/OvarianCancers

The Biology of Ovarian Cancer

Ovarian Carcinomas – Not one disease

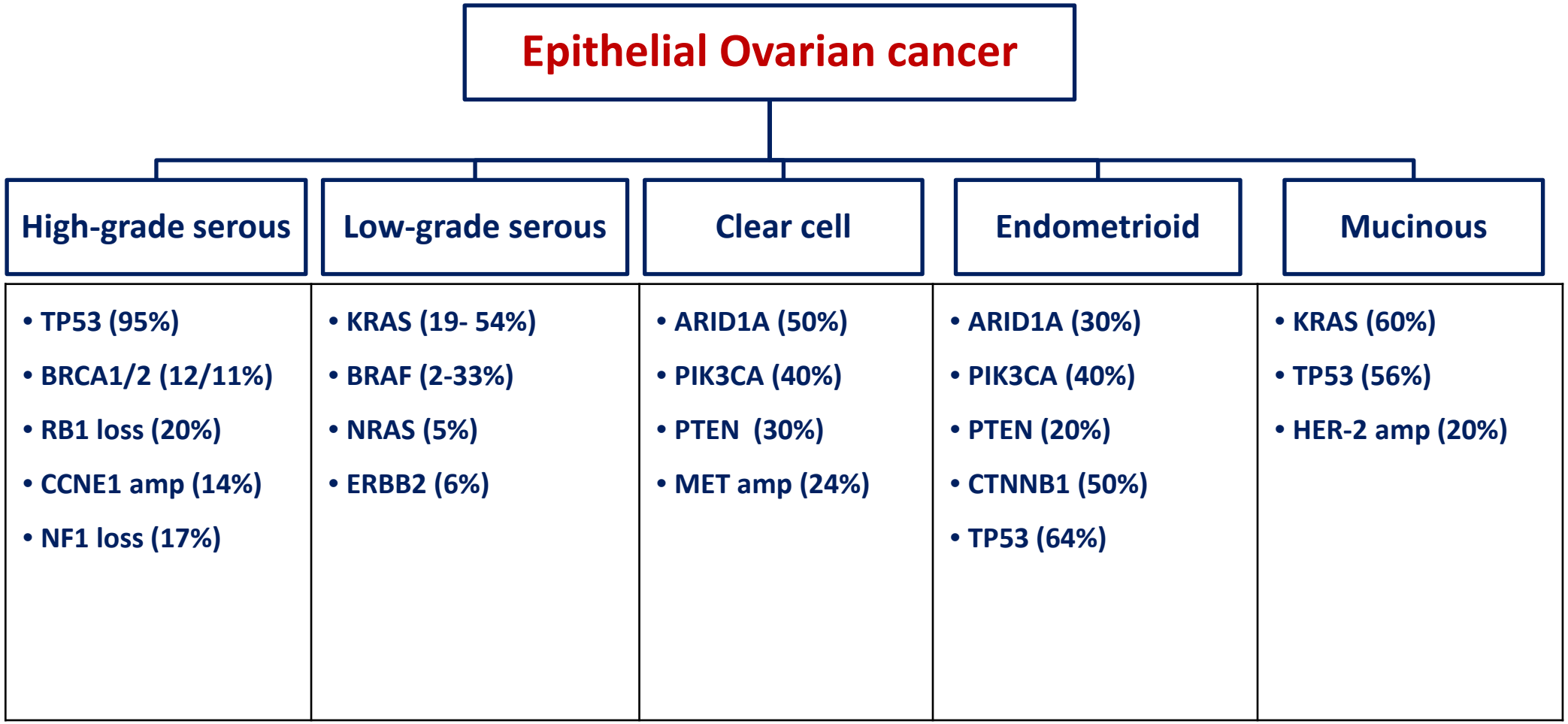


www.nas.edu/OvarianCancers

Recommendation 2

- **Reach consensus on diagnostic criteria, nomenclature, and classification schemes that reflect the morphological and molecular heterogeneity of ovarian cancers**
- **Promote universal adoption of standardized taxonomy**

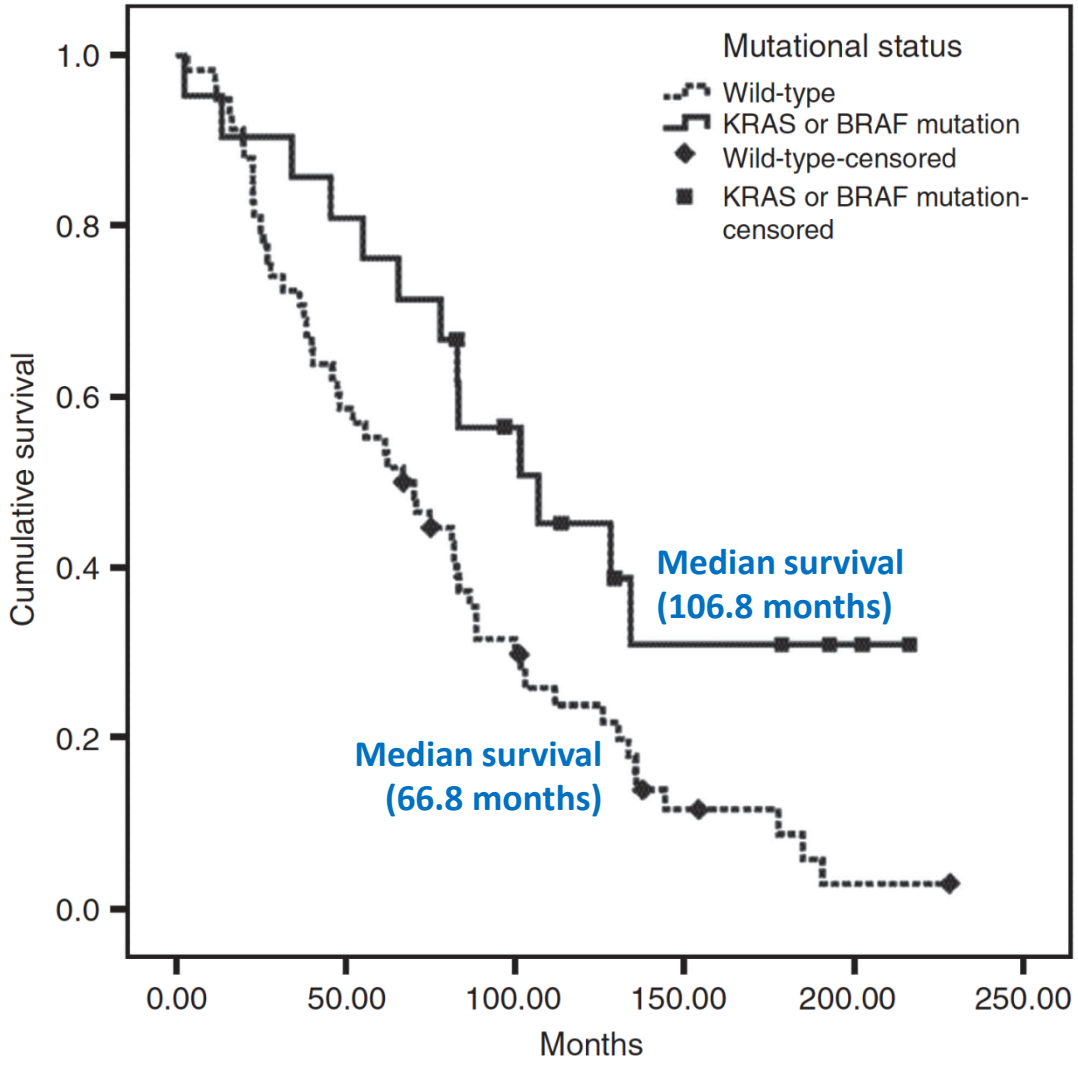
Molecular features of ovarian cancers



Mutations in major epithelial ovarian cancer subtypes

KK Wong

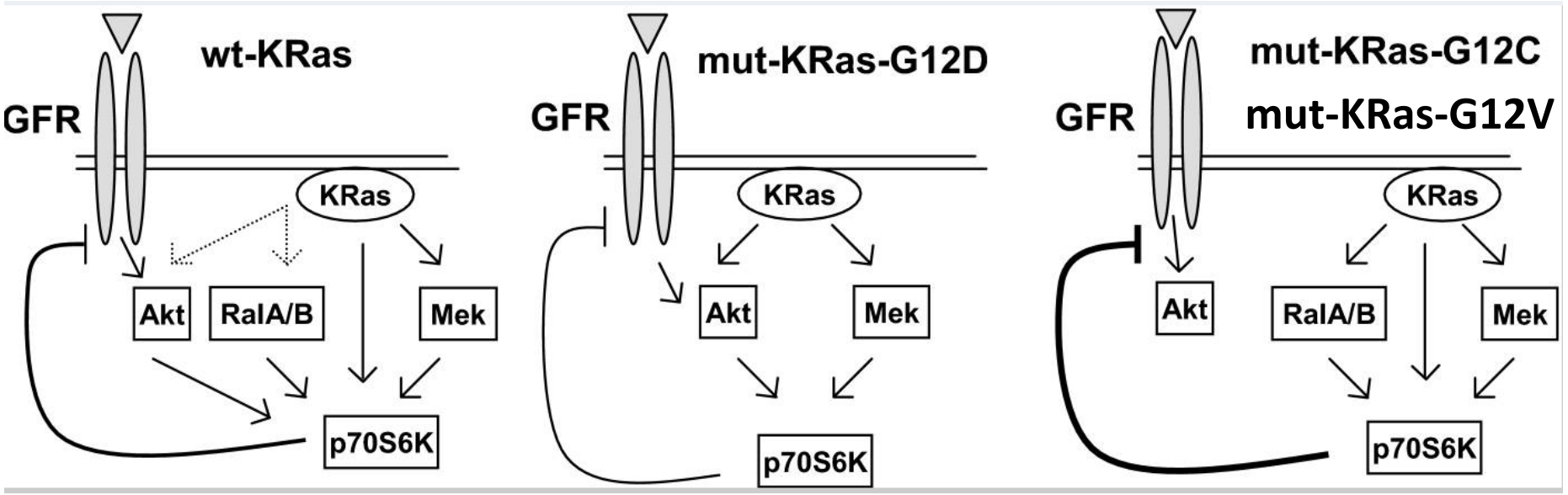
Low-grade serous carcinoma (LGSC): Impact of mutational status on survival



Median OS for women with KRAS or BRAF mutation was 106.8 months (95% CI, 50.6, 162.9) compared with 66.8 months (95% CI, 43.6, 90.0) for women whose tumors contained no KRAS or BRAF mutations (P = 0.018)

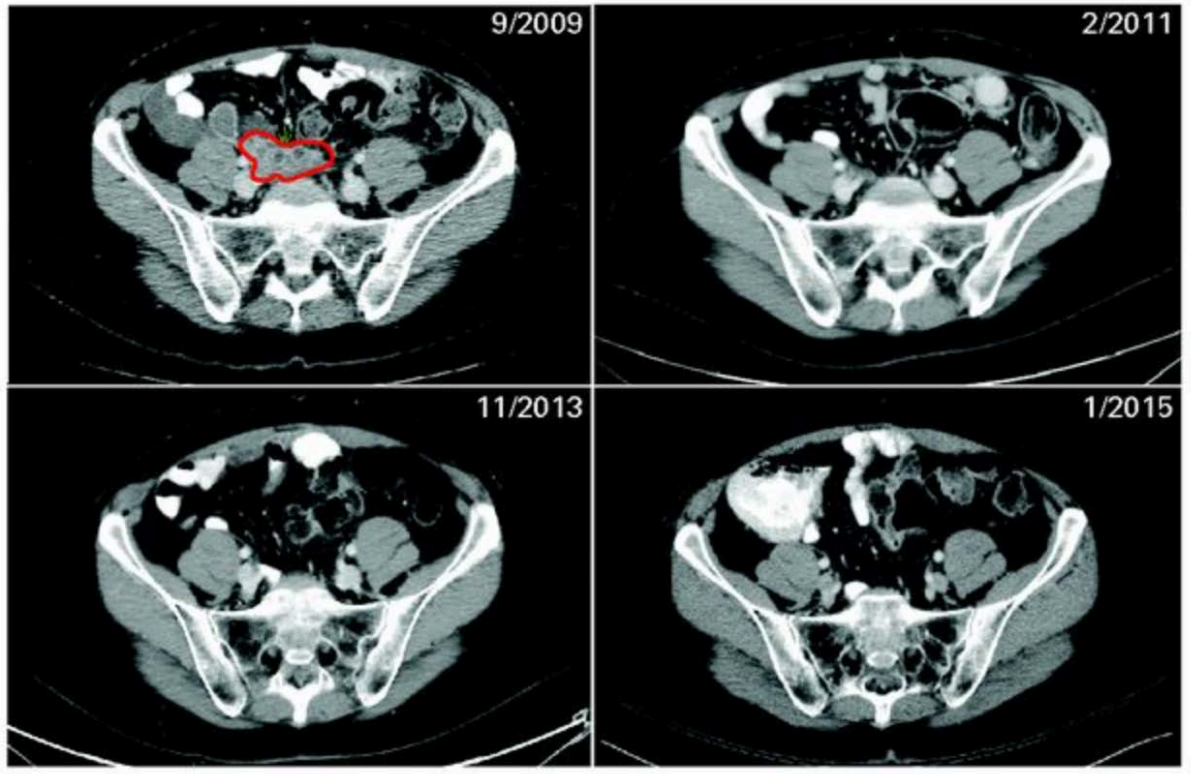
Gershenson, Sun and Wong. 2015 BJC

$KRAS^{G12D}$ and $KRAS^{G12V}$ have different cell signaling



Ihle et al., 2012. JNCI 104:228-39

An Extreme Responder with a 15–base pair deletion in *MAP2K1* gene, an activating mutation in the GOG0239 (selumetinib) study



Complete radiographic response after 17 months of therapy, which was durable at 4 and 5 years

Grisham, Gershenson et al. JCO, 2015

Ovarian clear cell adenocarcinoma (OCCC)

- A distinct histological type of cancer in the WHO-classification
- Most patients present with early stage disease (FIGO I and II)
- Incidence: 5-10% of epithelial ovarian cancers
- OCCC occurs more frequently in Japan and Taiwan (15-25%)
- More resistant to systemic chemotherapy than other types; late stage associated with poorer prognosis than other types

Molecular abnormalities in ovarian clear cell carcinoma

Gene	Overall genomic alteration frequency
PIK3CA	52.8%
ARID1A	51.2%
TP53	21.6%
ZNF217	17.6%
ERBB2	12.8%
KRAS	8%
CCNE1	7.2%
CRKL	4.8%

- N = 125 advanced/recurrent OCCCs
- FoundationOne® genomic profiling
- Genomic alterations: base pair substitutions, insertions/deletions, copy number, rearrangements

Therapeutic opportunities:

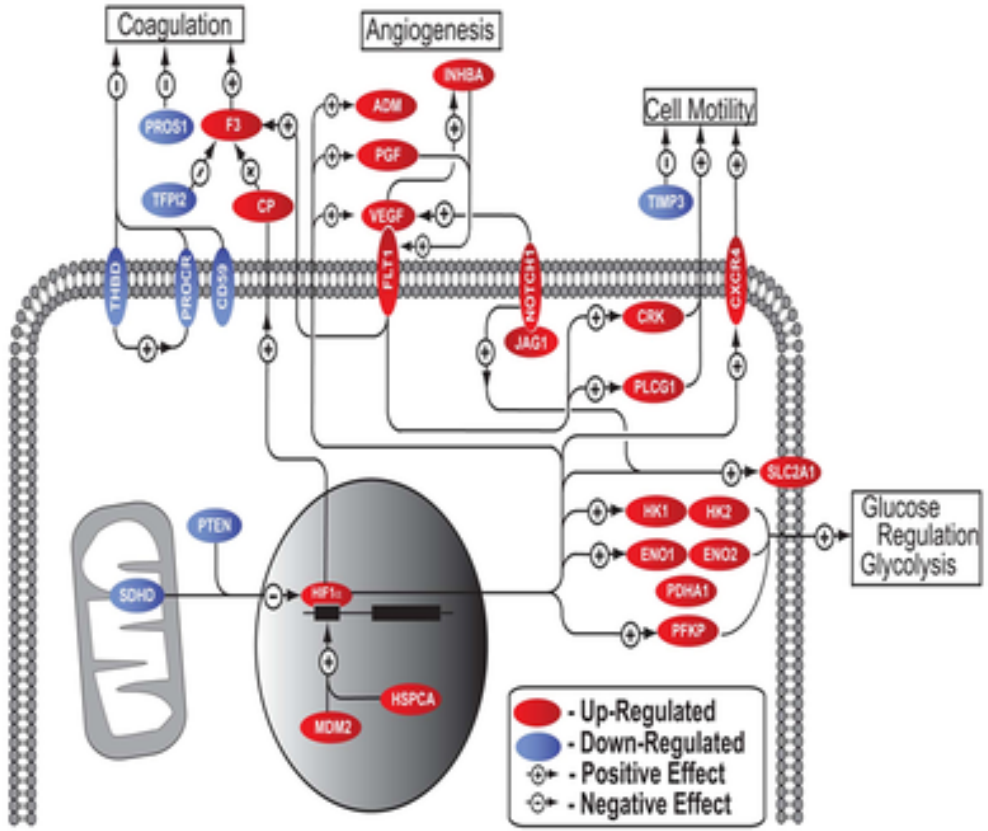
- Everolimus
- HDACi
- EZH2i
- VEGF/VEGF-R blockers
- Trastuzumab

- MMR deficiency: ~6% (check-point blockers)

Elvin et al., Gyn Onc Rep, 2017
Stewart et al., Histopathol, 2017

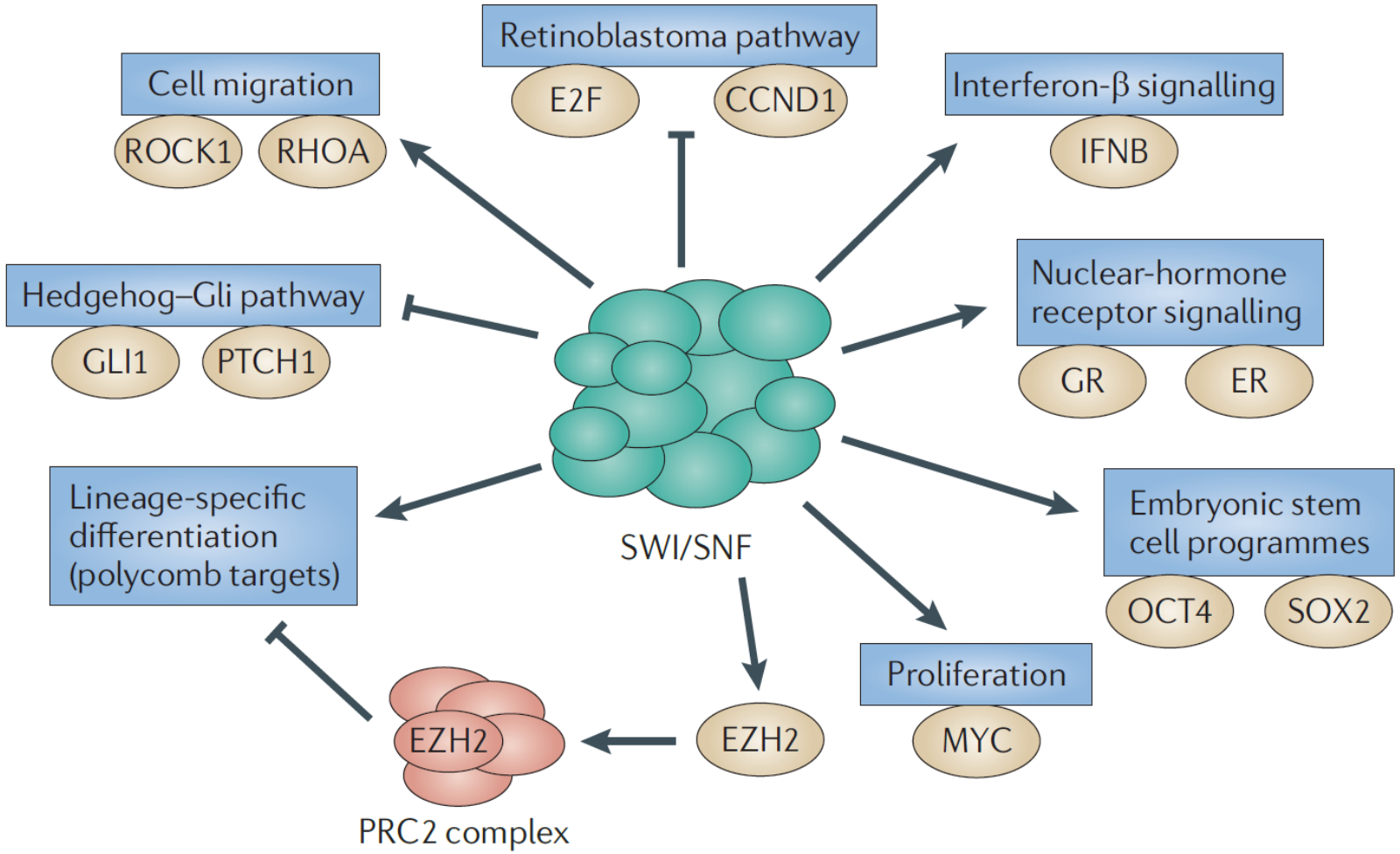
Activated pathways in ovarian clear cell carcinoma

- Microdissected clear cell cancers
- Activated pathways:
  - Angiogenesis
  - Coagulation
  - Glucose metabolism



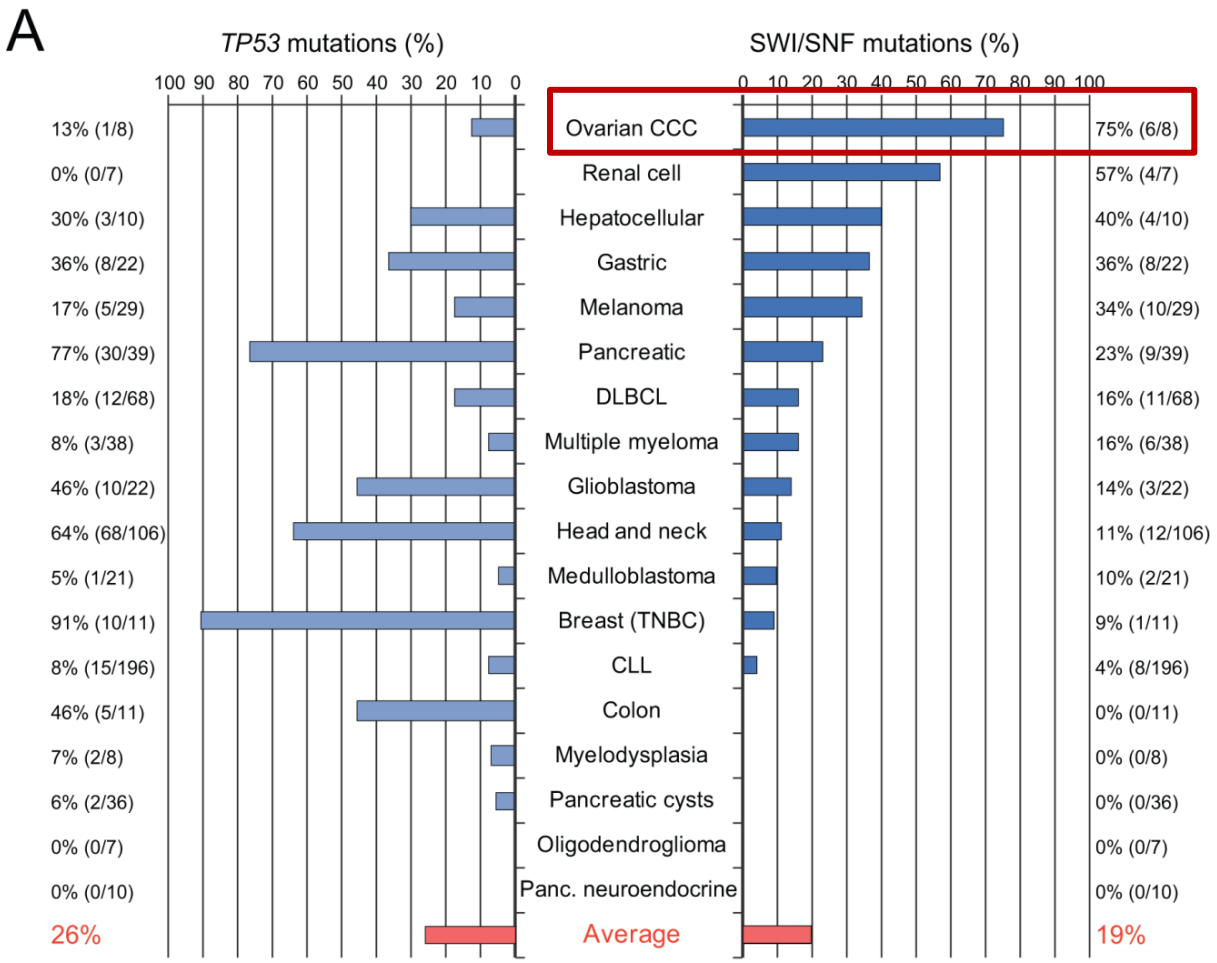
Stany et al., PLoS One, 2011

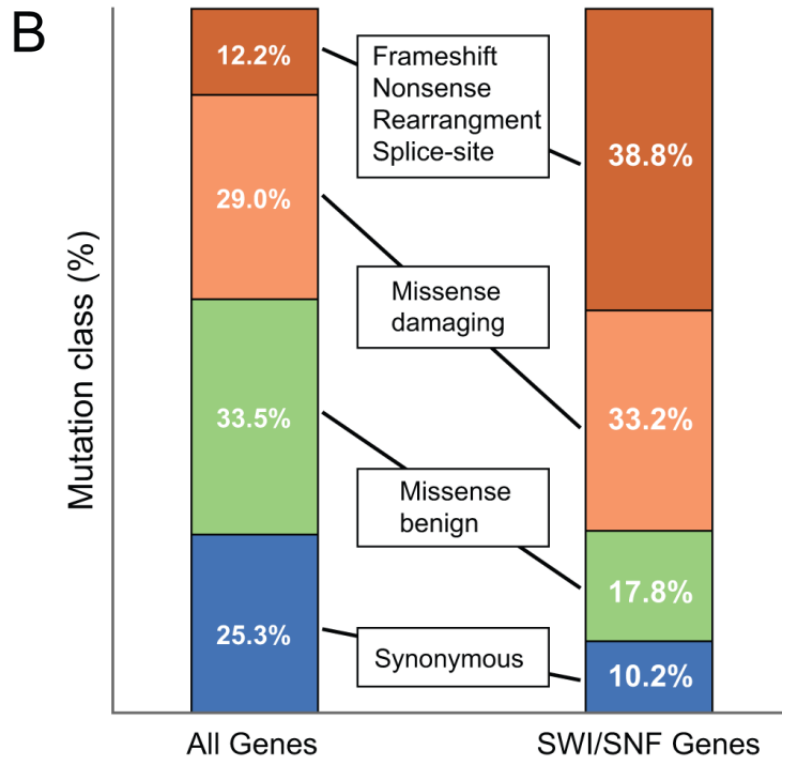
Targeted pathways implicated in the tumor suppressor activity of SWI/SNF complexes



Wilson and Roberts (2011), Nature Reviews Cancer

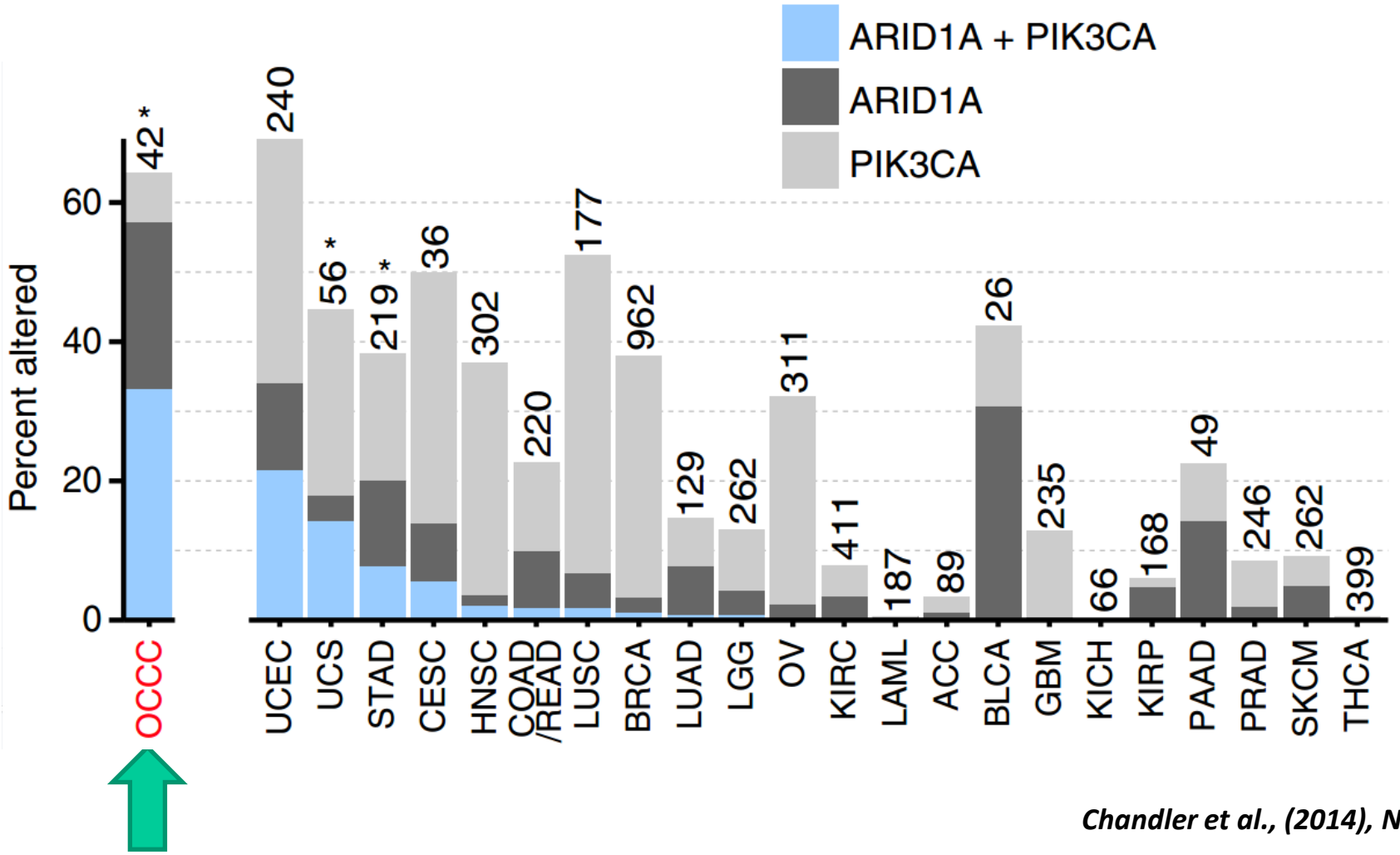
Broad spectrum of SWI/SNF mutations in human cancers





Shain and Pollack (2013), PLoS One

High frequency of co-occurring *PIK3CA* and *ARID1A* mutations in Ovarian clear cell carcinomas (OCCCs)



Chandler et al., (2014), Nature Communications

Mucinous ovarian carcinoma

Molecular features:

- Her2 amplification
- Kras mutation
- Src activation
- MSI-H
- No BRCA mutations; low rate of p53 mutations

Therapeutic opportunities:

- Ras-targeted drugs
- VEGF/VEGF-R inhibition
- Trastuzumab
- Src inhibitors
- PI3K/Akt inhibitors
- Immune therapies

Frumovitz et al., Gyn Oncol 2010
Matsuo et al., Clin Cancer Res 2011

Small cell carcinomas of the gynecologic tract

Small cell carcinoma of the ovary:

- Pulmonary type (SCCOPT)
  - Alterations in *TP53, BRCA2*
- Hypercalcemic type (SCCOHT)
  - Inactivating mutations in *SMARCA4*; loss of SMARCA2 expression

Conventional therapy:

- Chemotherapy
- Radiation

Emerging options:

- Immune therapy (PD-1/PD-L1 blockade)
- EZH2i, HDACi

Patibandla et al., Gyn Oncol 2018

Clinical trial considerations: Rare Cancers

- Create national and international networks
- Accepting greater type I and type II error
- Select trial population to minimize sample size
- Balancing scientific value and feasibility
- Incorporating Bayesian elements to quantify the resulting level of information
- N-of-1 trials; basket trials

Eur J Cancer, 2015
Lancet Oncol, 2016

Thank you!