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MEDICAL CENTER

Rare tumors under the streetlight

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Perlmutter Cancer Center, NYU Langone Medical Center

Outline

- Case studies of useful NGS that could lead to therapeutic response
- Clinical trials guide implementation of NGS
- NGS can identify driver mutations and lead to novel therapies in rare tumors

Low grade serous carcinoma

- 59yo Dx with serous LMP tumor in 1985, 1989 bowel resection for recurrent dz, 2011-2015 various chemo agents for LGSC
- 2015 – IR bx of recurrent tumor
- BRAF V600E in 31% of 447 reads

PATIENT RESULTS

- 1 genomic alteration
- 4 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 4 clinical trials

TUMOR TYPE: OVARY SEROUS CARCINOMA

Genomic Alteration Identified[†]

BRAF V600E

[†]For a complete list of the genes assayed and performance specifications, please refer to the Appendix
[#]See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (In patient's tumor type)	FDA Approved Therapies (In another tumor type)	Potential Clinical Trials
BRAF V600E	None	Dabrafenib Regorafenib Trametinib Vemurafenib	Yes, see clinical trials section

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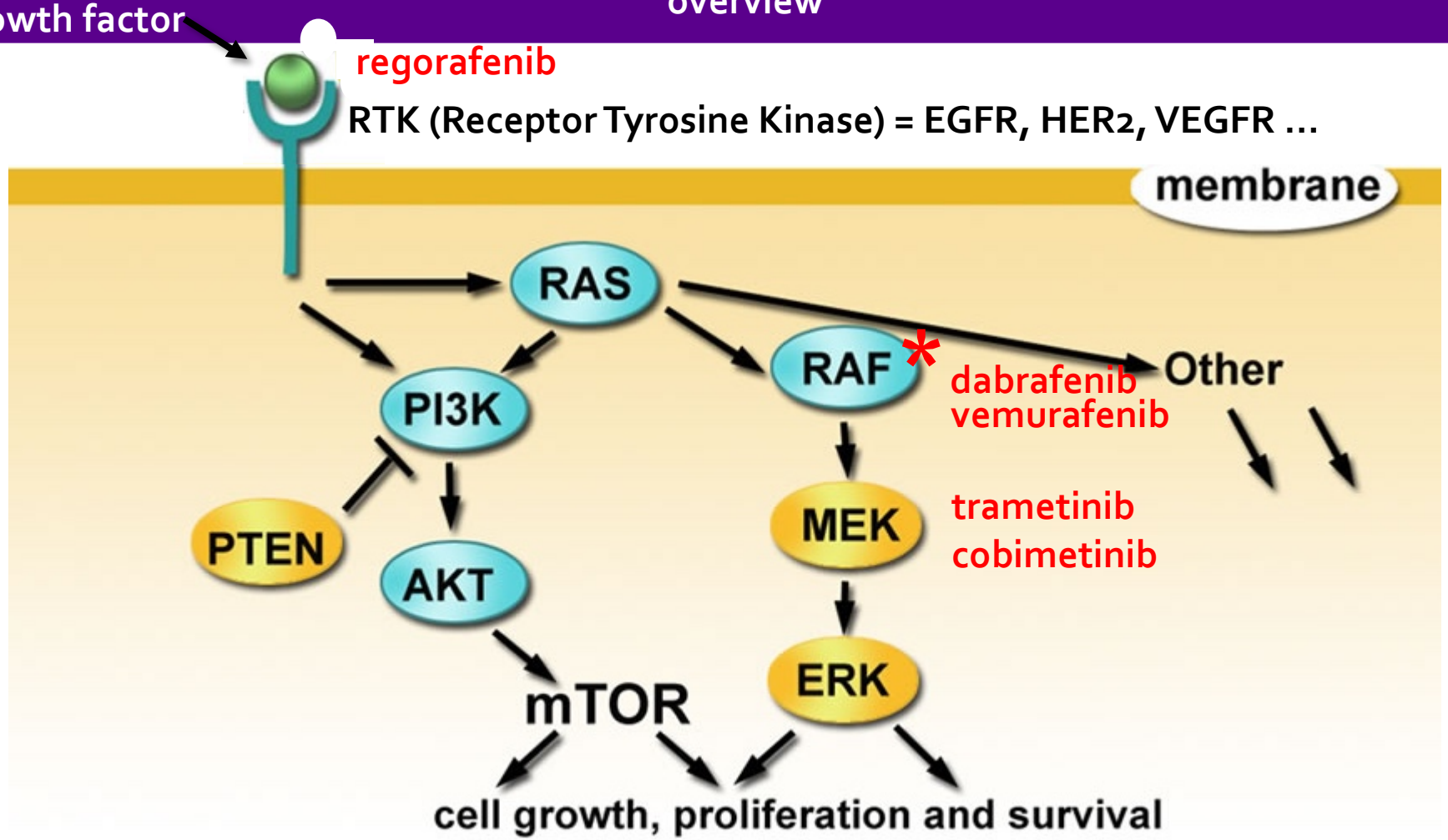
RAS/RAF/PI3K/Akt/mTOR pathway overview



The RAF-inhibitors **dabrafenib** and **vemurafenib**, alone and in combination with the MEK-inhibitors **trametinib** and **cobimetini**b respectively, are FDA-approved for the treatment of patients with BRAF V600E and V600K mutant melanoma. Data support using the combination therapies dabrafenib plus trametinib or vemurafenib plus cobimetinib instead of single agent dabrafenib, vemurafenib, or trametinib.

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Adapted from: Han CB et al. *Journal of Cancer Therapy*; 2011

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Low grade serous carcinoma

- 59yo Dx with serous LMP tumor in 1985, 1989 bowel resection for recurrent dz, 2011-2015 various chemo agents.
- 2015 – IR bx of recurrent tumor
- Pt enrolled on trametinib (MEK1/2i) trial and had initial minimal response after a short course of treatment
- She had subsequent progression in the chest and died six months later

PATIENT RESULTS

- 1 genomic alteration
- 4 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 4 clinical trials

TUMOR TYPE: OVARY SEROUS CARCINOMA

Genomic Alteration Identified†

BRAF V600E

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‡See Appendix for details

THERAPEUTIC IMPLICATIONS

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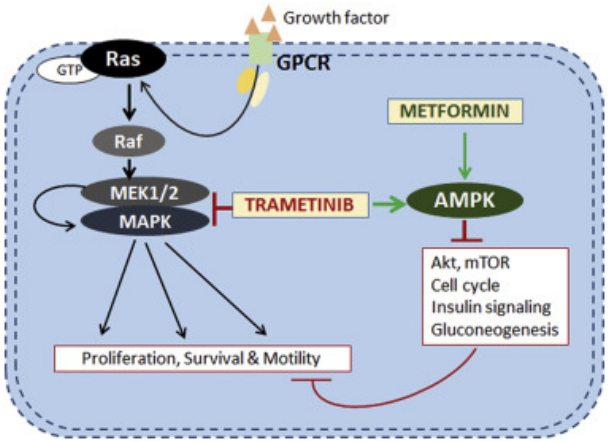

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Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study

John Farley, William E Brady, Vinod Vathipadiekal, Heather A Lankes, Robert Coleman, Mark A Morgan, Robert Mannel, S Diane Yamada, David Mutch, William H Rodgers, Michael Birrer, David M Gershenson

	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**

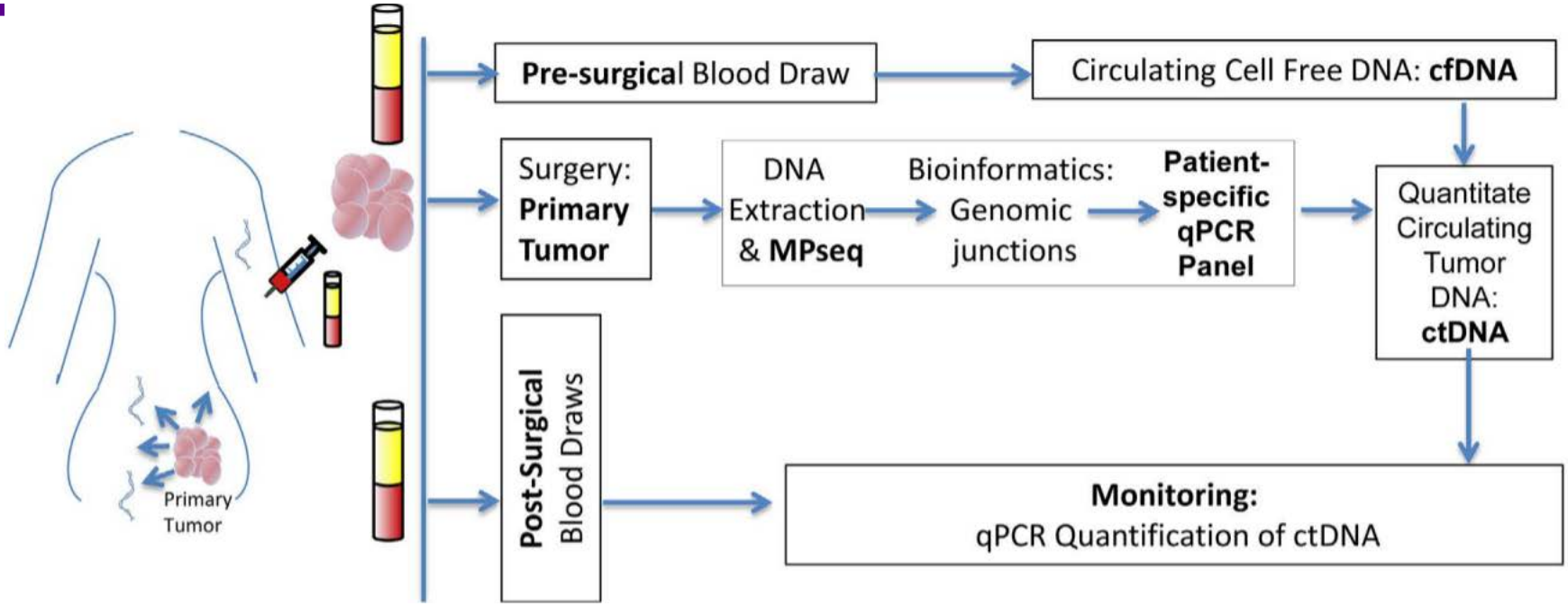
Lancet Oncol 2013; 14: 134–40

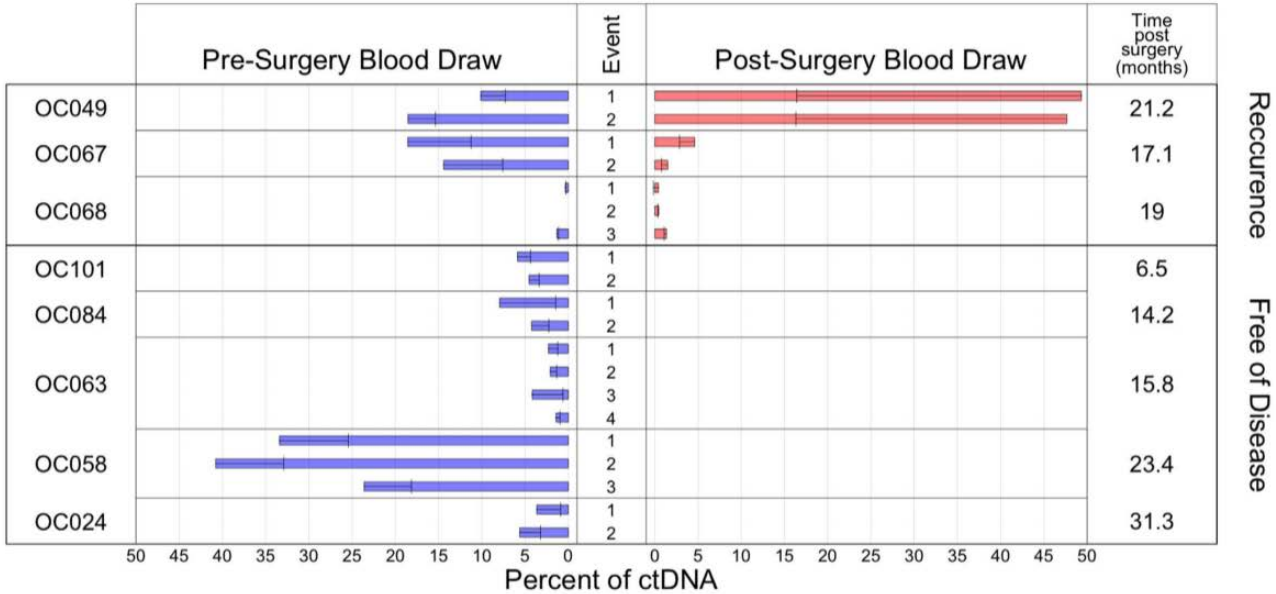
Can we do better?

Low grade serous carcinoma

- 47yo Dx with LGSC in 1997 and was treated with initial surgical resection followed by BMT
- She was disease free for 10 years and then recurred and was found to have recurrent disease and was treated with letrozole, avastin, and stopped ERT
- Then switched to pazopanib with minimal response; an orally administered, multi-targeted kinase inhibitor; targets include VEGFR1-3, PDGFRs, and FGFR
- She did not want to have further biopsies so she requested ctDNA testing

Quantification of Somatic Chromosomal Rearrangements in Circulating Cell-Free DNA from Ovarian Cancers





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Harris FR *et al Sci Rep. 2016*

one ENTER

- a validated comprehensive genomic profile that interrogates the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumor cancers.

- Coverage ~500X

- blood-based circulating tumor DNA assay, designed to interrogate the 62 most druggable cancer-related genes.

- Coverage 5000-10,000x

Genes assayed in FoundationACT

DNA Gene List: Entire Exonic Sequence for the Detection of Base Substitutions, Insertions/Deletions, and Copy Number Alterations

BRCA1 *CDK4* *ERBB2* *KRAS* *MYCN* *PTPN11*

BRCA2 *CDK6*

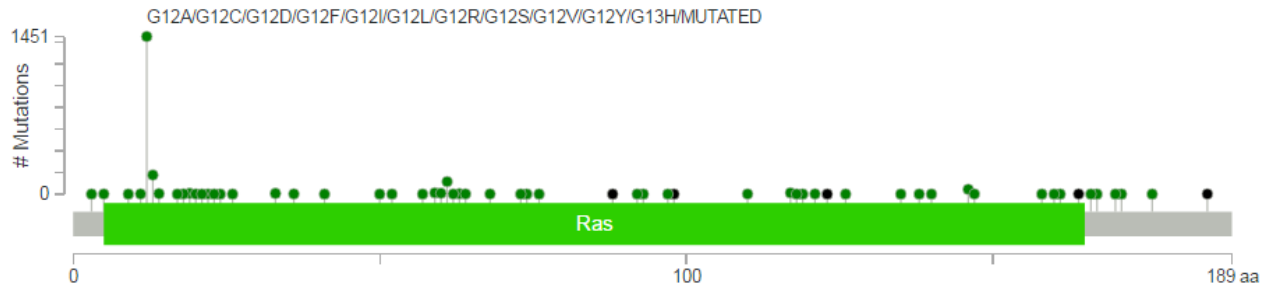
CCND1 *CDKN2A*

CD274 (PD-L1) *CRKL*

CDH1 *EGFR*

KRAS:

RASK_HUMAN



DNA Gene List: For the Detection

ALK *EGFR*

DNA Gene List: Select Exonic Sequence for the Detection of Base Substitutions, Insertions/Deletions, and Copy Number Alterations

ABL1 Exons 4-9	*CTNNB1* Exon 3	*GNA11* Exons 4,5	*JAK2* Exon 14	*MTOR* Exons 19,30,39,40, 43-45,47,48,53,56	*PIK3CA* Exons 2,3,5-8,10,14, 19,21
AKT1 Exon 3	*DDR2* Exons 5,17,18	*GNAQ* Exons 4,5	*JAK3* Exons 5,11-13,15,16	*MYD88* Exon 4	*RAF1* Exons 3,4,6,7,10,14, 15,17

ALK Exons 20-29

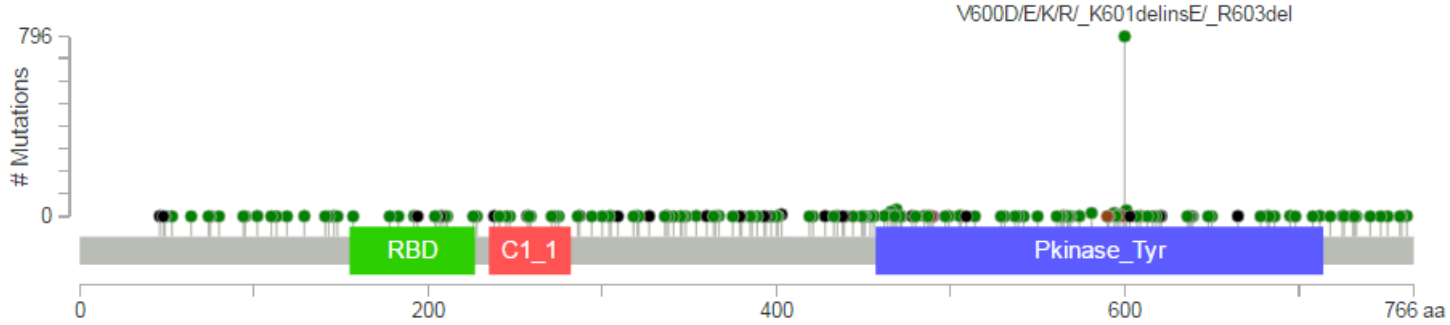
BRAF:

BRAF_HUMAN

ARAF Exons 4,5,7,11,13, 15,16

BRAF Exons 11-18

BTK Exons 2,15



@
http://www.cbioportal.org

BRAF V600E and KRAS G12V in LGSOC tumorigenesis

BRAF mutations appear to be more common in serous ovarian borderline tumors (SOBTs) and in early-stage LGSOC, but rare in advanced LGSOC. KRAS mutations are common in SOBTs and LGSOC.

Table 1. Frequency of Braf mutations in ovarian serous borderline tumor (OSBT) and ovarian low grade serous carcinoma (OLGSCa)

OSBT	OLGSCa	Reference
28%	33%	Singer et al. [19]
31%	N/A	Mayr et al. [20]
48%	N/A	Anglesio et al. [21]
41%	N/A	Verbruggen et al. 2009 [43]
30%	2%	Wong et al. [22]
23%	0%	Vereczkey et al. [23]
41%	0%	Schlosshauer et al. [24]
N/A	0%	Sundov et al. [25]
45%	5.3%	Grisham et al. [26]
N/A	5.9%	Farley et al. [27]

Table 2. Frequency of Kras mutations in ovarian serous borderline tumor (OSBT) and ovarian low grade serous carcinoma (OLGSCa)

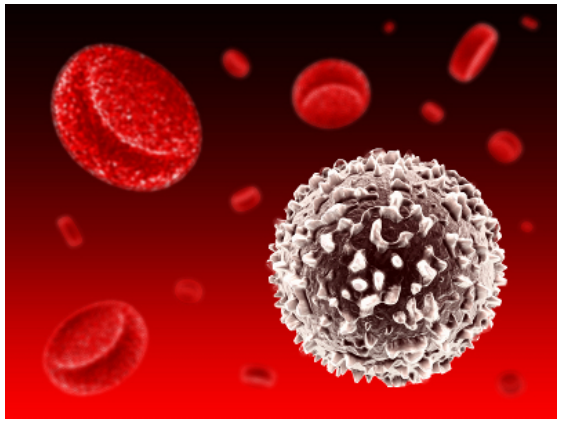
OSBT	OLGSCa	Reference
36%	NA	Mok et al. [28]
35%	33%	Haas et al. [29]
33%	35%	Singer et al. [19]
22%	N/A	Mayr et al. [20]
18%	N/A	Anglesio et al. [21]
17%	19%	Wong et al. [22]
39.5%	23%	Vereczkey et al. [23]
N/A	54.5%	Sundov et al. [25]

BRAF mutations are more frequently detected in SOBTs that do not recur. This could indicate a protective role of this mutation against progression to LGSOC.

BRAF mutation is associated with early stage disease and improved outcome in patients with LGSOC (Grisham RN et al. *Cancer*; 2013).

Low grade serous carcinoma ctDNA

- Expecting to find KRAS or BRAF
- Dependent on tumor burden and proliferation rate



FoundationACT™ (Assay for Circulating Tumor DNA) is a next-generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating tumor DNA and matches them to targeted therapies and clinical trials.

PATIENT RESULTS	TUMOR TYPE: OVARY SEROUS CARCINOMA
0 genomic alterations	**Genomic Alterations Identified**†
0 therapies associated with potential clinical benefit	No Reportable genomic alterations were detected
0 therapies associated with lack of response	
0 clinical trials	

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

Metachronous tumor profiling

- 2010 lymph node
- 2017 trachea

PATIENT RESULTS

- 3 genomic findings
- 5 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 10 clinical trials

TUMOR TYPE: OVARY SEROUS CARCINOMA

Genomic Alterations Identified†

BRAF V600E
MYC amplification – equivocal#
NOTCH2 P6fs*27

Additional Disease-relevant Genes with No Reportable Alterations Identified†

BRCA1
BRCA2

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix
# See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
BRAF V600E	None	Cobimetinib Dabrafenib Regorafenib Trametinib Vemurafenib	Yes, see clinical trials section
MYC amplification - equivocal	None	None	Yes, see clinical trials section
NOTCH2 P6fs*27	None	None	None

PATIENT RESULTS

- 2 genomic findings
- 5 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 5 clinical trials

TUMOR TYPE: OVARY SEROUS CARCINOMA

Genomic Alterations Identified†

BRAF V600E
DOT1L T306M

Additional Disease-relevant Genes with No Reportable Alterations Identified†

BRCA1
BRCA2

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
BRAF V600E	None	Cobimetinib Dabrafenib Regorafenib Trametinib Vemurafenib	Yes, see clinical trials section
DOT1L T306M	None	None	None

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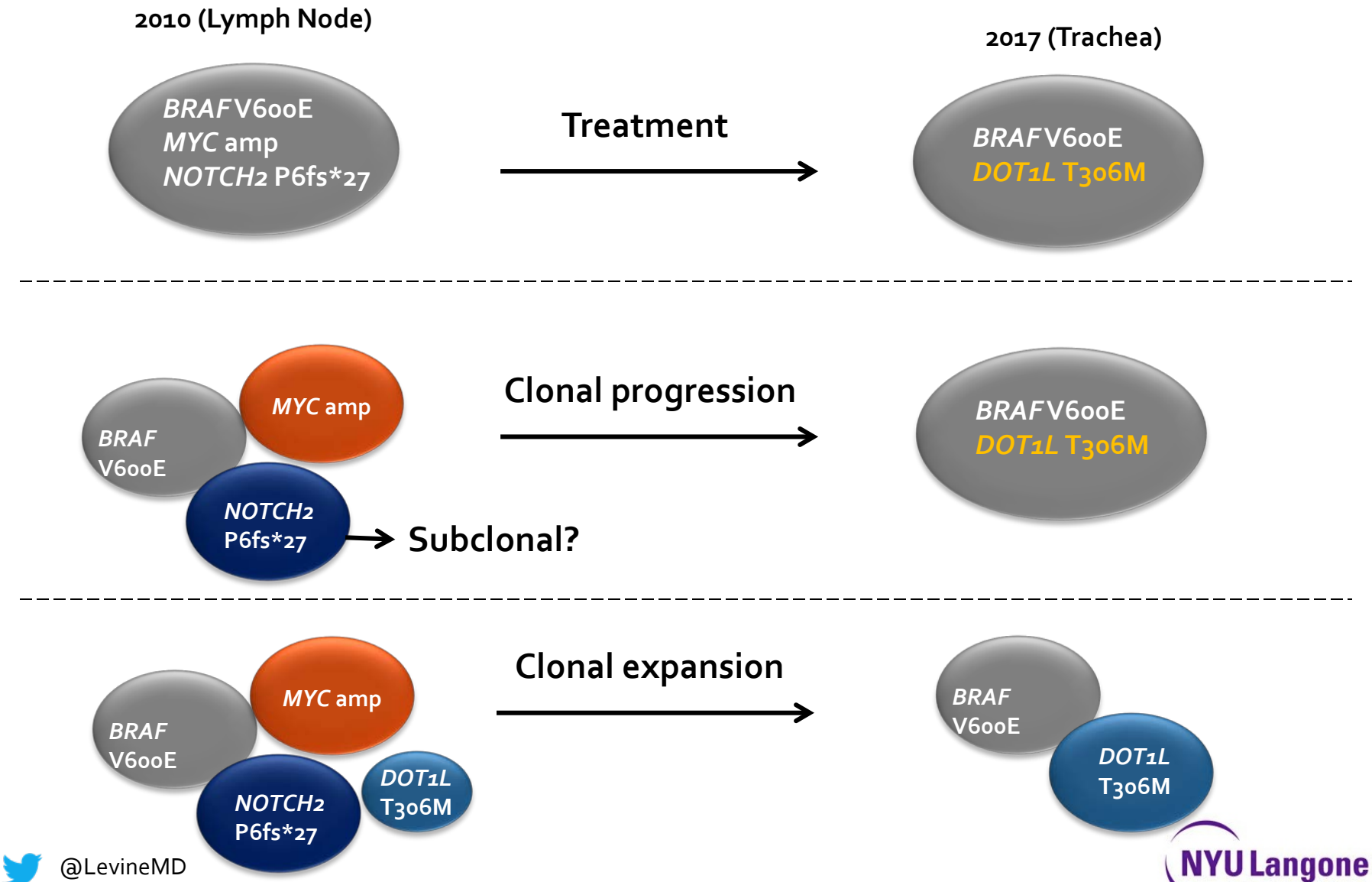
Tumor progression/selection/evolution?

BRAF V600E in LGSOC is associated with early stage disease.



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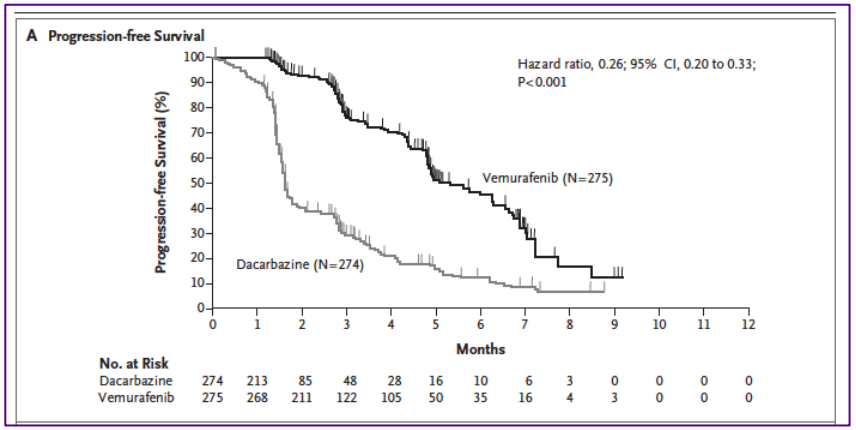
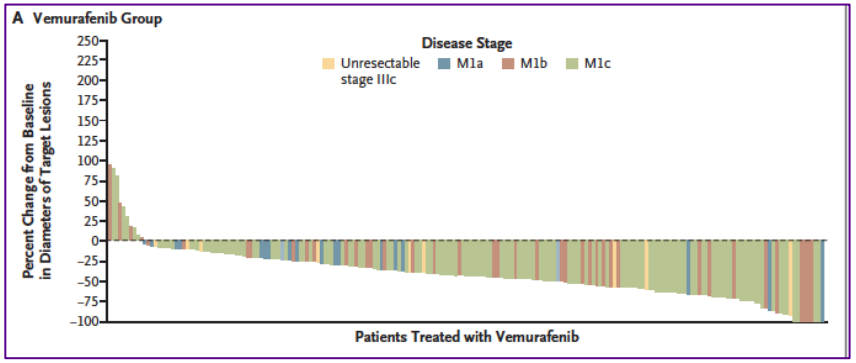
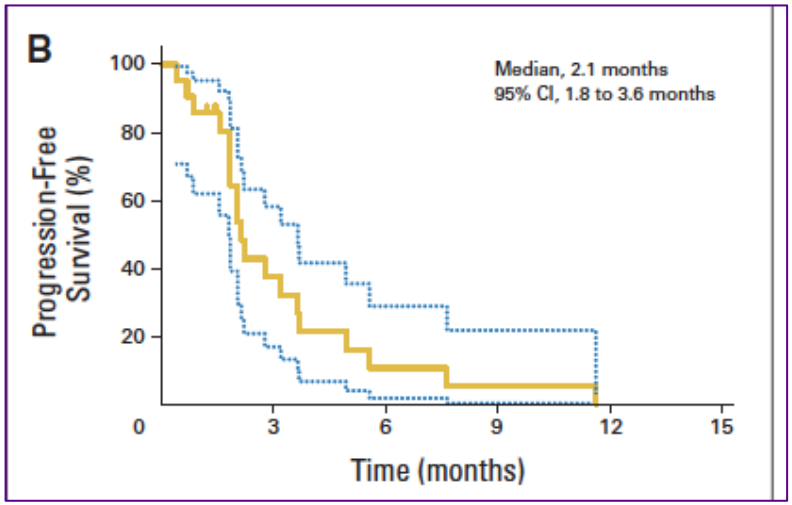
All tumors are not created equally

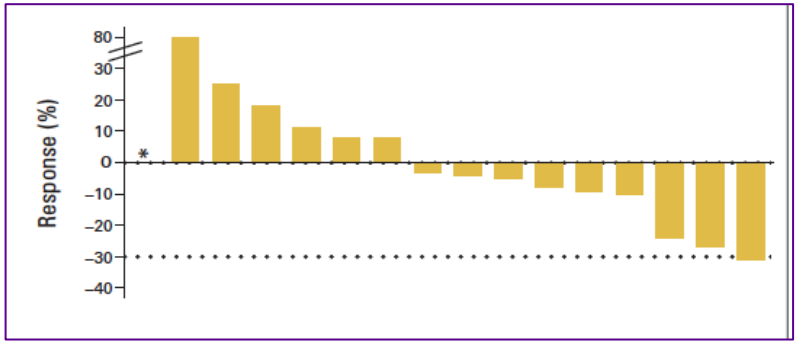
Vemurafenib is highly effective in BRAF V600E mutant melanoma





Not so much in BRAF V600E mutant CRC





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N ENGL J MED 364;26 NEJM.ORG JUNE 30, 2011

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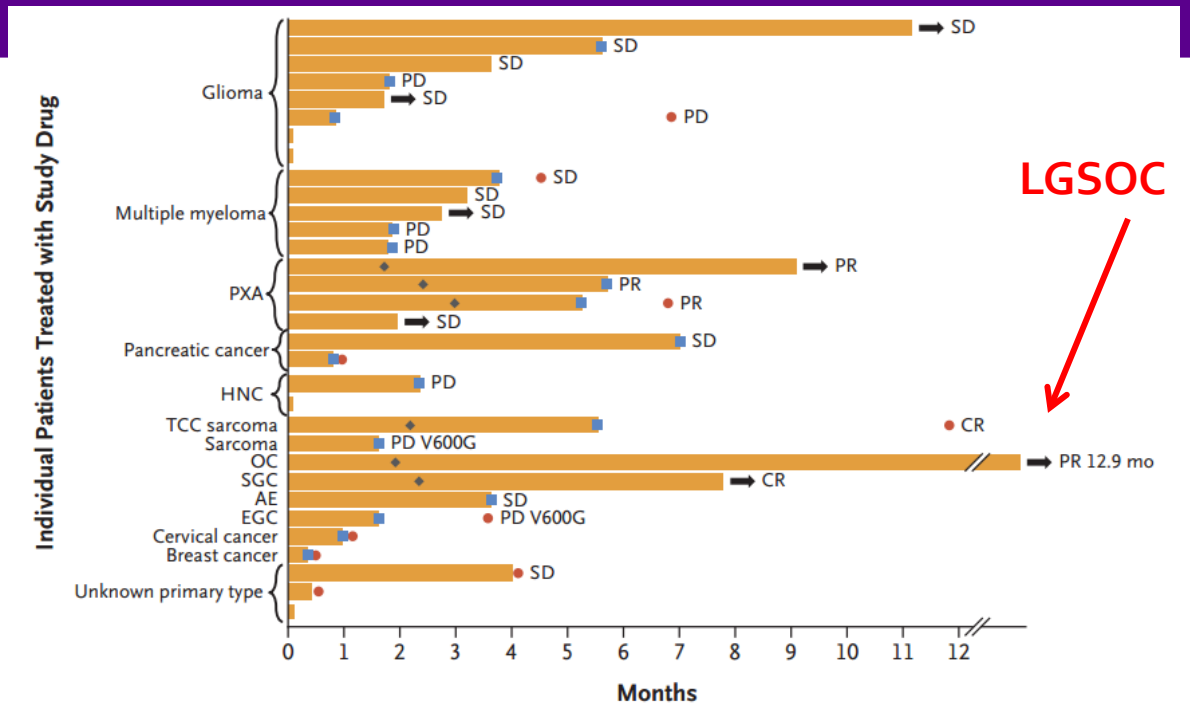
Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations

Time to Events in Individual Patients and According to the Best Overall Response. The bar length represents the duration of progression-free survival. Arrows indicate patients who were still receiving the study drug, and asterisks patients in the dose-escalation stage (dose levels 1 and 2).

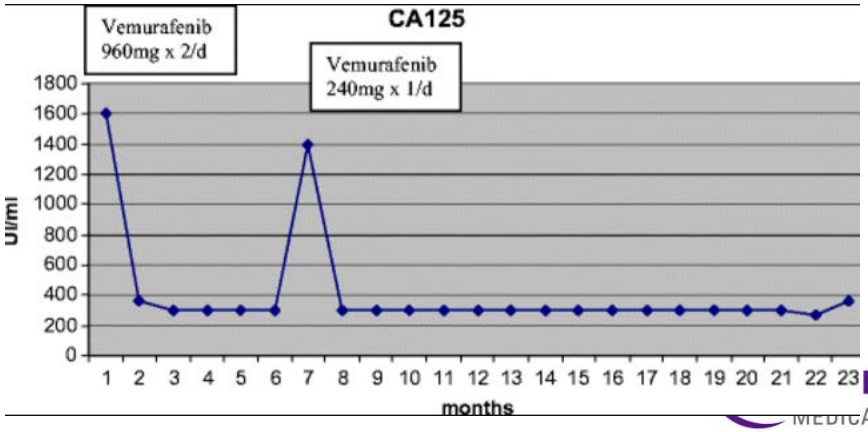
Hyman DM *et al. N Engl J Med*; 2015



Sustained response to vemurafenib in LGSOC with a BRAF V600E mutation.

Kinetic curve of CA125 (IU/ml) during vemurafenib administration. IU/ml. Vemurafenib at the full dose (960 mg twice a day). Vemurafenib was stopped after 10 days of treatment due to grade 3 skin toxicity. After 4 months without treatment, peritoneal progression confirmed by CT scan and CA125 increase to 1400 IU/ml. Continue with vemurafenib at a lower dose of 240 mg/day – resulted in a partial response (RECIST)

Comito F *et al. Invest New Drugs*; 2015



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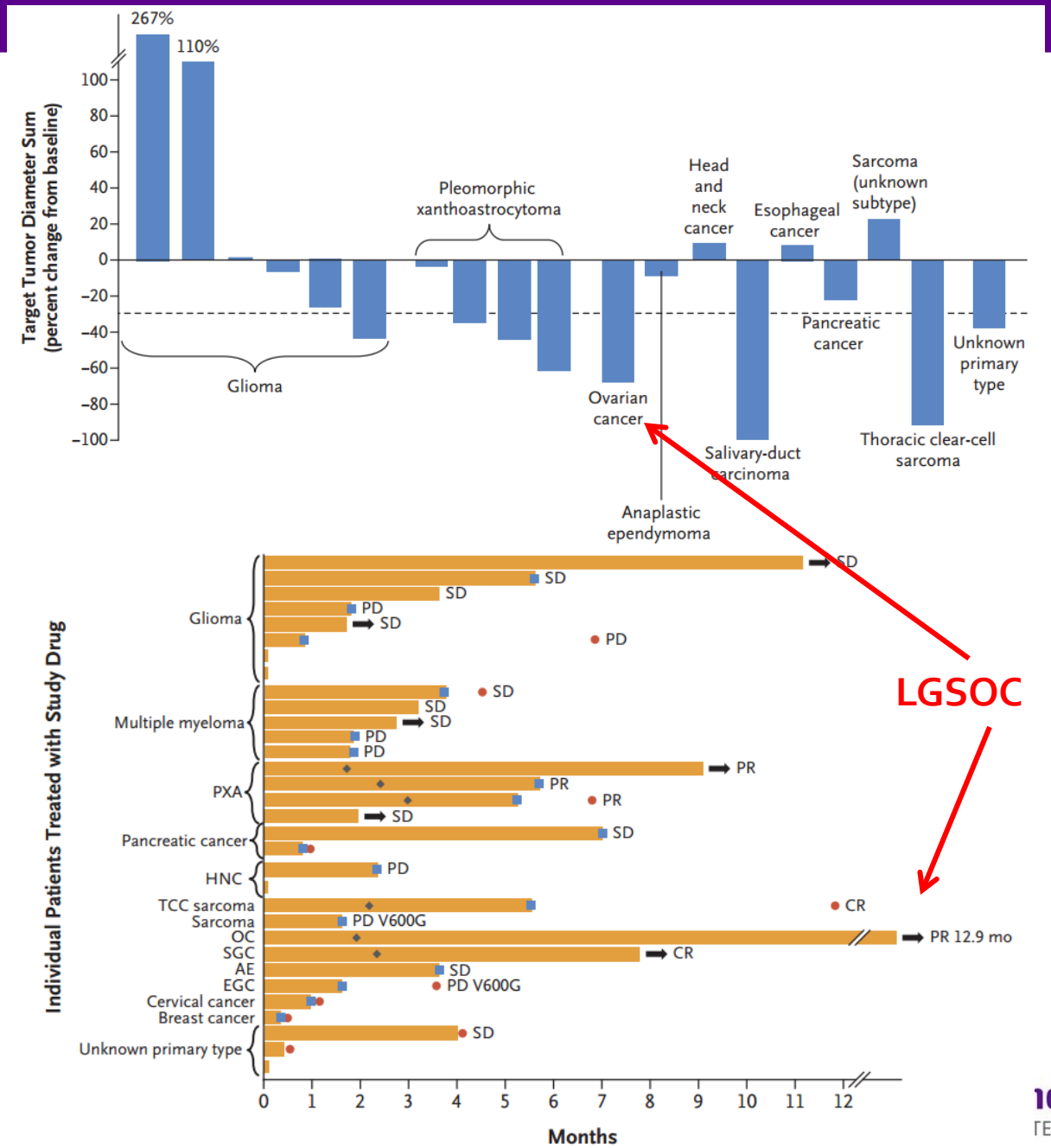
Vemurafenib in Multiple Nonmielanoma Cancers with BRAF V600 Mutations

Maximum Percent Change from Baseline in the Sum of the Diameters of Target Lesions. The change from baseline in the target lesion diameter is shown for patients who had measurable disease at baseline according to Response Evaluation Criteria in Solid Tumors (RECIST) and who underwent at least one post-treatment evaluation; dashed lines indicate −30% change, the minimum necessary to qualify for partial response according to RECIST



This patient will start vemurafenib treatment at her next visit.

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Hyman DM *et al. N Engl J Med*; 2015

Rare Tumor Research

Small cell carcinoma of the ovary hypercalcemic type (SCCOHT)

- **Rare and aggressive ovarian cancer**

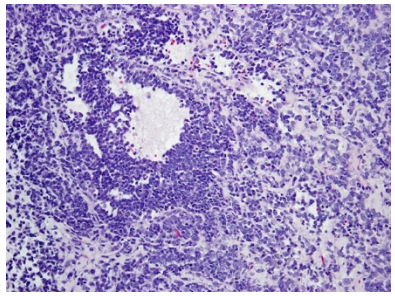
- **Clinical presentation**
  - Mean age at diagnosis of 23 years
  - Recurrences often occur within 1 year
  - Familial cases have been reported

Robert E. Scully, MD

- **Tumor morphology**
  - Small round nuclei
  - Pseudo-follicular spaces

- **Immunohistochemistry**

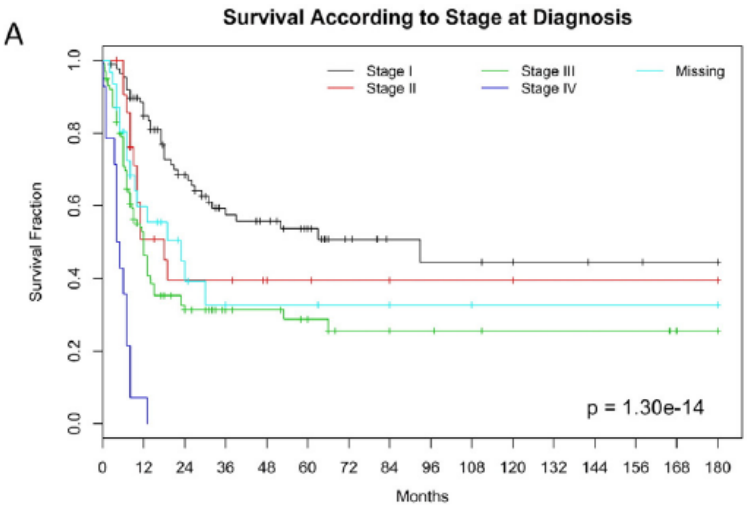
+	-
WT1	Inhibin
CD10	S100
Calretinin	Chromogranin



The influence of clinical and genetic factors on patient outcome in small cell carcinoma of the ovary, hypercalcemic type

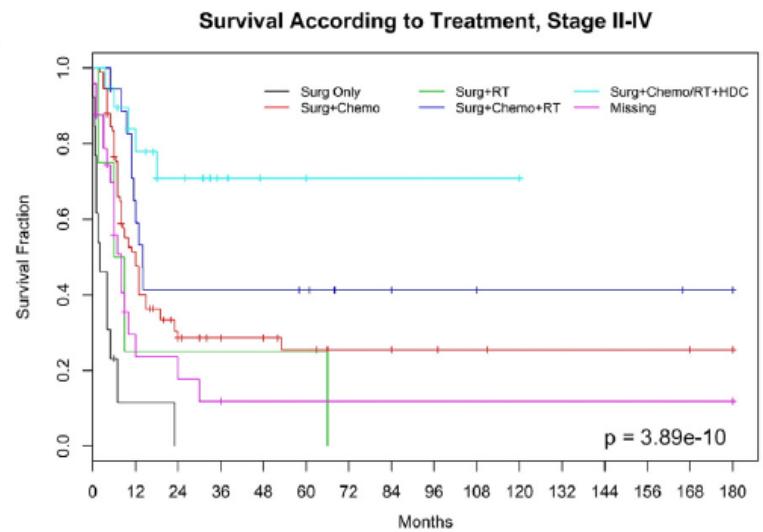
Leora Witkowski [a,1], Catherine Goudie [b,1], Pilar Ramos [c], Talia Boshari [d], Jean-Sebastien Brunet [e], Anthony N. Karnezis [f], Michel Longy [g], James A. Knost [h], Emmanouil Saloustros [i], W. Glenn McCluggage [j], Colin J.R. Stewart [k], William P.D. Hendricks [c], Heather Cunliffe [l], David G. Huntsman [f], Patricia Pautier [m], Douglas A. Levine [n], Jeffrey M. Trent [c], Andrew Berchuck [o], Martin Hasselblatt [p], William D. Foulkes [a,d,q,*]

A



Total	257	145	88	60	51	41	24	20	16	15	12	10	9	9	7	6
Stage I	88	72	48	33	29	23	12	8	7	7	6	5	4	4	3	3
Stage II	23	10	7	7	5	4	3	3	2	2	2	1	1	1	1	1
Stage III	101	48	25	15	13	10	6	6	5	4	3	3	3	3	2	1
Stage IV	14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Missing	31	14	8	5	4	4	3	3	2	2	1	1	1	1	1	1

C



Total	169	73	40	27	22	18	12	12	9	8	6	5	5	5	4	3
Surg Alone	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Surg + Chemo	91	41	19	12	11	8	6	6	4	3	2	2	2	2	2	1
Surg+RT	4	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
Surg + Chemo + RT	18	11	7	7	7	6	4	4	3	3	2	2	2	2	1	1
Surg + Chemo/RT + HDC	19	14	9	5	2	2	1	1	1	1	1	0	0	0	0	0
Missing	24	5	4	2	1	1	1	1	1	1	1	1	1	1	1	1

Less than 50% of stage II-IV pts survive more than two years

HDC showed best results in advanced stages; n=19

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Gynecol Oncol. 2016 Mar 19.

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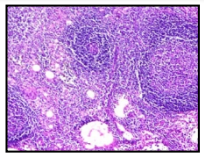
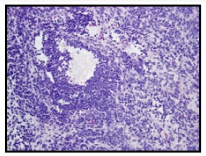
After seeing two SCCOHT cases in <6 months we decided to sequence all the cases we could find at MSK (n=3)

NML SCCOHT Unstained slides

12 tumor/normal pairs

50% minimum tumor purity





IMPACT assay

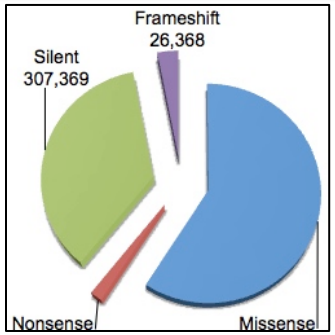
(next generation seq)

Illumina HiSeq 2000

Illumina HiSeq 2000 DNA sequence analyser

Align sequence
Filter sequence

Call variants
Annotate variants



Burrows-Wheeler Align Tool
Genome Analysis Toolkit

MuTect
SomaticIndelDetector

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Good news and bad news and need for more pts

Human hg19 | chr19 | chr19:11,141,549-11,141,590 | Go

p13.3 p13.2 p13.13 p13.11 p12 p11 q11 q12 q13.11 q13.12 q13.2 q13.31 q13.33 q13.41 q13.43

43 bp

11,141,550 bp 11,141,560 bp 11,141,570 bp 11,141,580 bp 11,141,590 bp

NAME
DATA FILE
DATA TYPE

DL-scco-01-N_bc16_Bla

Normal

DL-scco-01-N_bc16_BladderSCP3_L001_mrg_cl_aln_srt_MD_IR_BR.bam

DL-scco-01-T_bc15_Bla

Tumor

DL-scco-01-T_bc15_BladderSCP3_L001_mrg_cl_aln_srt_MD_IR_BR.bam

Breadth of the sequence covered
97% of target exons in tumors

MEAN DEPTH OF COVERAGE (440X)

Reference Transcript

A G C G A C T G G A A T C C T C A C C A G G T A A A A G C G G G C C G G G C C C C A

S D W N P H Q

amino acid

SMARCA4

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SMARCA4 mutations are universally detected in SCCOHT.

Patient	Year†	Age†	Mutation
101	2003	40	p.Q1182 splice site
102	2009	22	p.K1357 splice site
103	2010	19	homozygous deletion
104	1998	21	p.K587 splice site p.R978 nonsense
105	2009	25	p.Q331 nonsense p.I542 frameshift
106	2012	40	p.L389 frameshift p.R1093 nonsense
107	2010	18	p.ETVN1267 deletion
108	2011	22	p.Q847 nonsense
109	2010	32	p.L762 frameshift p.G836 nonsense
110	2011	42	p.Q1166 nonsense
111	2012	35	p.R1005 nonsense¥
112	2011	28	p.K953 splice site

7 Nonsense

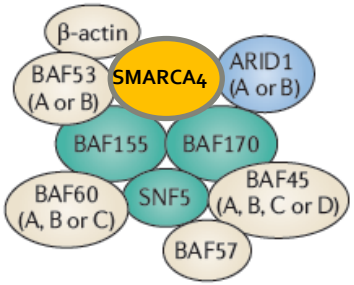
4 Splice site

3 Frameshift

2 Deletions

- **No copy number alterations or other mutations – tumors are diploid**

SWI/SNF complex



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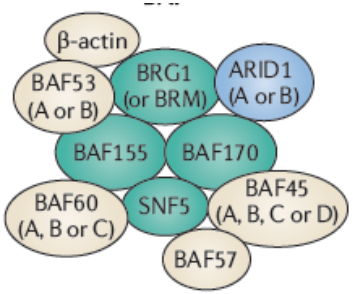
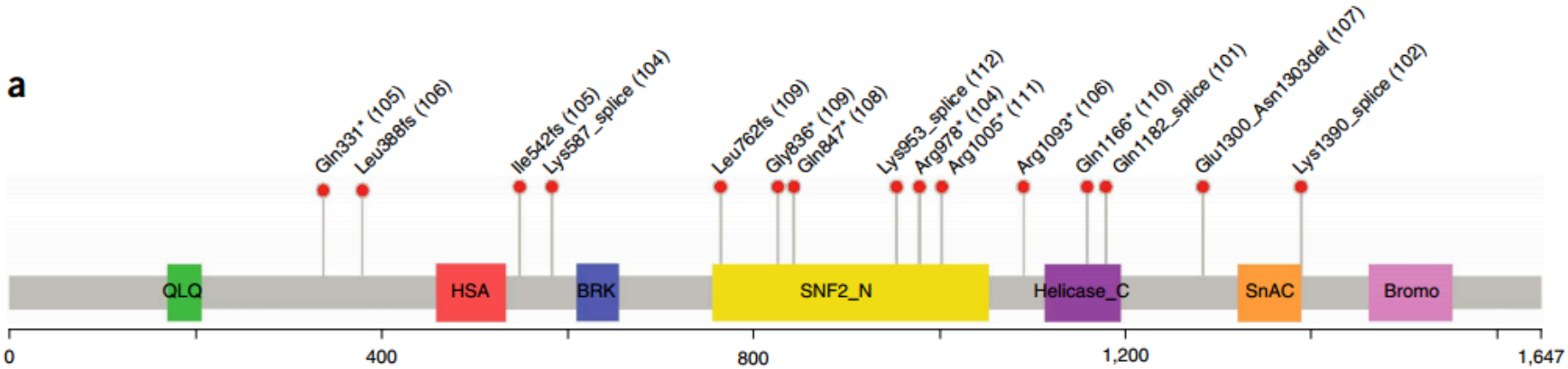
nature genetics

SWI/SNF complex



Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary

Petar Jelinic[1,5], Jennifer J Mueller[1,5], Narciso Olvera[1], Fanny Dao[1], Sasinya N Scott[2], Ronak Shah[2], JianJiong Gao[3], Nikolaus Schultz[3], Mithat Gonen[4], Robert A Soslow[2], Michael F Berger[2] & Douglas A Levine[1]



- *SMARCA4* contains essential enzymatically active domains
- SMARCA4 is a key subunit in SWI/SNF chromatin remodeling complex
- Chromatin remodeling complex behaves like a tumor suppressor in other cancers

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BRIEF COMMUNICATIONS

nature genetics

Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary

Petar Jelinic[1,5], Jennifer J Mueller[1,5], Narciso Olvera[1], Fanny Dao[1], Sasinya N Scott[2], Ronak Shah[2], JianJiong Gao[3], Nikolaus Schultz[3], Mithat Gonen[4], Robert A Soslow[2], Michael F Berger[2] & Douglas A Levine[1]

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare, highly aggressive form of ovarian cancer primarily diagnosed in young women. We identified inactivating biallelic *SMARCA4* mutations in 100% of the 12 SCCOHT tumors examined. Protein studies confirmed loss of SMARCA4 expression, suggesting a key role for the SWI/SNF chromatin-remodeling complex in SCCOHT.

BRIEF COMMUNICATIONS

nature genetics

Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*

Pilar Ramos[1,14], Anthony N Karnezis[2,3,14], David W Craig[1], Aleksandar Sekulic[1,4], Megan L Russell[1], William P D Hendricks[1], Jason J Corneveaux[1], Michael T Barrett[1], Karey Shumansky[5], Yidong Yang[5], Sohrab P Shah[2,5], Leah M Prentice[3], Marco A Marra[6], Jeffrey Kiefer[1], Victoria L Zismann[1], Troy A McEachron[1], Bodour Salhia[1], Jaime Prat[7], Emanuela D'Angelo[7], Blaise A Clarke[8], Joseph G Pressey[9], John H Farley[10], Stephen P Anthony[11], Richard B S Roden[12], Heather E Cunliffe[1,13], David G Huntsman[2,3,15] & Jeffrey M Trent[1,15]

S100 calcium-binding protein A1 and α-fetoprotein (AFP)[5]. Unlike most poorly differentiated, highly malignant tumors, SCCOHT is characteristically diploid, but its cellular and molecular mechanisms of pathogenesis remain poorly understood[1].

To analyze the genetic etiology of SCCOHT, we performed next-generation sequencing on a series of tumors and germline samples from 12 SCCOHT cases (9 tumors with 4 matched germline samples and 3 additional germline samples) and on the SCCOHT cell line BIN-67 (ref. 6). DNA from tumor and blood specimens was analyzed

LETTERS

nature genetics

Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type

Leora Witkowski[1–3,26], Jian Carrot-Zhang[3,4,26], Steffen Albrecht[5], Somayyeh Fahiminiya[3,4], Nancy Hamel[1,6], Eva Tomiak[7], David Grynspan[8], Emmanouil Saloustros[9], Javad Nadaf[3,4], Barbara Rivera[1,3], Catherine Gilpin[7], Ester Castellsagué[1,3], Rachel Silva-Smith[1,2], François Plourde[1,2], Mona Wu[1,3], Avi Saskin[3], Madeleine Arseneault[3,4], Rouzan G Karabakhtsian[10,25], Elizabeth A Reilly[10], Frederick R Ueland[10], Anna Margiolaki[9], Kitty Pavlakis[11], Sharon M Castellino[12], Janez Lamovec[13], Helen J Mackay[14], Lawrence M Roth[15], Thomas M Ulbright[15], Tracey A Bender[15], Vassilis Georgoulias[9], Michel Longy[16], Andrew Berchuck[17], Marc Tischkowitz[18], Inga Nagel[19], Reiner Siebert[19], Colin J R Stewart[20], Jocelyne Arseneau[21], W Glenn McCluggage[22], Blaise A Clarke[23], Yasser Riazalhosseini[3,4], Martin Hasselblatt[24], Jacek Majewski[3,4] & William D Foulkes[1–3,6]

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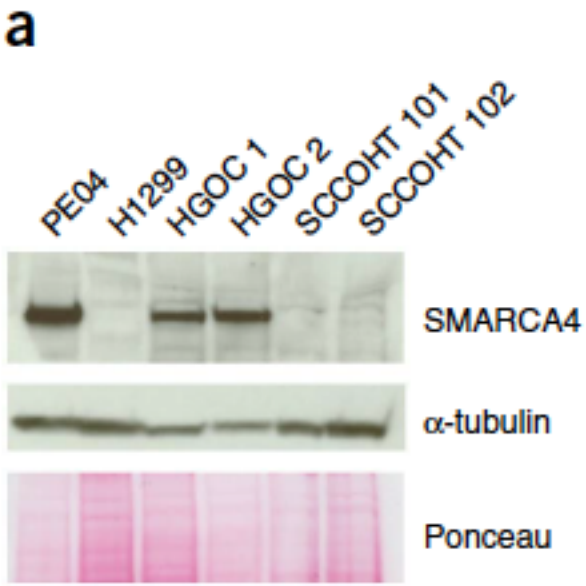
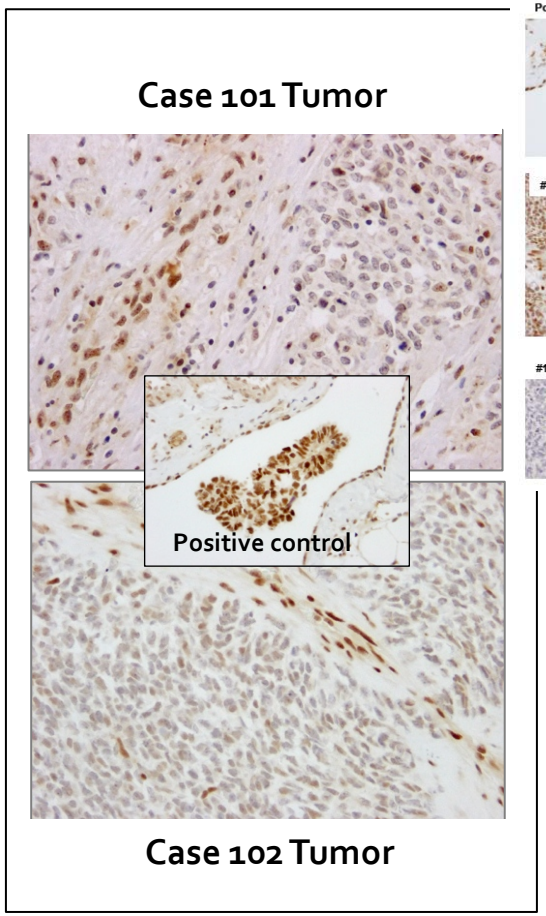
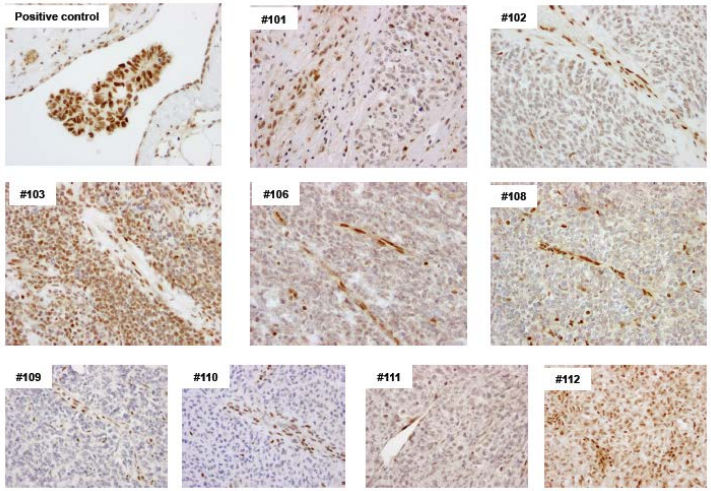
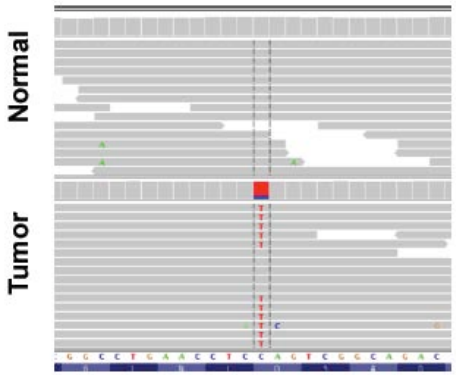
SMARCA4 mutations









SMARCA4 is mutated in various cancers.

***SMARCA4* is frequently mutated in:**

- **Burkitt Lymphoma (15%)**

  (Love C *et al.* Nat Genet 2012)

- **Non-small cell lung carcinoma (NSCLC) (10% cases; 35% cell lines)**

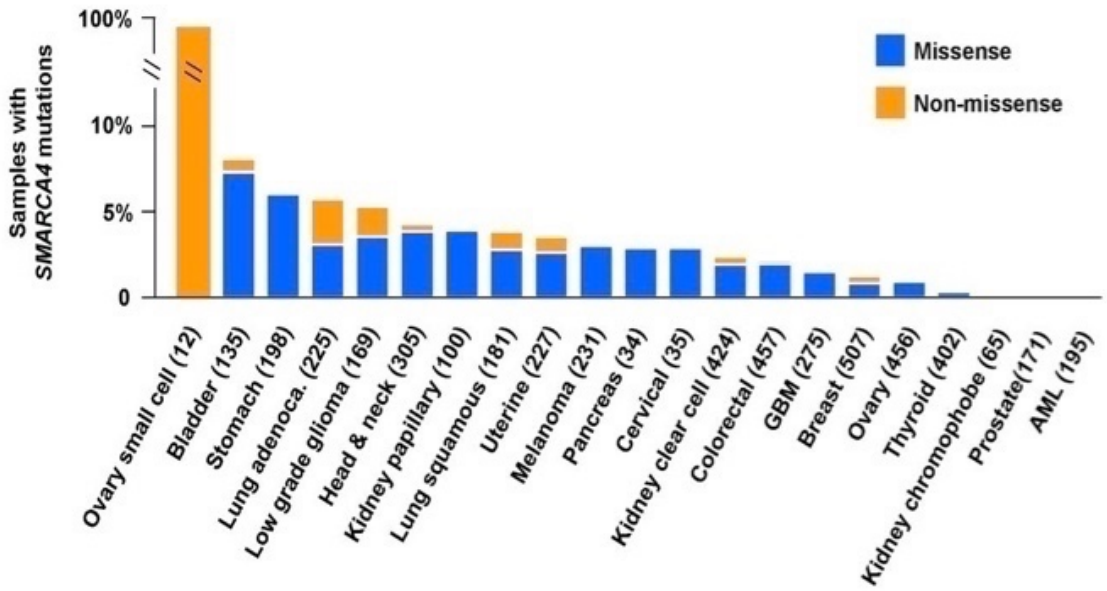
  (Reisman DN *et al.* Cancer Res 2003; Medina PP *et al.* Hum Mutat 2008)

- **Medulloblastomas (3-8%)**

  (Parsons DW *et al*. Science 2011; Jones DT *et al*. Nature 2012; Robinson G *et al.* Nature 2012)

- **Atypical teratoid/rhabdoid tumors (AT/RT) (19%)**

  (Hasselblatt M *et al.* Acta Neuropathol 2014)



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- *SMARCA4* is mutated in 3% of 4,784 TCGA tumors

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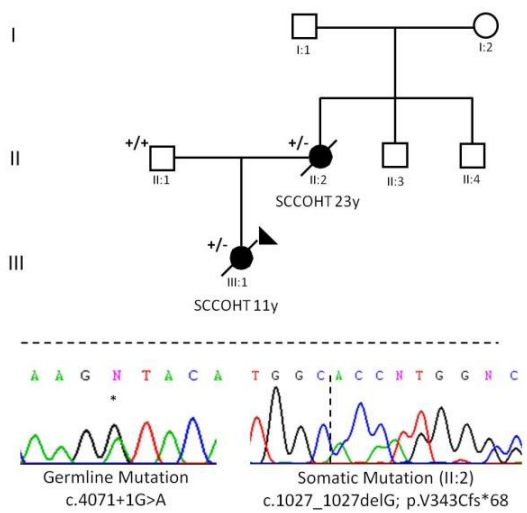
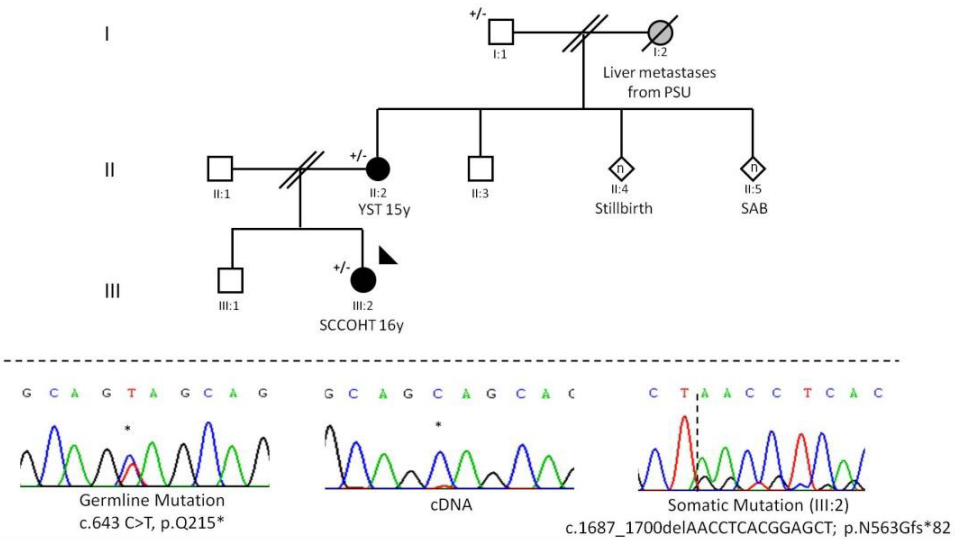
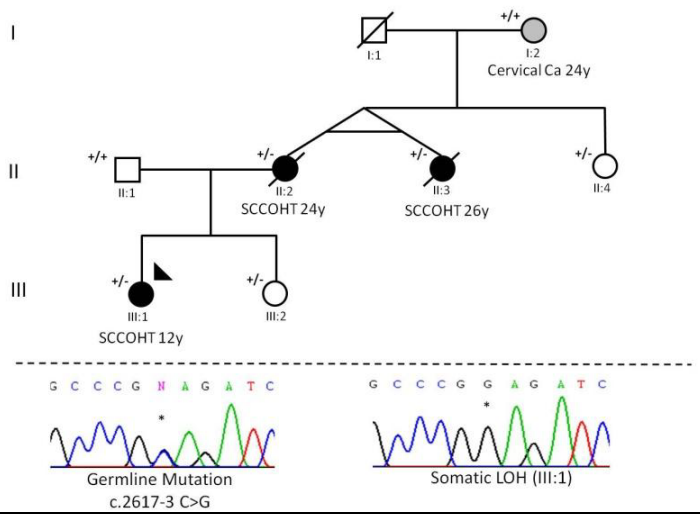
Family 1



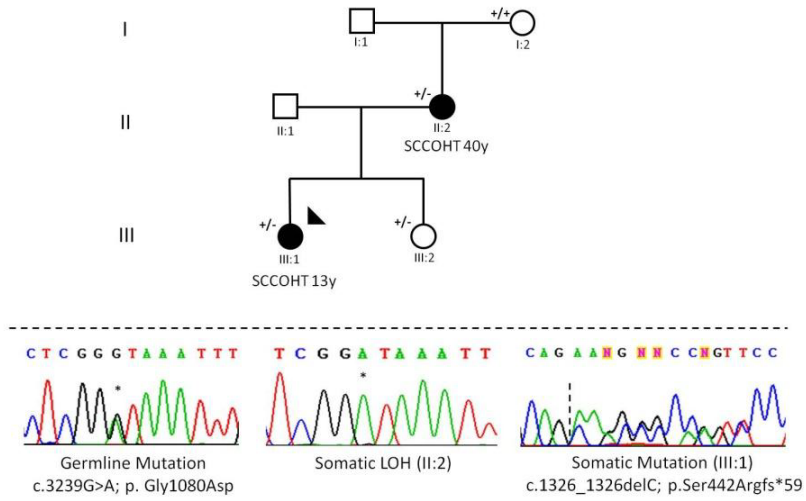
Family 2



Family 3



Family 4



Witkowski, L. et al. Nature Genetics 46, 438-443 (2014).

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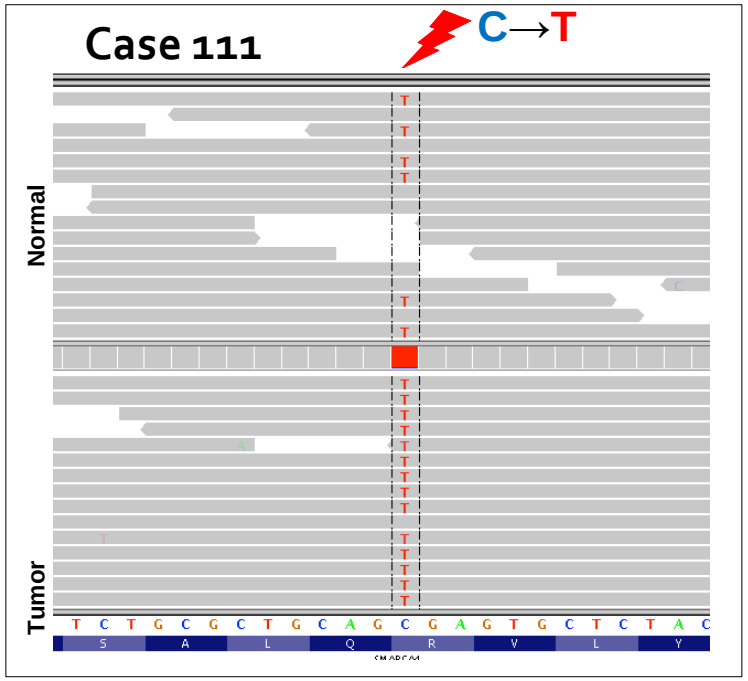
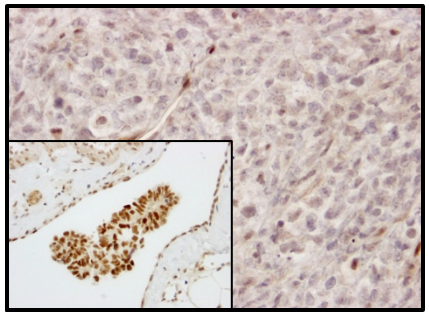
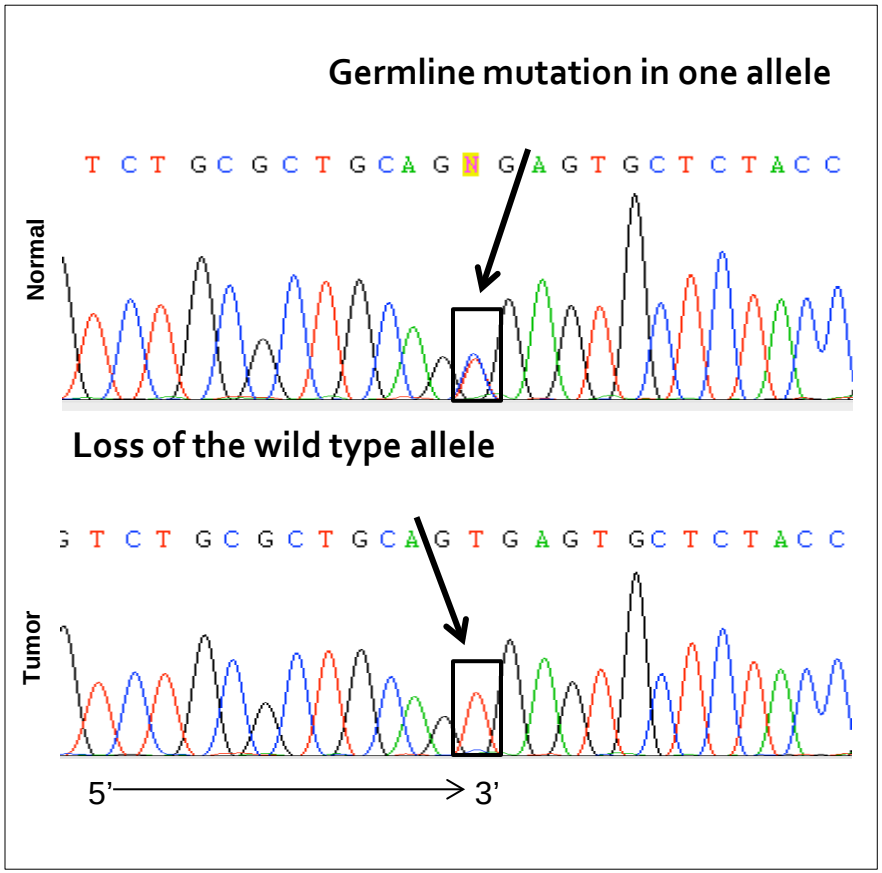
Germline mutations (10+%)





Positive control



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SCCOHT familial case

- 15yo with SCCOHT diagnosed with pelvic mass, completely resected
- 12yo sister diagnosed with SCCOHT died one month earlier after a 14 month survival
- Testing on 15yo shows biallelic inactivation of SMARCA4 with no other identified mutations
- Germline genetic testing underway for all family members

PATIENT RESULTS	TUMOR TYPE: PEDIATRIC OVARY SMALL CELL CARCINOMA
2 genomic findings	Genomic Alterations Identified†
0 therapies associated with potential clinical benefit	*SMARCA4* A573fs*40, R381*
0 therapies associated with lack of response	
4 clinical trials	

† For a complete list of the genes assayed and performance specifications

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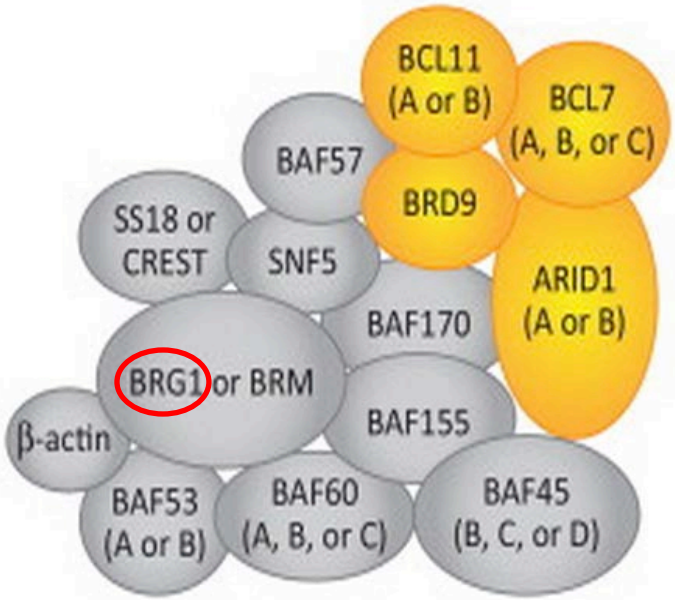
SMARCA4 is a catalytic subunit of the SWI/SNF chromatin remodeling complex

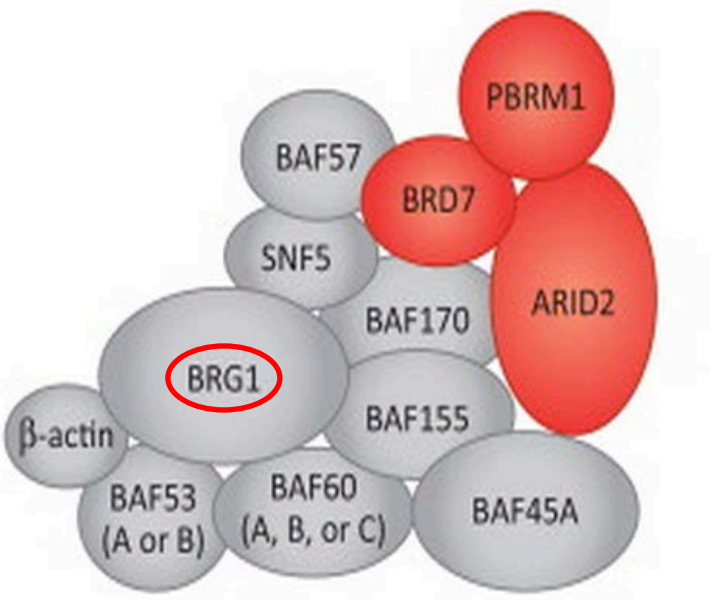
SMARCA4 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of
Chromatin, Subfamily A, Member 4) or **BRG1** (Brahma Related Gene 1)

SWI/SNF (SWItch/Sucrose NonFermentable)

SWI/SNF-A
(BAF; BRG1-Associated Factors)



SWI/SNF-B
(PBAF; PolyBromo-Associated Factors)



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Adapted from: Hofmann AF *et al*. Trends Genet 2014

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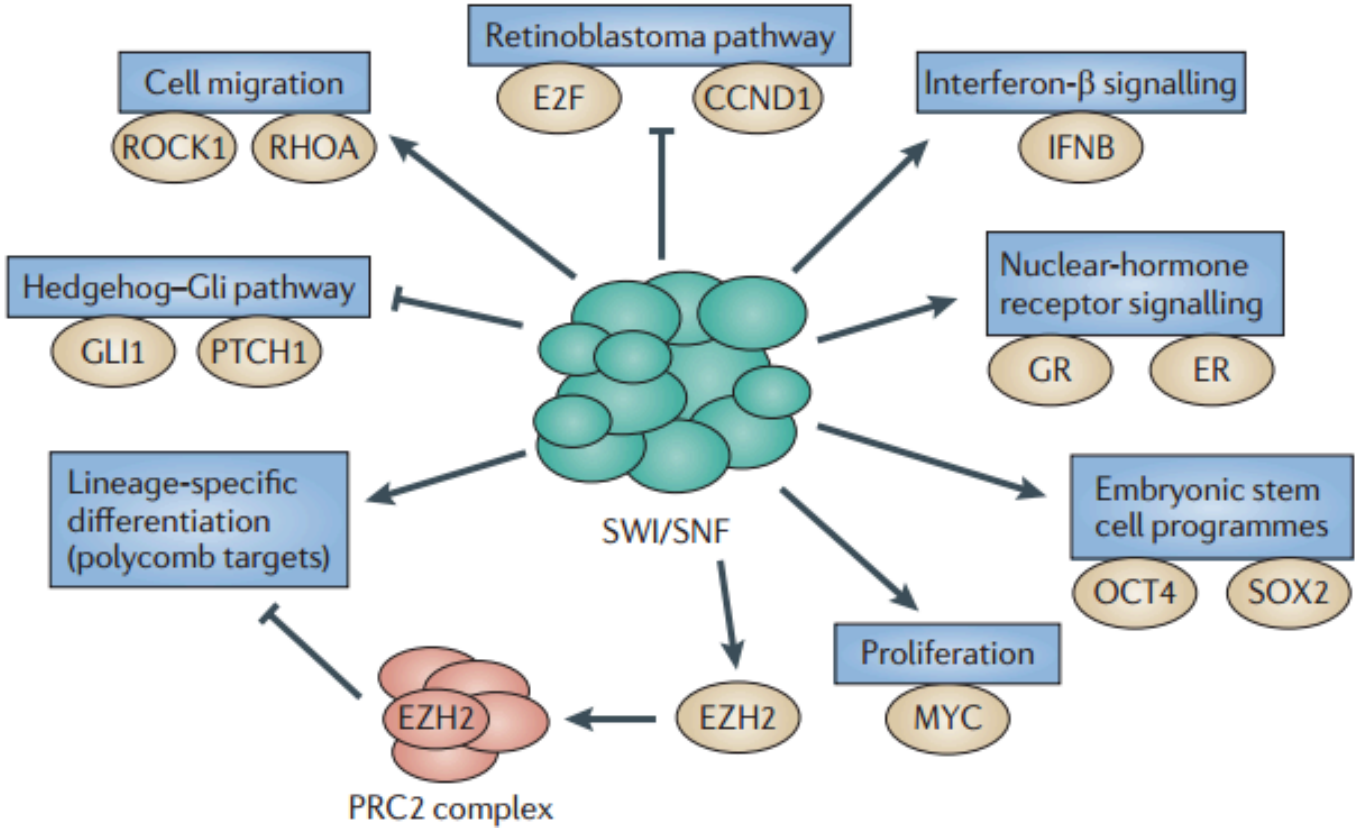
SWI/SNF complexes target multiple pathways



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Adapted from: Wilson BG *et al*. Nat Rev Cancer 2011

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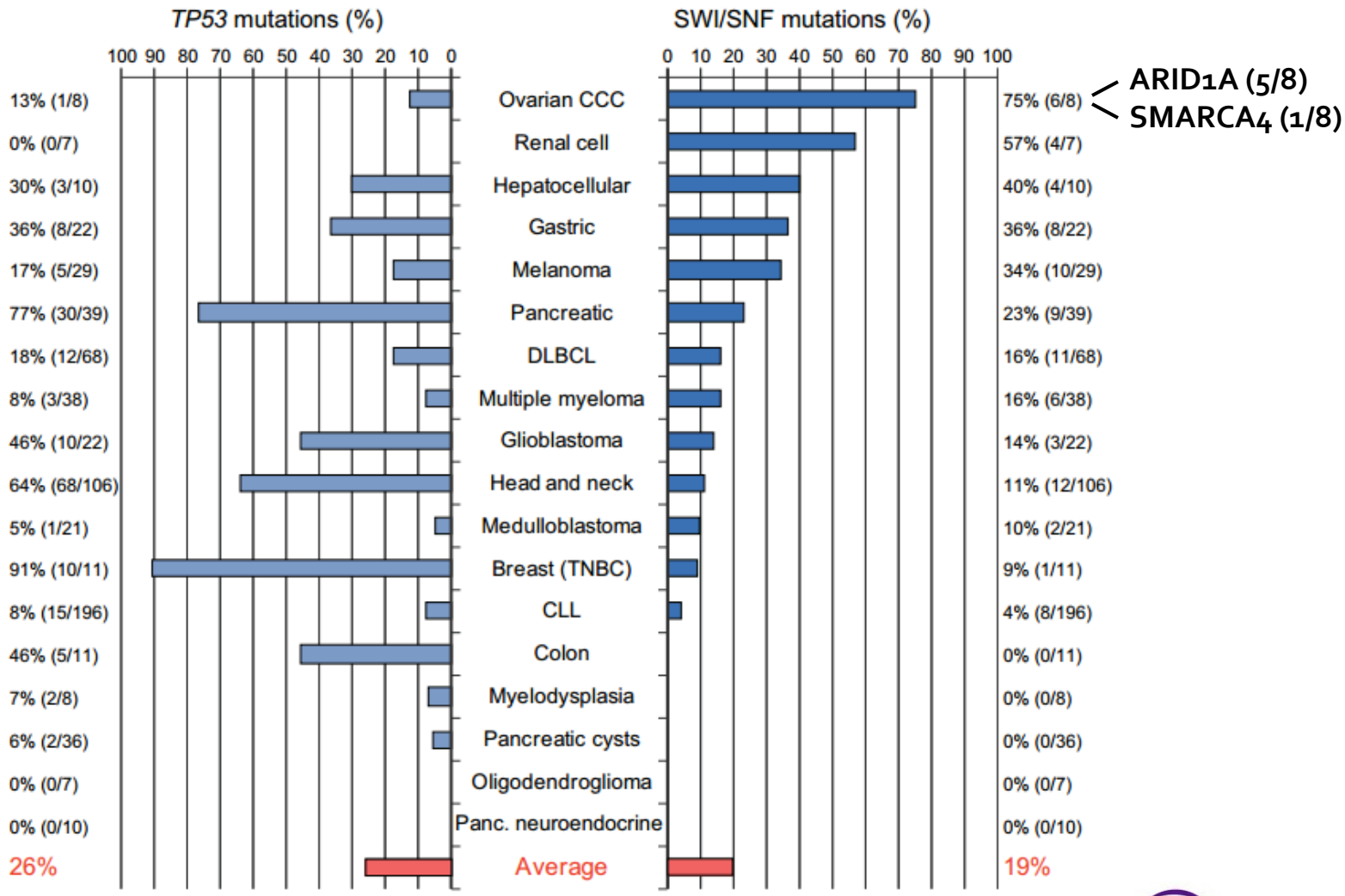
SWI/SNF complex alterations are common in cancer.

Subunits of the SWI/SNF complex are mutated in over 20% of all tumors



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Shain HA *et al*. PLoS ONE 2013

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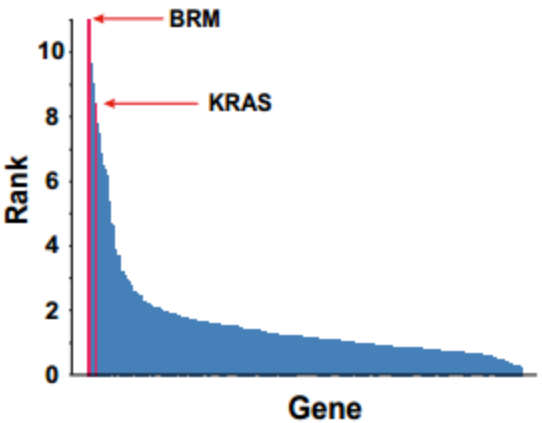
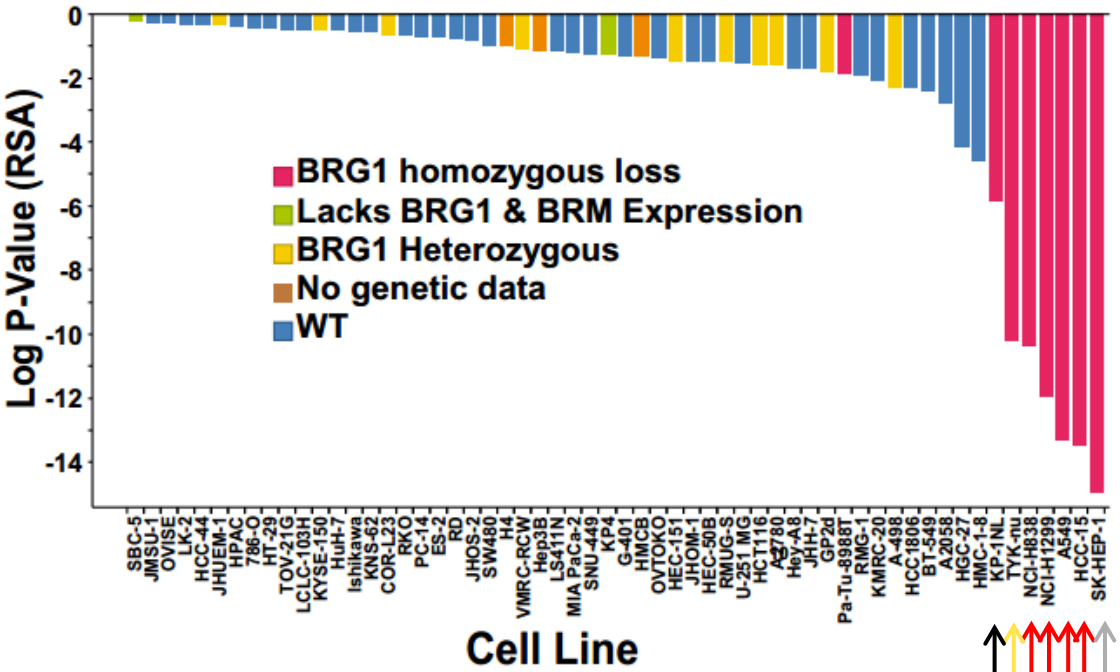
Depletion of SMARCA2 in *SMARCA4*-mutant cancer cells

An epigenome-wide pooled shRNA screen (384 genes) identifies SMARCA2 as a synthetic lethal target in *SMARCA4*-mutant cancer cells





pancreas
ovar
lung
liver
y

Senescence is likely the major mechanism for growth arrest in the SMARCA2 KD *SMARCA4-mutant cells*

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Hoffman GR *et al* PNAS 2014

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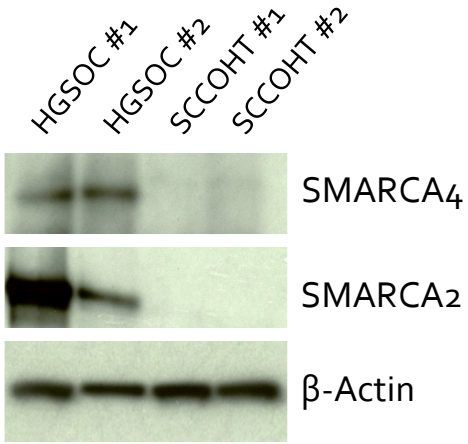
Loss of SMARCA2 protein expression in SCCOHT cases

SMARCA2 is not detectable by western blot in SCCOHT cases



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Modern Pathology (2015), 1–7
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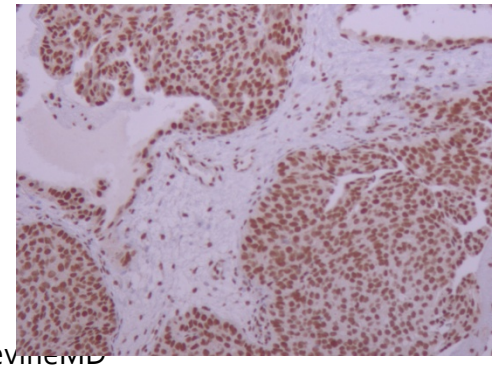
Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type

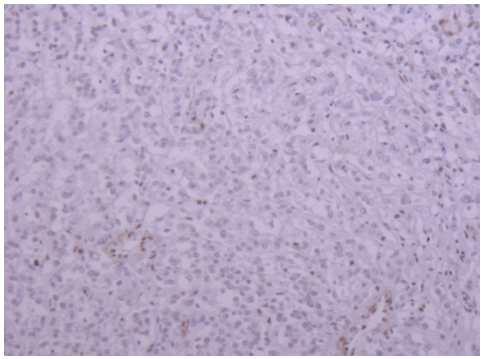
Petar Jelinic[1], Brooke A Schlappe[1], Niamh Conlon[2], Jill Tseng[1], Narciso Olvera[1], Fanny Dao[1], Jennifer J Mueller[1], Yaser Hussein[2], Robert A Soslow[2] and Douglas A Levine[1]

SMARCA2 IHC confirms loss of expression in SCCOHT cases

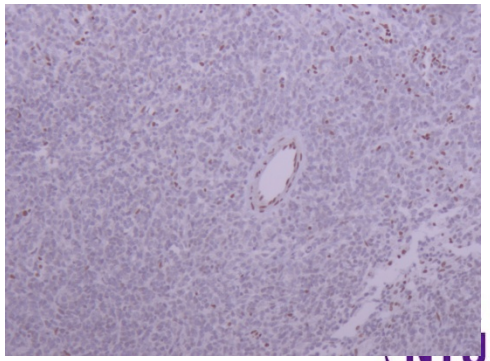
HGSOC



SCCOHT#1



SCCOHT#2

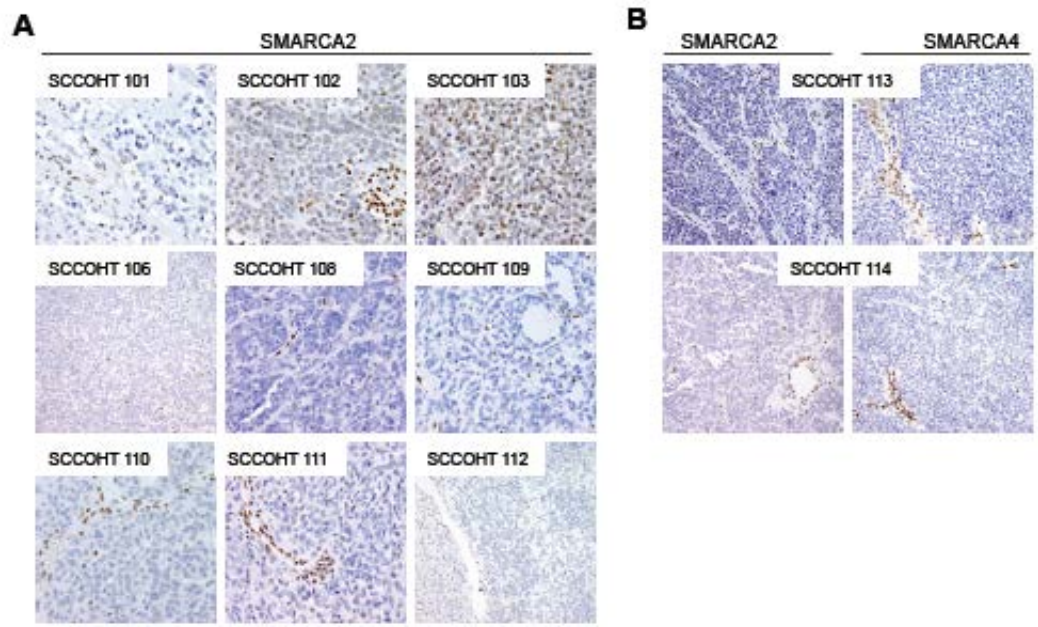


Universal loss of SMARCA2 in SCCOHT

Table 1. Summary of SMARCA2 and SMARCA4 mutation and IHC status in SCCOHT cases

Case number	Age at diagnosis (years)	SMARCA4			SMARCA2	
		Gene mutations		IHC	Gene status	IHC
		Protein Change	Domain affected			
101*	40	p.Q1182_splice	Helicase	Loss	wt	Loss
102*	22	p.K1390_splice		Loss	wt	Loss
103*	19	In-frame Deletion	Helicase	Retained	wt	Retained
106*	40	p.R1093*& p.L388fs	Helicase	Loss	N/A	Loss
108*	22	p.Q847*	SNF2	Loss	N/A	Loss
109*	32	p.L762fs& p.G836*	SNF2	Loss	N/A	Loss
110*	42	p.Q1166*	Helicase	Loss	N/A	Loss
111*	35	p.R1005*	SNF2	Loss	wt	Loss
112*	28	p.K953_splice	SNF2	Equivocal	wt	Loss
113	N/A	p.415_splice		Loss	wt	Loss
114	27	p.991_splice	SNF2	Loss	wt	Loss

Figure 1



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Non SCCOHT tumors

OPEN

Modern Pathology (2015), 1–7
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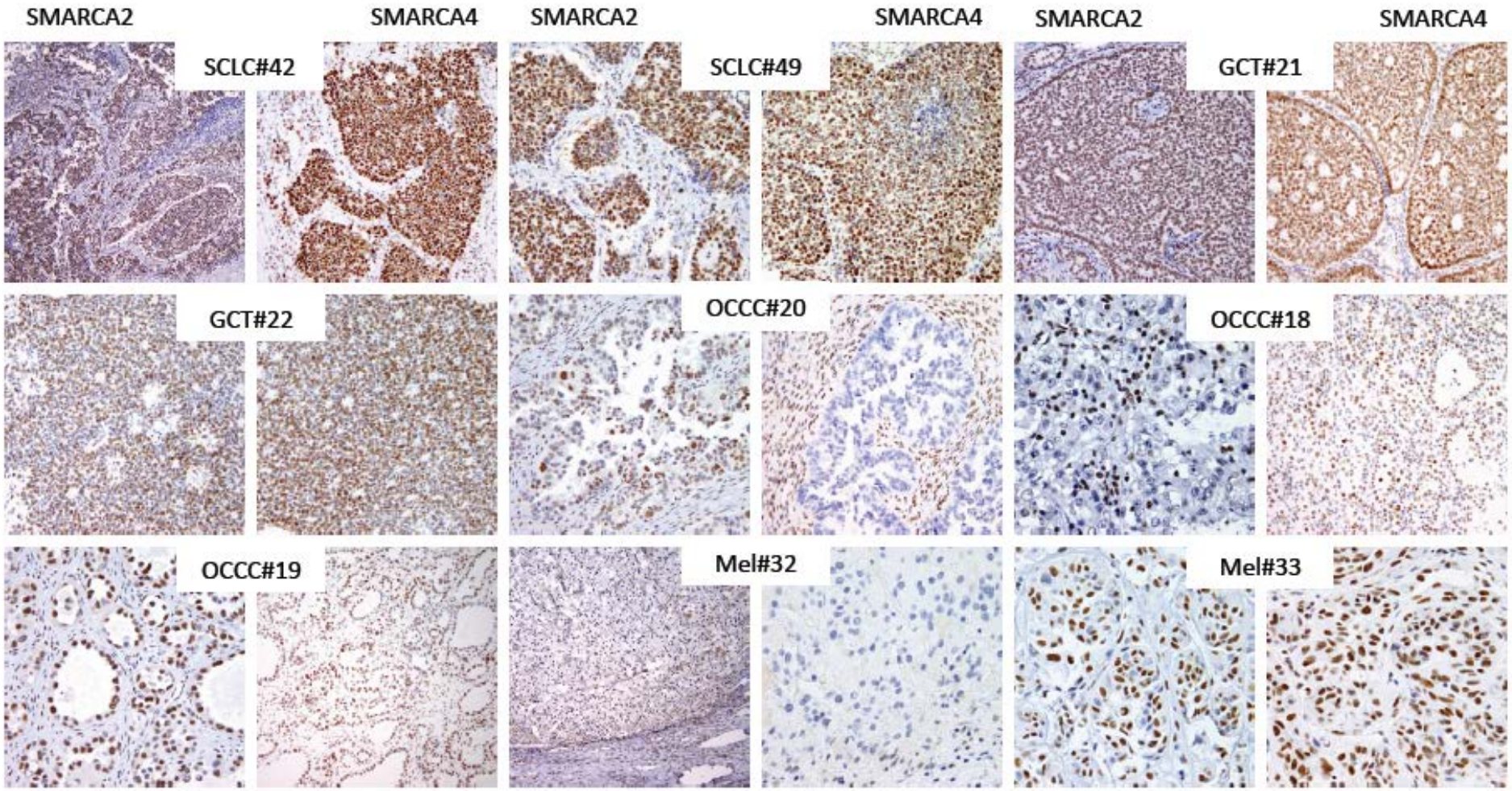
Concomitant loss of SMARCA2 and SMARCA4 expression in small cell carcinoma of the ovary, hypercalcemic type

Petar Jelinic[1], Brooke A Schlappe[1], Niamh Conlon[2], Jill Tseng[1], Narciso Olvera[1], Fanny Dao[1], Jennifer J Mueller[1], Yaser Hussein[2], Robert A Soslow[2] and Douglas A Levine[1]



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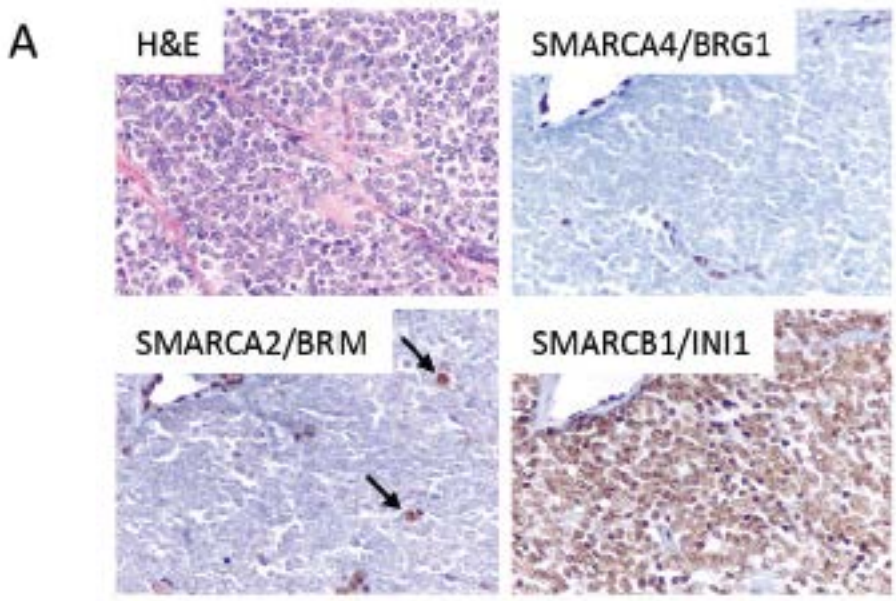
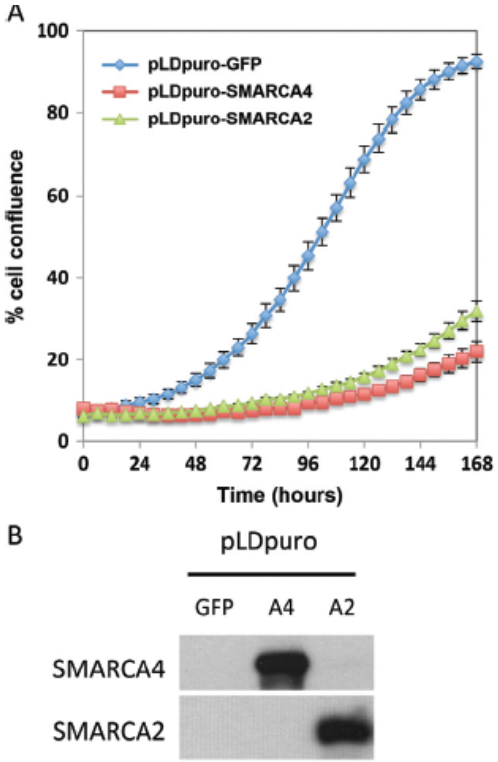
Dual loss of the SWI/SNF complex ATPases SMARCA4/BRG1 and SMARCA2/BRM is highly sensitive and specific for small cell carcinoma of the ovary, hypercalcaemic type

Anthony N Karnezis,[1†] Yemin Wang,[1†] Pilar Ramos,[2†] William PD Hendricks,[2] Esther Oliva,[3] Emanuela D'Angelo,[4] Jaime Prat,[4] Marisa R Nucci,[5] Torsten O Nielsen,[1] Christine Chow,[6] Samuel Leung,[6] Friedrich Kommoss,[7] Stefan Kommoss,[8] Annacarolina Silva,[9] Brigitte M Ronnett,[10] Joseph T Rabban,[11] David D Bowtell,[12] Bernard E Weissman,[13] Jeffrey M Trent,[2] C Blake Gilks[1*] and David G Huntsman[1,6,14*]





J Pathol 2016; 238: 389–400

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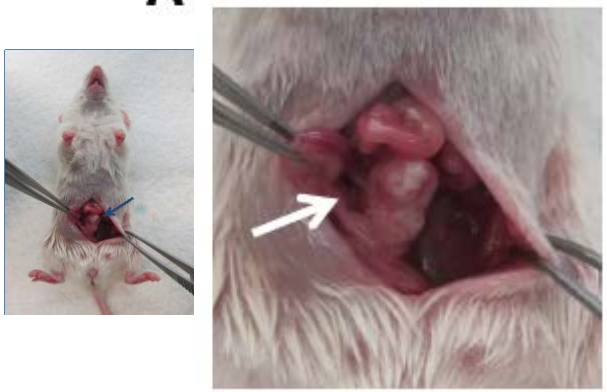
PDX mouse model of SCCOHT

A



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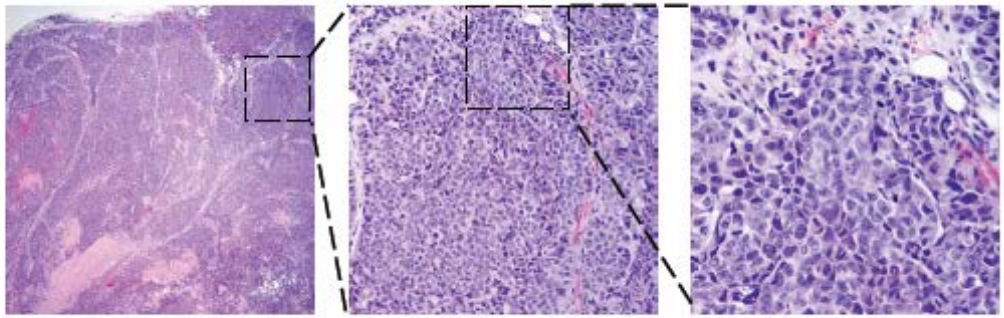

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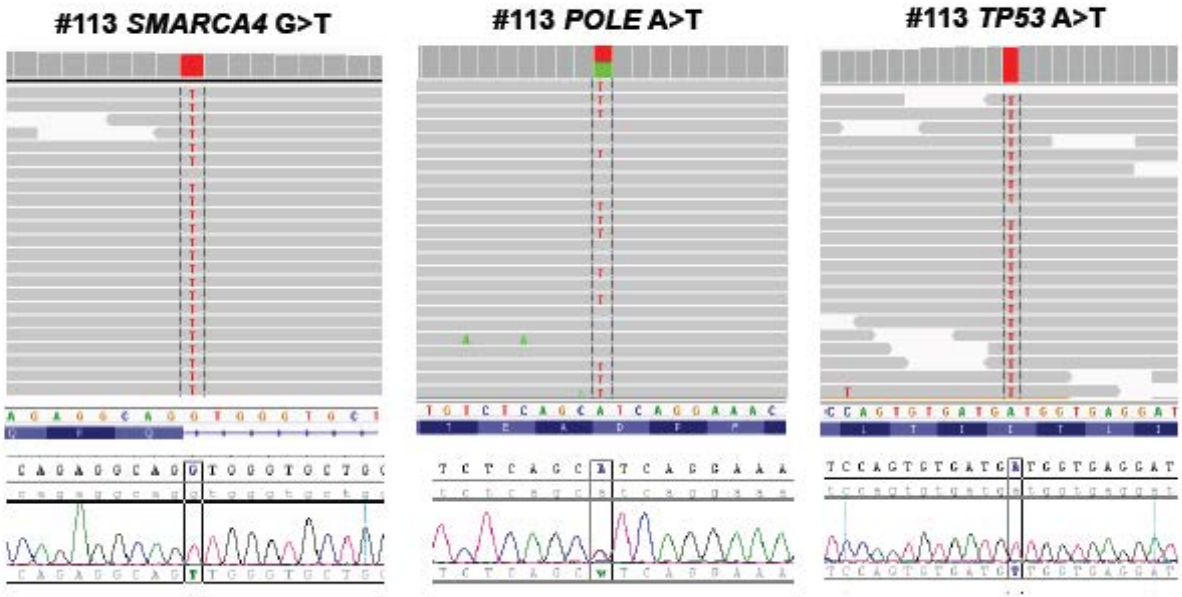

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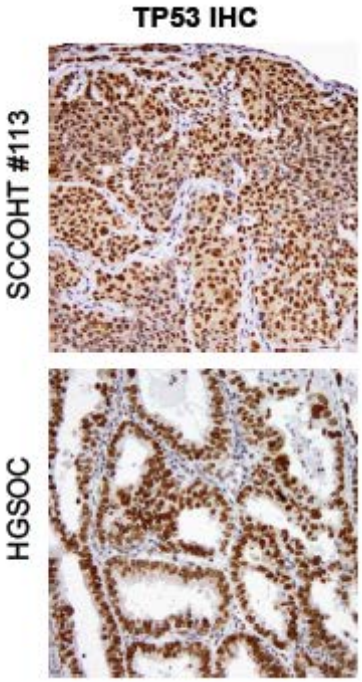

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SCCOHT pts respond to checkpoint blockade

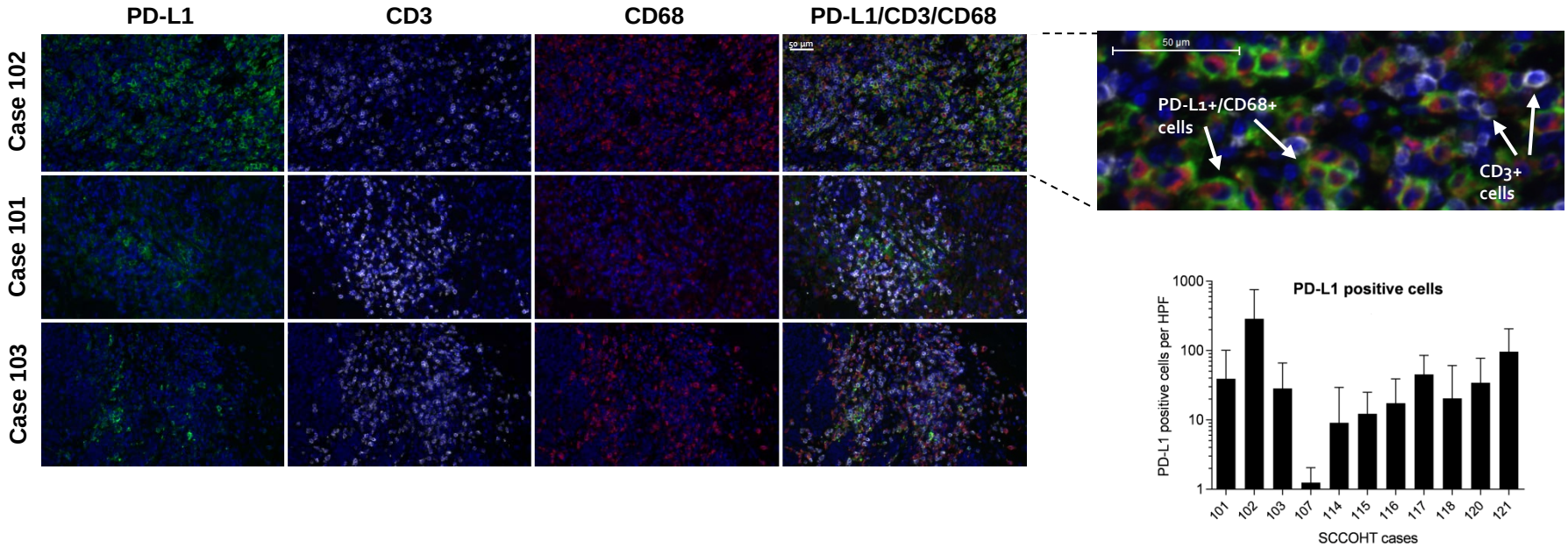
Patient 1
A 29yo was diagnosed with a large ovarian tumor that was completely resected. She received initial treatment with bleomycin/etoposide/cisplatin. She was then disease-free for ~1.5 years and suffered a recurrence in the abdomen and pelvis that was treated with investigational therapy with disease progression in less than 3 months. She was then treated with local radiation and pembrolizumab. She remains on pembrolizumab and continues to have a sustained partial response for 6 months.

Patient 2
A 22yo was diagnosed with an ovarian tumor completely resected. She did not receive and initial adjuvant treatment and remained disease-free for one year when a recurrence was found in the abdomen and pelvis. She was treated with etoposide/cisplatin followed by surgical resection and then platinum/taxane therapy followed by abdominal RT. She remained disease-free for 9 months and suffered an upper abdominal recurrence treated with RT. She then went on an investigational vaccine study and recurred 12 months later. She started nivolumab and remains disease-free for 1.5 years.

Patient 3
A 25yo was diagnosed with an ovarian mass that was completely resected. She received initial treatment with doxorubicin / cyclophosphamide /etoposide/cisplatin followed by RT. She was then disease-free for ~1 year and suffered a recurrence in the abdomen. This was surgically resected and taxane/platinum adjuvant therapy was given with concurrent RT. She remained disease-free for six months when she suffered a recurrence in the same area that was treated with additional RT followed by nivolumab. She remains disease free for ~1.5years.

Patient 4
An 18yo was diagnosed with a large ovarian tumor that was completely resected. She received initial treatment with etoposide/platinum followed by chemoRT to the abdomen. She was then disease-free for ~3 years and suffered a recurrence in the chest that was treated with PARP inhibition followed by retreatment with etoposide/platinum, an investigational agent, local radiation and then two cycles of nivolumab. Nivolumab was stopped due to an exacerbation of rheumatoid arthritis and she remains off treatment for more than 1.5 years without any evidence of disease progression.

SCCOHT tumors are responsive to immunotherapy and strongly express checkpoint targets



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NGS is useful for rare tumor research and patient care

- NGS can identify germline mutations of inherited risk
  - Screen for SMARCA4 mutations in SCCOHT patients
  - Somatic testing for diagnosis confirmation, then germline testing for identified mutations; single loci testing
- Clinical trials demonstrate applications of NGS results that can be readily translated for patient care
- Continued NGS will provide experience with testing and interpretation for doctors and patients alike
- NGS is not for everyone, but the extent of use will increase through research, drug development and insurance coverage

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