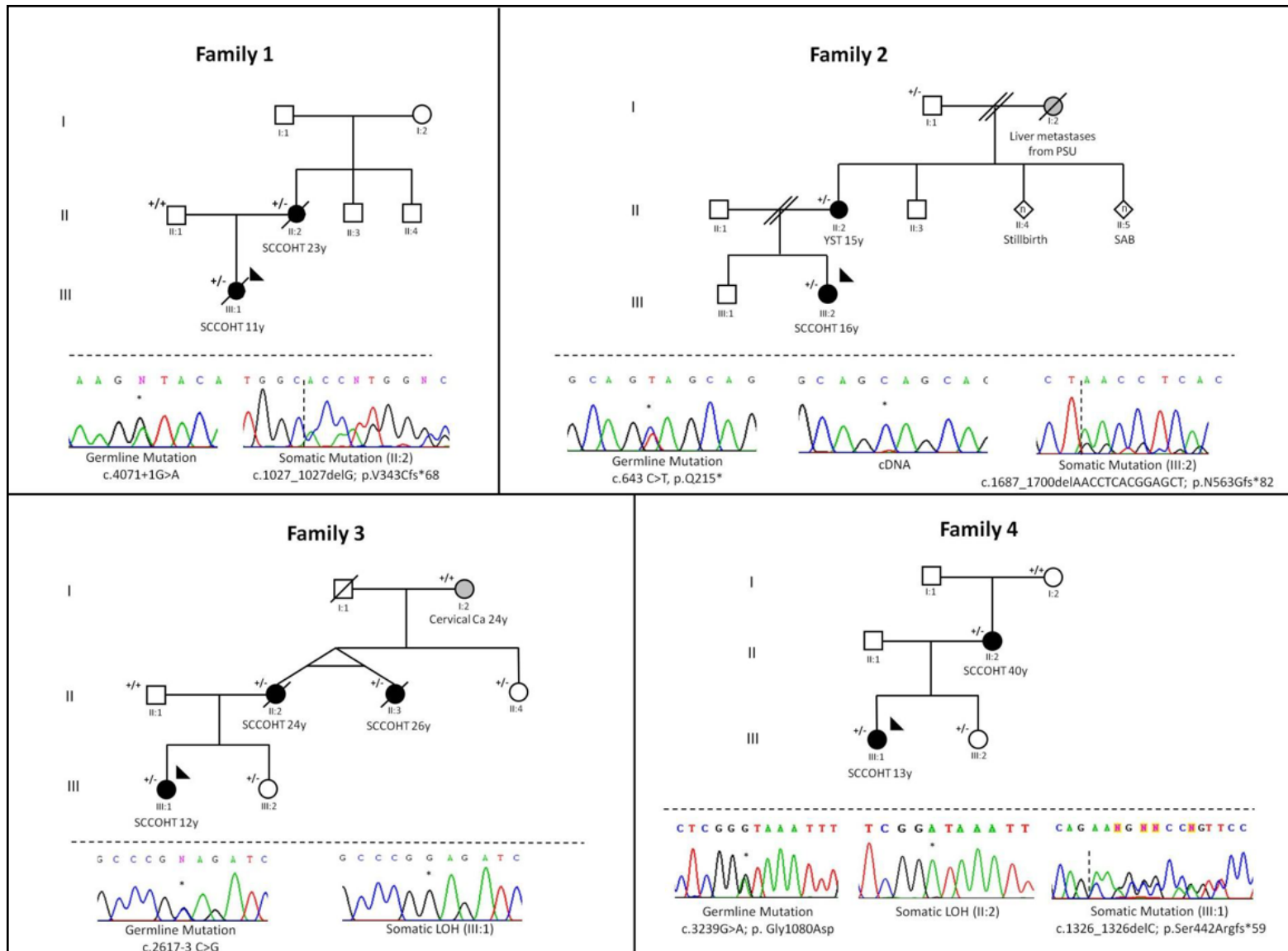


# Unexpected role for immuno- oncology in SCCOHT

(Mechanism in progress)

Douglas A. Levine, MD  
Director, Gynecologic Oncology  
Head, Gynecology Research Laboratory  
Professor, Obstetrics and Gynecology  
Perlmutter Cancer Center, NYU Langone Medical Center

# Penetrance?



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

@LevineMD

# SCCOHT familial case #1

- 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

2 genomic findings

0 therapies associated with potential clinical benefit

0 therapies associated with lack of response

4 clinical trials

## TUMOR TYPE: PEDIATRIC OVARY SMALL CELL CARCINOMA

### Genomic Alterations Identified<sup>†</sup>

*SMARCA4* A573fs\*40, R381\*

<sup>†</sup> For a complete list of the genes assessed and performance specifications

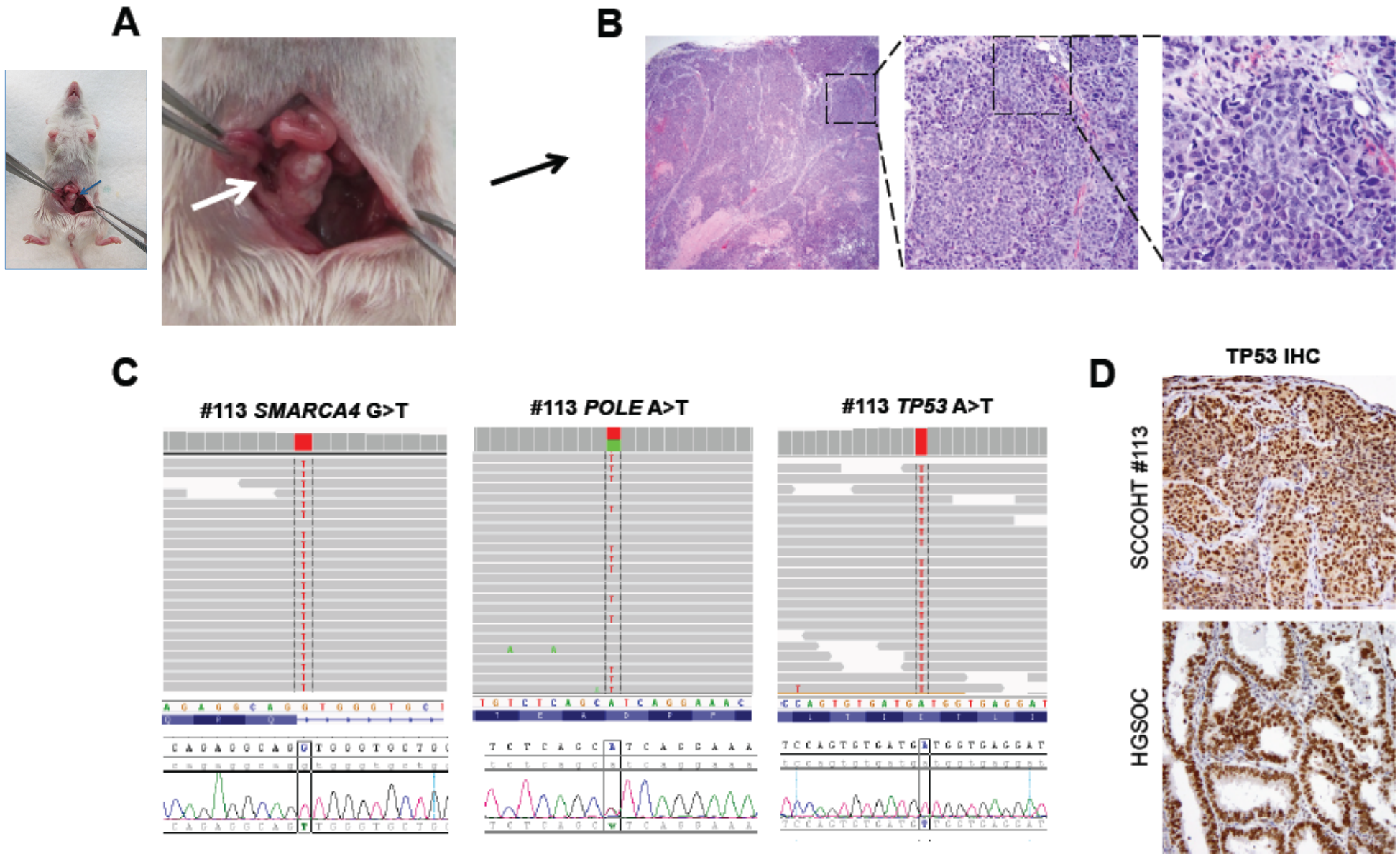
# SCCOHT sporadic case #1

- 18yo diagnosed with pelvic mass and widely metastatic SCCOHT
- Incompletely resected
- Excellent sense of humor – “I couldn’t get into Hopkins, but my tumor did”
- Started in Hollywood, Florida on Etoposide, platinum
- Recommended six drug regimen
- Local doctor indicated that it was very toxic

# SCCOHT familial case #2

- 13 yo girl positive for SMARCA<sub>4</sub> mutation – c.3081+1G>T
- Mother died at 26 from SCCOHT – 8 years ago
- Maternal aunt diagnosed with SCCOHT at 16, died at 18 – 9 years ago
- Local gyn oncologist and consultant gyn oncologist recommended ultrasounds q six months
- Recommended egg harvesting and BSO by age 14 if post-puberty

# PDX mouse models of SCCOHT



# 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 an 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.

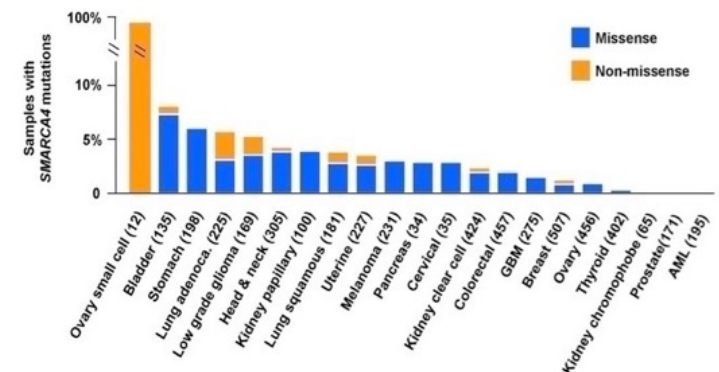
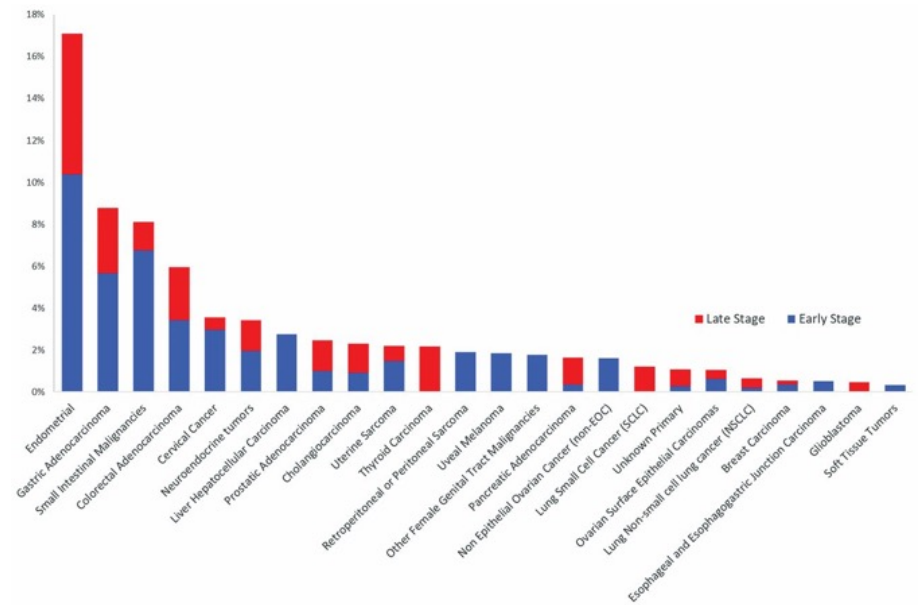
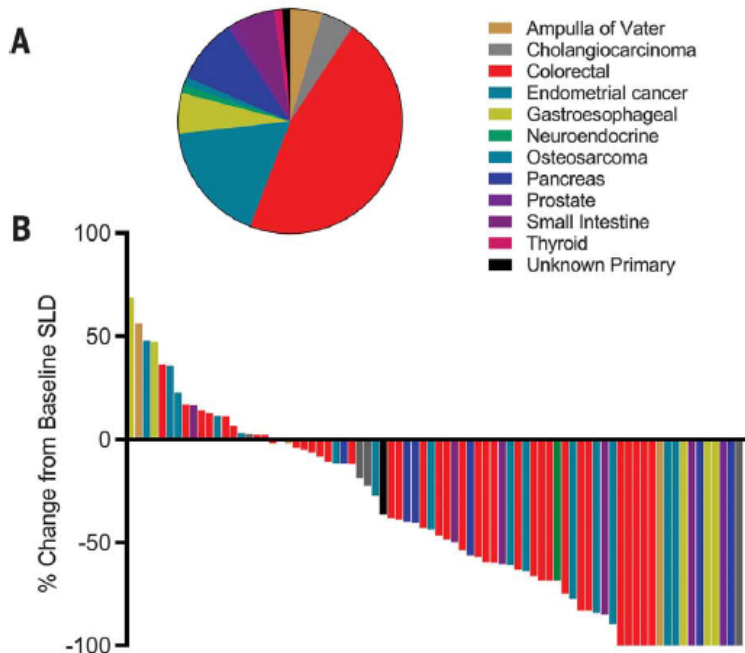
## Patient 4

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.

# Responses typically correlates with mutational load

## Patient survival and clinical response to pembrolizumab

Fig. 3 Mismatch repair deficiency across 12,019 tumors.

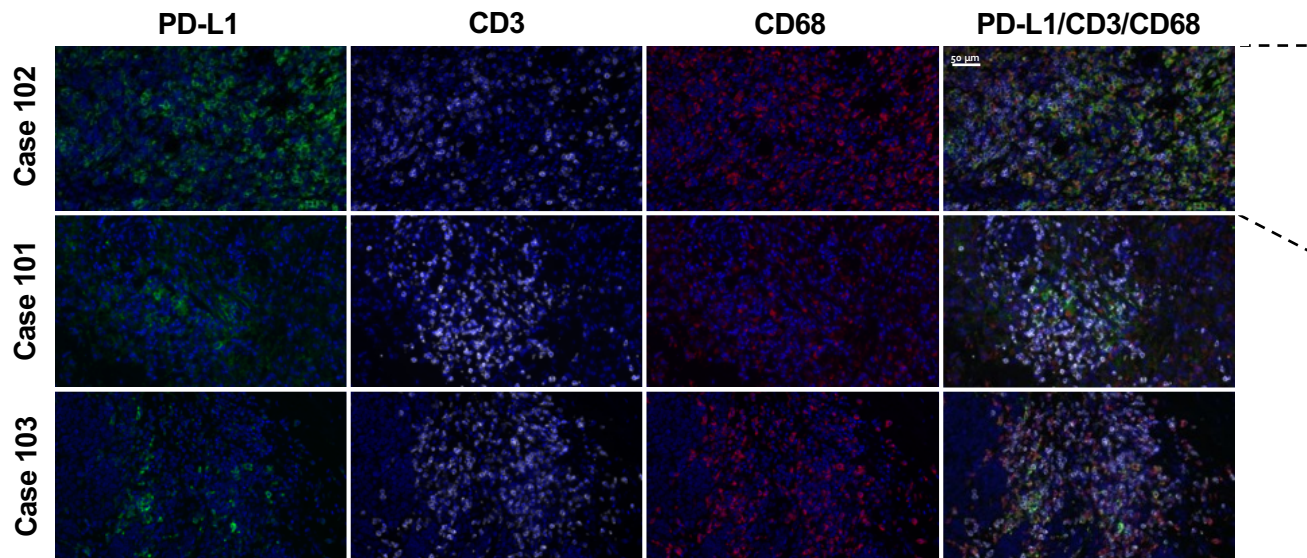




## BRIEF COMMUNICATION

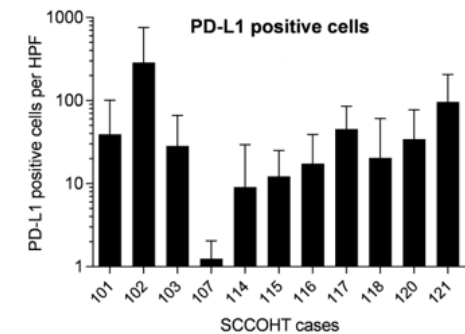
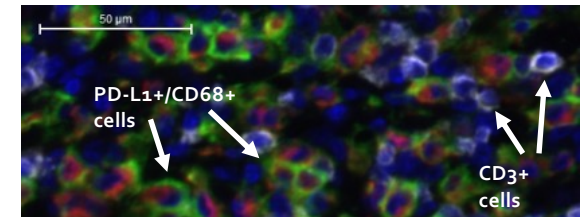
# Immune-Active Microenvironment in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: Rationale for Immune Checkpoint Blockade

Petar Jelinic\*, Jacob Ricca\*, Elke Van Oudenhove, Narciso Olvera, Taha Merghoub, Douglas A. Levine\*, Dmitriy Zamarin\*

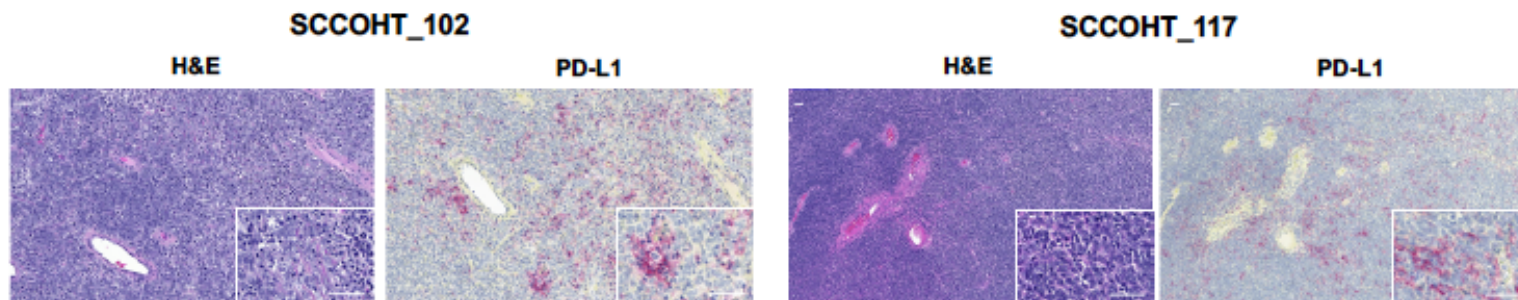


# SCCOHT tumors are responsive to immunotherapy and strongly express checkpoint targets

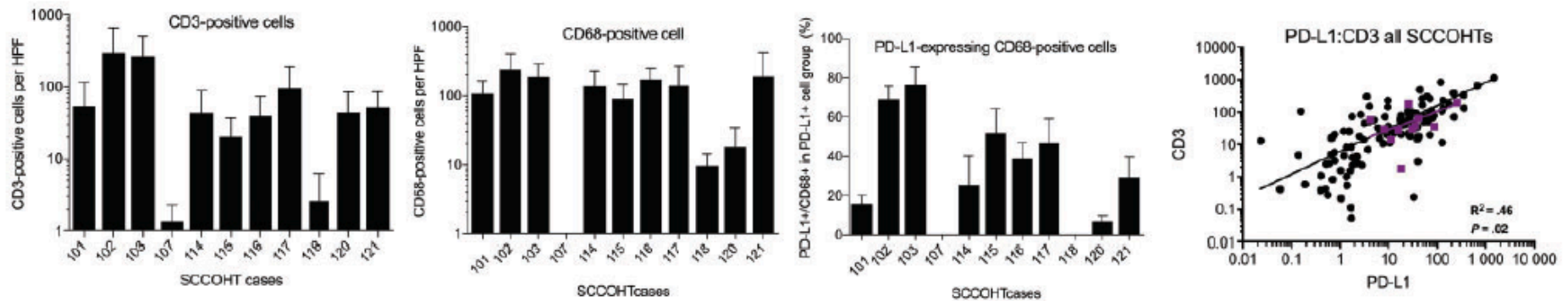
Case number	Age at diagnosis (years)	SMARCA4		
		Gene mutations		IHC
		Protein Change	Domain affected	
101*	40	p.Q1182_splice	Helicase	Loss
102*	22	p.K1390_splice		Loss
103*	19	In-frame Deletion	Helicase	Retained
107*	18	p.E1300_N1303.del		Loss
114*	27	p.X991_splice	SNF2	Loss
115	29	p.L792P and p.X587_splice	SNF2	Equivocal
116	30	p.X813_splice	SNF2	Equivocal
117	32	p.M649Nfs*6 and pE488*		Loss
118	N/A	N/A		Loss
120	31	p.X1072_splice	Helicase	Loss
121	24	p.X1318_splice		Equivocal



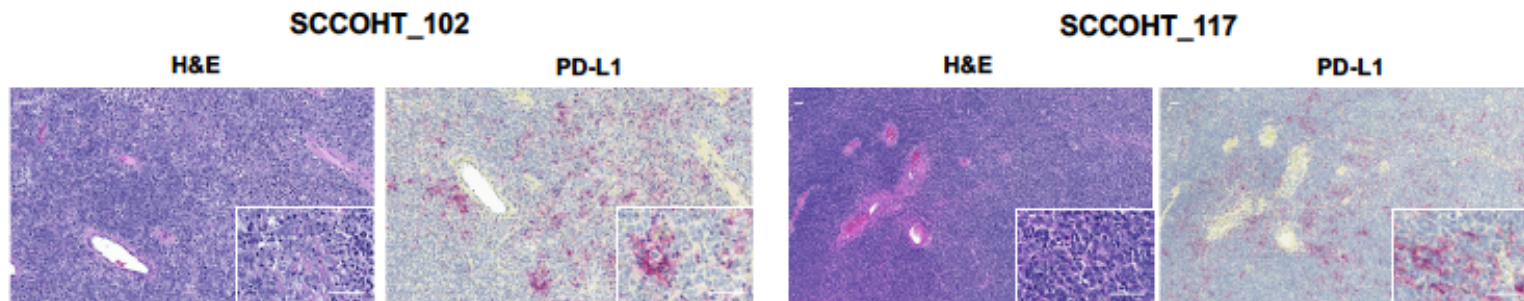
PD-L1 expression and response to checkpoint blockade is unusual for a monogenic disease.



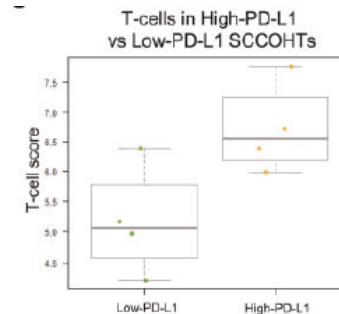
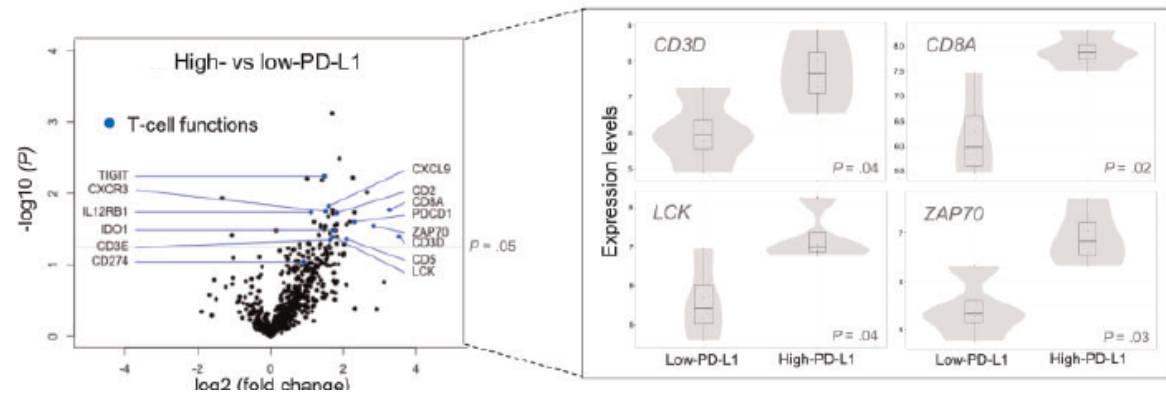
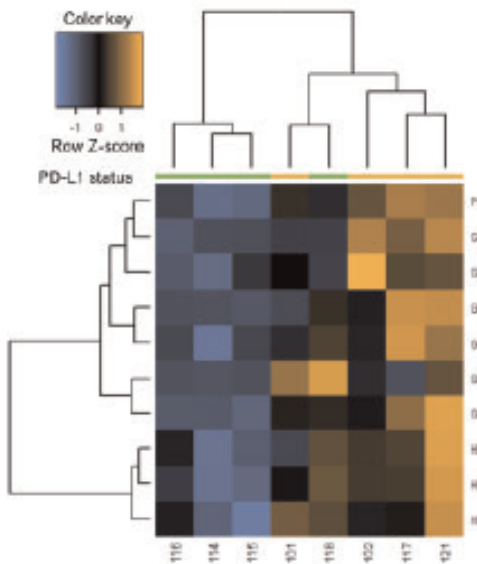
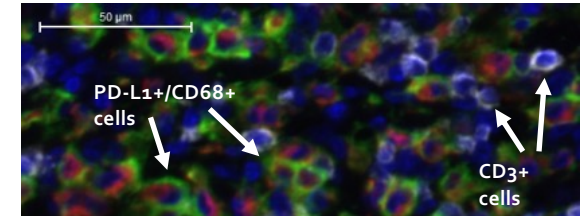
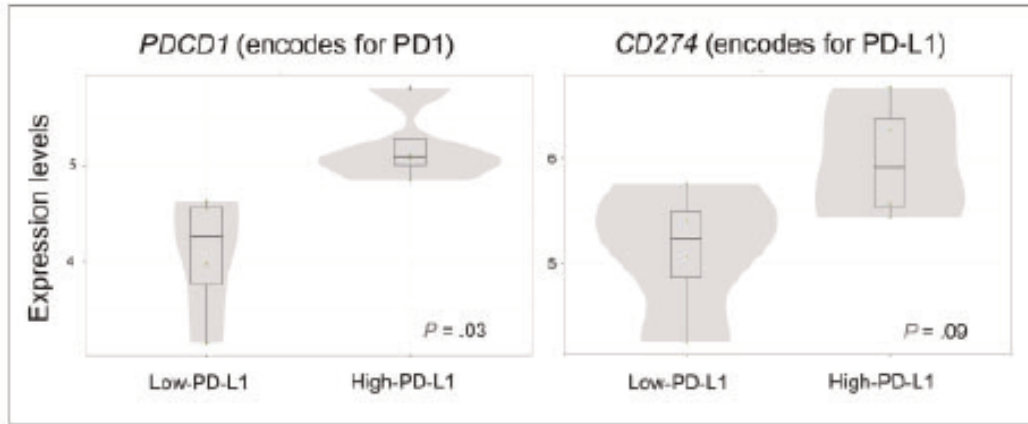
# SCCOHT tumors are responsive to immunotherapy and strongly express checkpoint targets



**PD-L1 expression and response to checkpoint blockade is unusual for a monogenic disease.**



# Gene expression (nanosttring) supports expression of checkpoint targets



Cytolytic and APC genes increased in high PD-L1 tumors

# Summary

- ICB appears active
  - Is RT required?
- Model systems do not lend themselves to these studies
- Phase II clinical trial proposal rejected by NRG, Merck, BMS
  - Now onto FDA-not approved companies
  - May need to sequence RT and ICB (and study this)

This slide intentionally blank