



# Small-Cell Carcinoma of the Ovary, Hypercalcemic Type—Genetics, New Treatment Targets, and Current Management Guidelines

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## ABSTRACT

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and highly aggressive ovarian malignancy. In almost all cases, it is associated with somatic and often germline pathogenic variants in *SMARCA4*, which encodes for the *SMARCA4* protein (BRG1), a subunit of the SWI/SNF chromatin remodeling complex. Approximately 20% of human cancers possess pathogenic variants in at least one SWI/SNF subunit. Because of their role in regulating many important cellular processes including transcriptional control, DNA repair, differentiation, cell division, and DNA replication, SWI/SNF complexes with mutant subunits are thought to contribute to cancer initiation and progression. Fewer than 500 cases of SCCOHT have been reported in the literature and approximately 60% are associated with hyper-

calcemia. SCCOHT primarily affects females under 40 years of age who usually present with symptoms related to a pelvic mass. SCCOHT is an aggressive cancer, with long-term survival rates of 30% in early-stage cases. Although various treatment approaches have been proposed, there is no consensus on surveillance and therapeutic strategy. An international group of multidisciplinary clinicians and researchers recently formed the International SCCOHT Consortium to evaluate current knowledge and propose consensus surveillance and therapeutic recommendations, with the aim of improving outcomes. Here, we present an overview of the genetics of this cancer, provide updates on new treatment targets, and propose management guidelines for this challenging cancer.

## Introduction

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare and aggressive cancer which mainly occurs in adolescents and young women. It represents less than 0.01% of all ovarian malignancies (1), with fewer than 500 cases reported to date in the medical literature. The clinical and pathologic aspects of this tumor were initially described by Scully in 1979 (2). In describing these neoplasms, he noted: (i) the characteristic morphologic appearance of small hyperchromatic cells with scant cytoplasm and brisk mitotic activity, (ii) the occurrence in young females, and (iii) the presence of hypercalcemia. Although the mechanism underlying the commonly observed serum hypercalcemia is not well established, one study found that in four of seven cases, the tumor cells expressed parathyroid hormone-related protein (3). It has long been postulated that some cases could be familial (4) and in 2014, multiple groups discovered that SCCOHT is characterized by both germline and somatic deleterious mutations (henceforth termed pathogenic variants, PV) in *SMARCA4* (5–8). Studies have shown that *SMARCA4* appears as the only recurrently mutated gene in SCCOHT (6–8). Therefore, PVs in *SMARCA4* likely serve as the driver mutation for almost all cases of SCCOHT (8). The discovery of *SMARCA4* PVs in >95% of SCCOHTs has been the first step in the development and implementation of potential targeted treatment options (9). With these discoveries in mind we brought together international experts and formed the International SCCOHT Consortium (ISC) consisting of researchers, clinical scientists, and clinicians. We held the first symposium on SCCOHT in London in July 2018 to lay out the current state of knowledge regarding genetics and consider potential treatment targets. There have been 2–3 monthly follow-up conference calls since then to foster collaborative research and to develop a consensus guideline for the diagnosis and management of SCCOHT.

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## SWI/SNF Chromatin Remodeling Complex

Recent sequencing studies have identified mutations in subunits of the SWI/SNF chromatin remodeling complexes in over 20% of human cancers (10). Multiple configurations of the SWI/SNF complex exist, each consisting of approximately 15 proteins (11). With several isoforms existing for many of these proteins, theoretically, 100 or more different combinations may exist (12). While all SWI/SNF complexes contain one of the two mutually exclusive ATPase subunits, SMARCA4 (BRG1) or SMARCA2 (BRM), functional differences appear among them (13). This is likely due to the differential complex compositions and the cell type in which they exist, as some SWI/SNF subunits specifically target certain genomic regions and transcription factors (14). Depending on the cell type and timepoint in development, these complexes can both repress and activate gene expression (15). Thus, SWI/SNF alterations play important and varied roles in driving tumorigenesis.

## Normal SMARCA4 Functions

SMARCA4 is involved in a plethora of cellular processes including transcriptional regulation, DNA damage repair, differentiation, and mitosis, all of which may contribute to SCCOHT phenotypes. As a part of the diverse SWI/SNF (BAF, PBAF, and ncBAF) chromatin remodeling complexes, SMARCA4 utilizes energy from ATP hydrolysis to mobilize nucleosomes and remodel chromatin. This remodeling activity commonly makes DNA accessible for loading of transcriptional regulators or repressors. Thus, SMARCA4 is normally found at promoters and enhancers of actively transcribed genes. Because SCCOHTs do not possess complex genomes, transcriptional and epigenetic deregulation induced by SMARCA4 loss, which remains to be uncovered, likely play a central role in driving tumorigenic pathways.

## Clinical Management

The clinical management of SCCOHT has varied widely, although some clinical guidelines have previously been published (16). Outcome remains poor, with estimated long-term survival reported as 33% in stage I disease, and 10%–20% overall. The ISC here present consensus guidelines for the diagnosis and management of women and their families affected by this condition, summarized in **Table 1**. We discuss potential strategies in diagnosis, genetic counseling, surveillance, and treatment for SCCOHT as well as many issues arising from the lack of established data on this very rare malignancy. The Consortium unreservedly recommends further research to explore the effectiveness of current recommendations for this rare cancer. We also recommend conducting all work in liaison with specialist support groups, such as the Small Cell Ovarian Cancer Foundation, that provide psychosocial support and advocacy for affected families. (8)

## SCCOHT Pathology and Diagnosis

SCCOHT is currently classified as a miscellaneous neoplasm in the 2014 World Health Organization (WHO) Classification of Tumors of Female Reproductive Organs (17). The discovery of recurrent SMARCA4 mutations has resulted in alternative terminologies such as malignant rhabdoid tumor of the ovary (8) and SMARCA4-deficient ovarian neoplasm being proposed. However, the term SCCOHT will be retained in the upcoming 2020 WHO classification given that

this term is well established in the literature. SCCOHT is the prototypical ovarian neoplasm composed predominantly or exclusively of small round cells with scant cytoplasm (so-called “small round blue cell tumor”). Because of the wide range of differential diagnoses of the various neoplasms in this broad group, pathologists commonly struggle with these tumors due to overlapping morphology and IHC (18). In diagnosing the various tumor types, IHC and molecular studies are of value (19). While typical SCCOHT is part of the differential diagnosis of a small round blue cell tumor, the large cell variant of SCCOHT may be confused with other neoplasms composed of large cells (**Fig. 1**). Older studies investigated the immunophenotype of SCCOHT to try to elucidate the histogenesis but were inconclusive. The neoplastic cells are sometimes focally positive with epithelial membrane antigen, broad spectrum cytokeratins, calretinin, and CD10 (20), while desmin, S100, and inhibin are consistently negative. Occasional neoplasms are focally positive with neuroendocrine markers. Most cases also exhibit diffuse nuclear positivity with an antibody against the N-terminal of WT1 (20); this may be of some diagnostic use, although many other tumors, including some in the differential diagnosis of SCCOHT, are also positive. While estrogen receptor and progesterone receptor have not been widely investigated in SCCOHT, these neoplasms invariably do not stain using antibodies directed against hormone receptors.

The discovery of SMARCA4 mutations in almost all SCCOHT tumors resulted in the development of a SMARCA4 (also known as BRG1) antibody, which is highly useful in the diagnosis of this neoplasm and distinction from its many mimics (21). One of the original publications describing germline and somatic SMARCA4 mutations in these neoplasms showed loss of SMARCA4 nuclear immunoreactivity in 51 of 54 (94%) cases (8). Subsequent studies showed that over 95% of these neoplasms exhibit loss of nuclear immunoreactivity with this marker, making it an important diagnostic tool, although not all cases are negative (22, 23). Occasional tumors exhibit loss of SMARCB1 (INI1), or loss of SMARCA2 (BRM) IHC staining with retention of SMARCA4 (BRG1; ref. 7). Dual loss of SMARCA4 and SMARCA2 (the latter is a subunit of the SWI/SNF complex mutually exclusive with SMARCA4) occurs in many SCCOHT (23); SMARCA2 loss occurs through epigenetic inactivation as mutations or deletions rarely occur in human tumors and have not been demonstrated in SCCOHT (23–27). Potentially consistent with this notion, treatment with epigenetic inhibitors such as DNMTi or histone deacetylase inhibitor (HDACi), leads to reexpression of SMARCA2 in cancer cell lines (23, 28).

It should be stressed that SMARCA4 loss through mutations, deletions, and other mechanisms is observed in several other tumor types; for example, 10%–37% of primary non-small cell lung cancers (NSCLC) exhibit loss of IHC expression of SMARCA4 (29–32). Dual loss of SMARCA4 and SMARCA2 is also found in SMARCA4-deficient thoracic sarcomas (33), undifferentiated and dedifferentiated endometrial carcinomas, and rare undifferentiated uterine sarcomas (23, 34). Although the diagnosis of SCCOHT can usually be made on the basis of morphology and loss of SMARCA4 staining, SMARCA4 tumor sequencing could be considered in problematic cases of suspected SCCOHT with the minimum requirements to cover all exons and splice sites. SMARCA4 sequencing can help to distinguish SCCOHT from other cancers with SMARCA4 loss when combined with histologic features, or in the context of few other somatic mutations, which is much more frequently observed in SCCOHTs compared with most other tumors with SMARCA4 loss.

The age range at diagnosis is quite wide and has ranged from 7 months to 56 years, with an average age of 23.9 years (35). In one study, 26 of 60 patients (43%) had a germline SMARCA4 PV, including

**Table 1.** Summary of the ISC guidelines.

| Oncologic Management: Newly Diagnosed Disease   | Oncologic Management: Recurrent Disease  |
|---|--|
| <ul style="list-style-type: none"> <li>Resect primary ovarian tumor and base diagnosis on expert gynecologic pathology review.</li> <li>Initiate cytotoxic chemotherapy with cisplatin and etoposide combination regimens (e.g. BEP, bleomycin, etoposide, cisplatin; or VPCBAE, vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide; or similar).</li> <li>Consider high dose chemotherapy with autologous stem cell transplantation rescue following a complete response after chemotherapy is finished.</li> <li>Consider radiation therapy after chemotherapy for residual disease that can completely fit into a single radiation treatment portal or for consolidation of pelvic only disease.</li> <li>Observation (no defined role for maintenance therapy).</li> <li>Genetic testing for patient and family members, as appropriate.</li> </ul> | <ul style="list-style-type: none"> <li>Obtain biopsy as clinically indicated and/or to help with ongoing translational research<sup>a</sup>.</li> <li>Enroll in clinical trial, if available (see Table 2).</li> <li>Consider radiotherapy if disease field allows.</li> <li>Consider additional chemotherapy with cisplatin and etoposide combination regimens if disease-free interval &gt; 6 months.</li> <li>Alternative chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine; or carboplatin, paclitaxel; or topotecan; or similar).</li> <li>Consider secondary surgical cytoreduction if disease can be completely resected and disease-free interval &gt; 12 months<sup>b</sup>.</li> <li>Consider off-label immune checkpoint blockade treatment after radiotherapy based on drug availability (69).</li> <li>Consult with members of the ISC regarding off-label drug use based on unpublished data.</li> </ul> |
| Genetic Counseling  | Familial Surveillance  |
| <ul style="list-style-type: none"> <li>Refer all SCCOHT patients to a clinical genetics service and offer testing for germline <i>SMARCA4</i> PVs.</li> <li>Discuss risk-reducing contralateral oophorectomy in SCCOHT patients with a germline <i>SMARCA4</i> PV, due to increased risk of second primary malignancy.</li> <li>Tumor sequencing can confirm diagnosis and serve as a reference for germline sequencing. If no <i>SMARCA4</i> mutation is detected, SCCOHT diagnosis should be reconsidered.</li> <li>Germline sequencing without prior somatic sequencing can be performed where there is a confirmed diagnosis of SCCOHT through loss of <i>SMARCA4</i> on IHC coupled with appropriate histologic findings.</li> <li>Offer genetic counseling and predictive testing to all at-risk relatives of SCCOHT patients with germline <i>SMARCA4</i> PVs.</li> </ul>    | <ul style="list-style-type: none"> <li>Early detection using imaging remains unproven and is ineffective for other ovarian malignancies.</li> <li>Benefits of RRBSO performed prior to malignant transformation remain unproven.</li> <li>Counseling for RRBSO should include a discussion of surgical-based risks, onset of surgical menopause, estrogen replacement therapy, and reproductive preservation options including oocyte cryopreservation and preimplantation genetic diagnosis.</li> <li>RRBSO should be approached with extreme caution for incidental germline <i>SMARCA4</i> PVs that have been found as a result of genetic testing for another indication where there is no personal or family history of SCCOHT.</li> </ul>  |

<sup>a</sup>Contact members of the ISC if patients want to contribute to international research efforts.

<sup>b</sup>The role of cytoreductive surgery is not well defined for SCCOHT, but may be considered before initiating chemotherapy or at the time of recurrence in cases where residual disease appears completely resectable (such as in referral cases where attempted cytoreduction was never performed).

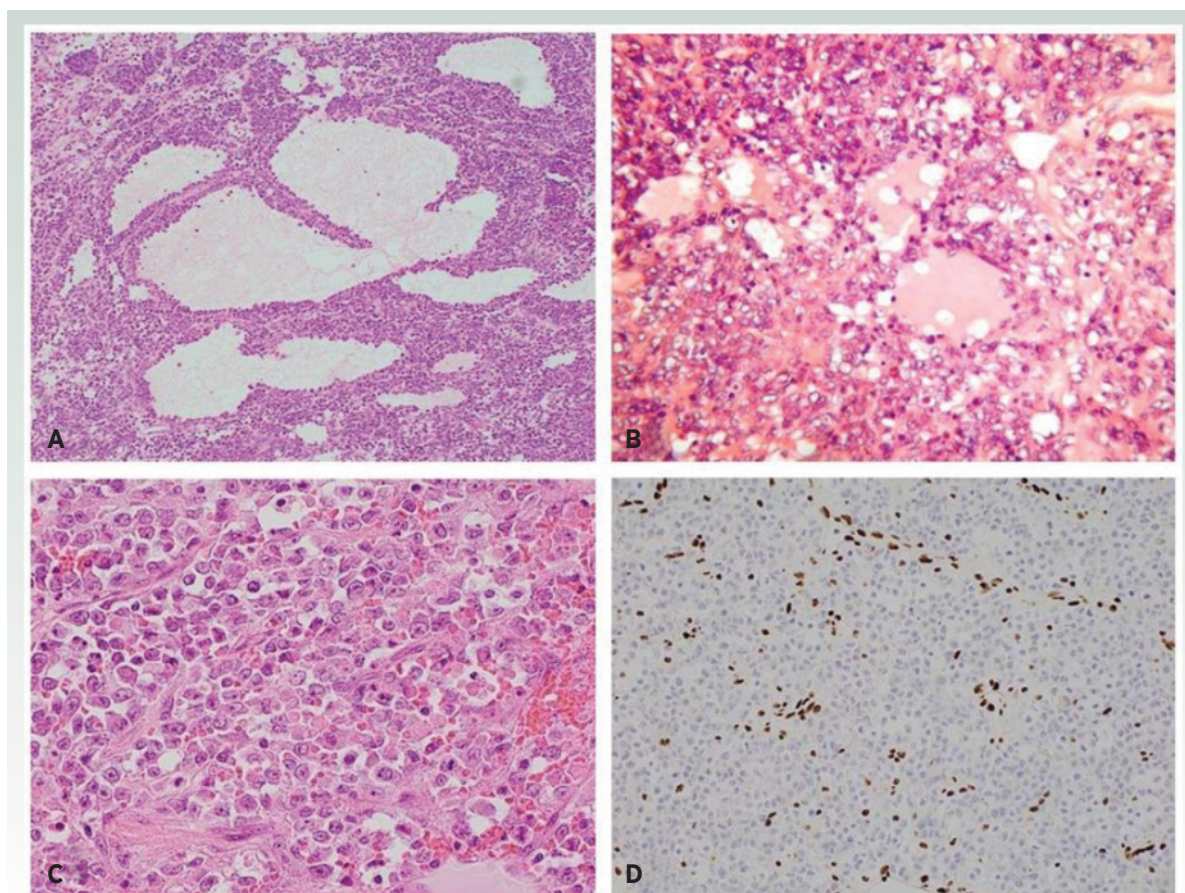
all patients diagnosed before the age of 15 years. Women with germline PVs present at a significantly younger age than those without ( $P = 0.02$ ; ref. 36). We recommend caution in diagnosing SCCOHT in females under 10 or over 50 years of age and although one publication reported a SCCOHT in a 71-year-old female, the lack of modern diagnostic markers used (immunostaining or *SMARCA4* mutation analysis), makes the validity of this diagnosis unclear (9). Given the importance of establishing a correct diagnosis and the wide differential diagnosis (18), we strongly recommend an expert opinion from a specialist gynecologic pathologist and *SMARCA4* IHC staining to establish the diagnosis in an ovarian neoplasm in which SCCOHT is considered in the differential diagnosis and where a firm diagnosis of an alternative neoplasm cannot be established. At present, most pathology laboratories do not perform *SMARCA4* IHC.

## Genetic Counseling and Screening in Patients and at-risk Family Members

Germline and somatic *SMARCA4* PVs causing SCCOHT are generally nonsense or frameshift, although in-frame indels and missense

mutations have been reported previously (6–8, 33, 36). The penetrance of these PVs remains uncertain, and interpretation of risk is complicated by our observation that germline PVs are often paternally inherited, with only two known cases caused by a *de novo* *SMARCA4* PV (37, 38). While *SMARCA4* PVs occur across the entire gene, with no obvious predilection for certain domains, loss of function variants in some exons may not be pathogenic for SCCOHT due to their lack of expression in transcripts expressed in the ovary (39). Furthermore, we do not know whether individuals with a germline *SMARCA4* PV associated with SCCOHT possess an increased risk for development of other types of cancers.

The risk of cancer in females with germline *SMARCA4* PVs remains uncertain but may be considerable. Only one publication reports a female with a *SMARCA4* germline mutation who remained cancer-free past her sixth decade (36). On the other hand, there is likely to be ascertainment bias in the literature, resulting in overestimation of cancer risk. Prospective studies will be needed to provide more accurate cancer risk estimates. Thus, one of the top priorities of this Consortium effort is the establishment of an international registry of patients with SCCOHT to facilitate follow-up of families and provide



**Figure 1.**

**A**, SCCOHT is composed of predominantly diffuse arrangement of cells with follicle-like structures. **B**, On higher power, the tumor cells have hyperchromatic nuclei and scant cytoplasm. **C**, Large cell variant of SCCOHT composed of tumor cells with abundant eosinophilic cytoplasm. **D**, There is loss of nuclear immunoreactivity with SMARCA4 (BRG1) with a positive internal control in the form of nuclear staining of endothelial cells.

opportunities for participation in research and clinical trials. Please see <https://smallcellovariancancer.com/contact-us/> for more details.

The Consortium recommends referral of all patients with SCCOHT to a clinical genetics service or provider, with an offer for testing for germline *SMARCA4* PVs (**Table 1**). It is important to use a clinical laboratory that offers full gene sequencing, including copy number calling, as PVs are typically scattered throughout the gene, and whole- or partial-gene deletions have been reported previously (40). The incidence of germline pathogenic PVs could be high (up to 43%), and the family history is not generally informative, especially if the germline PV was inherited from the proband's father (36). There are several different approaches to genetic testing for diagnostic confirmation and with the increasing use of matched tumor-normal sequencing, both germline and somatic mutations can be identified. If no *SMARCA4* mutation is detected, the diagnosis of SCCOHT should be reconsidered, along with sequencing of other related genes as a *SMARCB1* mutation has been reported in one case of SCCOHT (41). When there is a confirmed diagnosis of SCCOHT (appropriate histologic findings plus loss of *SMARCA4* expression), germline testing is strongly recommended, regardless of somatic testing.

We have recently identified a molecularly confirmed second primary SCCOHT in the right ovary of a young woman initially diag-

nosed with a left-sided SCCOHT in 2011. This suggests that the remaining ovary in females with SCCOHT and a germline *SMARCA4* PV is also at risk. Therefore, we recommend discussion of risk-reducing removal of the other ovary if a germline *SMARCA4* PV is detected. *SMARCA4* variants are inherited in an autosomal dominant manner. All at-risk relatives of those with SCCOHT due to a germline *SMARCA4* PV should receive genetic counseling and be offered predictive testing, which should be covered by personal or national health insurance. Males with germline *SMARCA4* PVs will not develop SCCOHT, but their daughters will have a 50% chance of inheriting the PV. Confidence in the pathogenicity of a germline variant can be enhanced by either IHC showing loss of *SMARCA4* protein expression in the tumor or by identifying a second PV in the tumor.

### Surveillance for at-risk Family Members

This remains controversial considering the lack of proven efficacy and the potential risks including a false sense of security, risk of false positive screens, and the potential exclusion of effective risk-reducing surgery. Although early detection methods using imaging offer an appealing alternative to risk-reducing bilateral salpingo-oophorectomy (RRBSO), this approach remains unproven and has

been ineffective to date for other more common ovarian malignancies (42, 43). While RRBSO performed prior to malignant transformation may prove more effective, its benefits for females at high risk for SCCOHT also remain unproven. Determining the optimal age for RRBSO is extremely challenging considering the early age of disease onset and the uncertain penetrance of germline *SMARCA4* PVs (36). RRBSO has been offered, on a highly selective basis, to females with germline *SMARCA4* PVs, typically for siblings in an affected family (42, 44). Counseling for such a procedure needs sensitivity, including a discussion of surgical-based risks, onset of surgical menopause, estrogen replacement therapy, and reproductive preservation options including oocyte cryopreservation and preimplantation genetic diagnosis. RRBSO should be only be considered with extreme caution where a germline *SMARCA4* PVs is identified incidentally during genetic testing for another indication and where there is no personal or family history of SCCOHT as the penetrance for these variants remains uncertain. There are no published studies that suggest any form of surveillance can prevent death from SCCOHT and therefore we do not recommend it. The similarities identified between rhabdoid tumors and SCCOHT (45) suggest that infant carriers of *SMARCA4* PVs may be at risk for both. However, the risk of *SMARCA4*-related rhabdoid tumors is likely confined to very young children because of its absence in children older than 46 months (36). We recommend the development of standard guidelines for the care of unaffected individuals with germline *SMARCA4* PVs.

In certain cases, testing other cancers by sequencing and/or IHC for *SMARCA4* can help to determine pathogenicity. Testing female relatives over the age of 60 years may also help to better estimate penetrance and cancer risk. Classifications of variants (46), particularly variants of uncertain significance, will require periodic review because they are likely to change over time.

## Recommendations for Oncological Management

Given the lack of prospective studies, treatment recommendations are based on small case series and management strategies remain heterogeneous. Despite the absence of data, the general principles of primary cytoreductive surgery for epithelial ovarian cancer apply to patients with SCCOHT, with the goal of complete surgical resection leaving no visible disease. A multimodal approach including radical surgery, chemotherapy, and radiotherapy after discussion at an in-person or virtual multidisciplinary tumor board is essential (47). Fertility-sparing surgery may be considered in comprehensively surgically staged Stage IA patients without germline *SMARCA4* PVs if they desire future pregnancies, although radical surgery for all patients remains the norm.

Adjuvant chemotherapy is recommended for all stages, generally cisplatin- and etoposide-based combination regimens (e.g., BEP: bleomycin, etoposide, and cisplatin; VPCBAE: vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide; and PAVEP: cisplatin, doxorubicin, and etoposide cyclophosphamide). For patients in whom initial surgery is not feasible (e.g., stage IV disease, unresectable disease, and medically unfit patient), administration of chemotherapy and interval cytoreductive surgery may be considered on an individual basis. High-dose chemotherapy (HDC) with autologous stem cell transplantation rescue following a complete response to initial chemotherapy, with or without surgery, may also be considered (48). Recently updated survival data suggest that multimodality therapy including surgery and multi-agent chemotherapy with possible stem cell transplantation and radiotherapy are most

effective (36). However, these nonrandomized studies may suffer from selection bias. Early-stage patients will more likely meet the criteria for HDC, which requires a complete response to initial chemotherapy, with the expectation of improved outcomes compared with patients with more advanced stage disease (16). Although SCCOHT is often chemosensitive initially, a substantial risk for relapse persists and the effectiveness of additional chemotherapy is limited. Reported options for chemotherapy in the recurrent setting include combinations of cyclophosphamide, doxorubicin, and vincristine, or carboplatin in combination with paclitaxel and topotecan (47). Subsequent responses are often short-lived, emphasizing the need for more clinical trials.

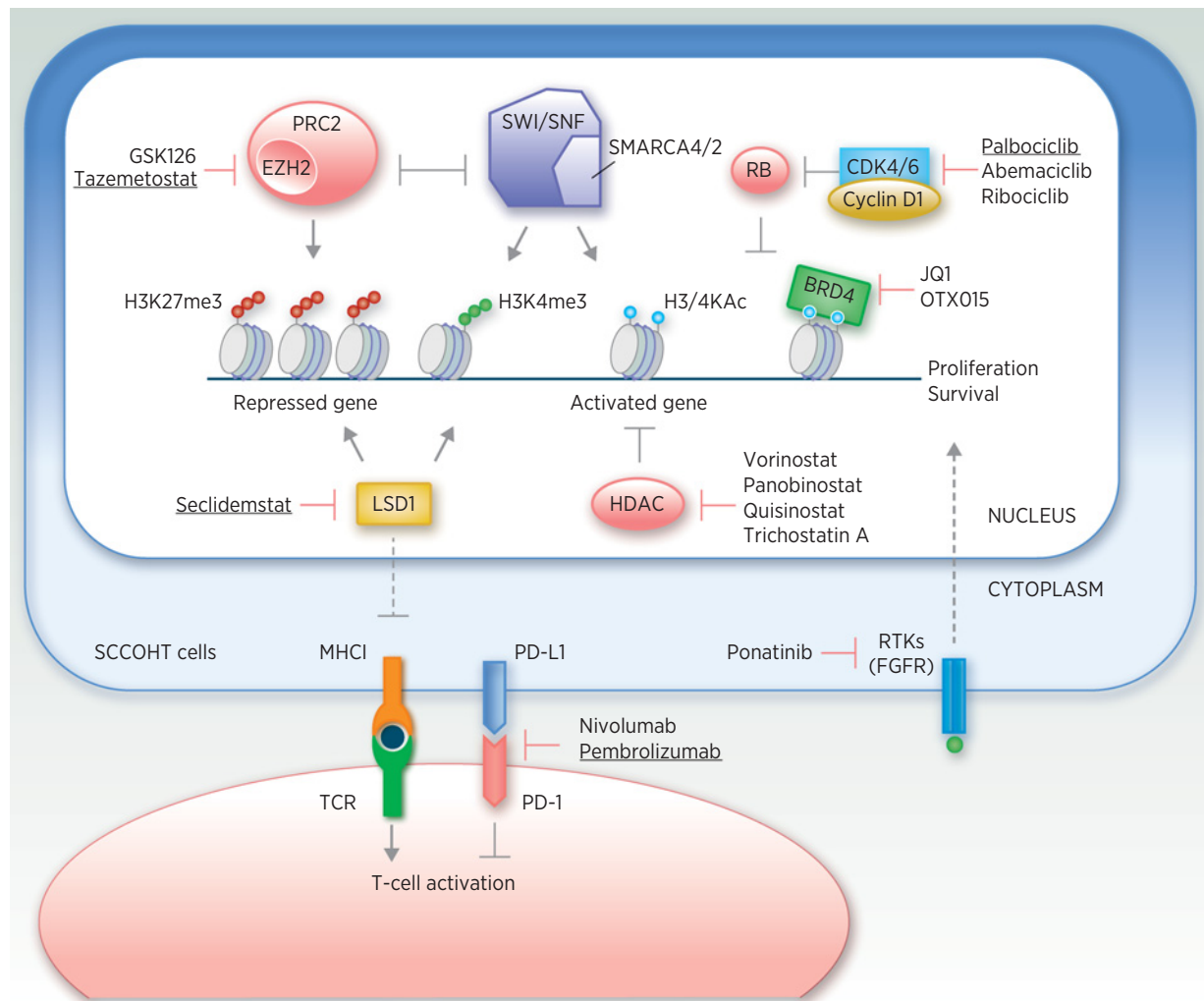
## Identification of SCCOHT Therapeutic Candidates

To date, a paucity of approved or investigational agents exists for SWI/SNF-mutant tumors. For SCCOHT specifically, there is no agreed standard of care and the usual care management includes surgery, platinum-based chemotherapy plus HDC with stem cell rescue, and consideration of radiation in select cases (36). Under the current usual care, SCCOHT portends a poor outcome, with approximately 30% survival, even following early diagnosis. Clinical trials have not yet been performed in patients with SCCOHT as a single entity, in large part because of the rarity of the disease, although some genetic basket studies have included patients with SCCOHT. This means that most efforts have focused on identifying effective targeted treatment strategies that can translate rapidly into clinical trials. Cancer therapeutic approaches aimed at restoring expression of inactivated tumor suppressor genes, such as *TP53*, *RBI*, or *BRCA1*, have not proven successful. Therefore, targeted drug development for SCCOHT has focused on several approaches, including exploiting known synthetic lethal interactions of *SMARCA4* loss and identifying novel targets through unbiased genetic screens. We discuss the most promising results from mainly preclinical studies below (summarized in Fig. 2 and Table 2).

### Epigenetic therapeutics

Because tumor suppressor loss is not directly druggable, most investigators have searched for therapeutic vulnerabilities by exploiting the concomitant changes in gene expression and signaling pathways. Cancer cells are often dependent on these alterations induced by tumor suppressor loss, resulting in a targetable synthetic lethality (49, 50). For example, suppression of *SMARCA2* is synthetically lethal with *SMARCA4* loss in NSCLC cells (30, 51, 52) likely driven by paralogous subunit compensation. However, *SMARCA2* is currently undruggable and cancer cells with *SMARCA4/2* dual loss, such as SCCOHT and most lung adenocarcinomas are unlikely to respond to *SMARCA2* inhibition.

The best developed therapeutic target comes from studies demonstrating that SWI/SNF complexes oppose the repressor function of PRC1 and PRC2 in regulating gene expression (24, 26). SWI/SNF loss leads to elevated PRC2 activity with a concomitant increase in H3K27me3 levels, providing a viable approach for treatment interventions. Indeed, *SMARCA4*-deficient cancer cells display sensitivity to suppression of enhancer of zeste homolog 2 (*EZH2*; refs. 53–55), the catalytic subunit of PRC2. In SCCOHT cells, *EZH2* inhibitors induce reexpression of *SMARCA2* (53, 56) and neuronal-like proteomic signatures, as well as potentially inhibiting growth of SCCOHT cell line xenografts (55). The only trial

**Figure 2.**

Graphic summary of SCCOHT therapeutic candidates and their corresponding drugs. Agents that are being tested in clinical trials available to patients with SCCOHT are underlined. See **Table 2** for more details.

(NCT02601950) to include patients with SCCOHT by name are investigating the most studied EZH2 inhibitor, tazemetostat (EPZ-6438), and early results from these phase I/II trials reported on 2 patients with SCCOHT, 1 with stable disease and 1 with a partial response after treatment. A tazemetostat trial sponsored by the NCI was recently suspended because of observations of secondary lymphomas. Of interest, one report has shown that growth inhibition of SMARCA4-deficient NSCLC appears primarily dependent on a noncatalytic role of EZH2 for stabilizing the PRC2 complex, which current EZH2 inhibitors do not target (54).

Targeting other histone modification complexes has also shown promise for treatment of patients with SCCOHT. HDACi have been clinically approved for the treatment of several hematologic malignancies but have proved less effective for solid tumors (57). Several studies have shown that HDACis in the context of SCCOHT result in reexpression of SMARCA2, which strongly suppresses growth of SCCOHT cells (23, 56). One of these reports also showed *in vivo* sensitivity of SCCOHT cells to the HDACi quisinostat (56). They further demonstrated that quisinostat acts synergistically with

EPZ-6438 *in vitro* and further reduces tumor growth *in vivo* (56). While HDACi may offer an attractive treatment option for patients with SCCOHT, a single case report did not find efficacy with this approach (58). A phase I trial (NCT03895684) of seclidemstat, a lysine-specific demethylase inhibitor, will open specifically for SWI/SNF-mutant gynecologic cancers, with an emphasis on SCCOHT, ovarian clear cell carcinomas, and endometrial carcinomas that show *SMARCA4* or *ARID1A* mutation or loss. Following dose escalation with the single agent, combination with pembrolizumab will be examined.

In addition to targeting EZH2 and HDAC, bromodomain and extraterminal motif containing protein inhibitors (BETi) have been explored in SCCOHT models, based on previous studies showing the dependency of *SMARCA4*-mutant esophageal cancer models for BET protein BRD4 (59) and the coregulation of an oncogenic network by BRD4 and SMARCA4 in acute leukemia (60). Consistent with these findings, SCCOHT cells were highly sensitive to BETi JQ1 and OTX015, the latter of which showed strong antitumor activities in an orthotopic xenograft model of SCCOHT (61). In addition to BRD4, other BET proteins have

**Table 2.** Potential treatments and trials for SCCOHT.

| Class                   | Target        | Drug          | Activities against SCCOHT |                | FDA-approved application | Clinical trial available for SCCOHT | Reference |
|-------------------------|---------------|---------------|---------------------------|----------------|--------------------------|-------------------------------------|-----------|
|                         |               |               | <i>In vitro</i>           | <i>In vivo</i> |                          |                                     |           |
| Epigenetic therapeutics | EZH2          | GSK126        | +                         | +              |                          |                                     | (55)      |
|                         |               | Tazemetostat  | +                         | +              |                          | Phase II NCT02601950                | (53, 55)  |
|                         | LSD1          | Seclidemstat  | n.a.                      | n.a.           |                          | Phase I, NCT03895684                | (77)      |
|                         |               | HDAC          | Vorinostat                | +              | n.a.                     | Cutaneous T-cell lymphoma           | (56)      |
|                         |               |               | Panobinostat              | +              | n.a.                     | Multiple myeloma                    | (56)      |
|                         |               |               | Quisinostat               | +              | +                        |                                     | (56)      |
|                         |               |               | Trichostatin A            | +              | n.a.                     |                                     | (23)      |
|                         | BET proteins  | JQ1           | +                         | n.a.           |                          | (61)                                |           |
| Kinase inhibitors       | Multi-kinases | OTX015        | +                         | +              |                          |                                     | (61)      |
|                         |               | Ponatinib     | +                         | +              | ALL, CML                 |                                     | (63)      |
|                         | CDK4/6        | Palbociclib   | +                         | +              | Breast cancer            | Phase II, NCT03297606               | (66)      |
|                         |               | Abemaciclib   | +                         | n.a.           |                          |                                     | (66)      |
|                         |               | Ribociclib    | +                         | n.a.           |                          |                                     | (66)      |
| Immunotherapies         | PD-1          | Pembrolizumab | n.a.                      | +              | Multiple cancers         | Phase II, NCT03012620               | (70)      |
|                         | PD-1          | Nivolumab     | n.a.                      | +              | Multiple cancers         |                                     | (70)      |

Abbreviations: LSD1, lysine-specific histone demethylase 1; n.a., not accessed.

been linked to SWI/SNF function. Inactivation of another key SWI/SNF subunit SMARCB1, also known as INI1 or SNF5, occurs in synovial sarcomas and rhabdoid tumors as well as in a small fraction of SCCOHTs. Recent evidence suggests that both synovial sarcomas and rhabdoid tumors require a noncanonical SWI/SNF complex (ncBAF, as opposed to BAF and PBAF), carrying BRD9 as an essential subunit, for their survival (10). Supporting this, CRISPR-knockout screens uncovered BRD9 as a therapeutic target in these cancers (62). However, pharmacologic inhibition of BRD9 did not recapitulate this phenotype, indicating ncBAF function requires protein domains beyond the BRD9 bromodomain. While these studies suggest that BRD9 inhibitors may prove effective for the treatment of patients with SCCOHT, Michel and colleagues showed that BRD9 forms complexes with SMARCA4 but not SMARCB1 (10). Therefore, the effects of BRD9 inhibition on SCCOHT remain untested. Currently, there is no available clinical study to investigate the effect of BETi in patients with SCCOHT.

### Kinase inhibitors

Functional genetic screening approaches have proven to be a powerful tool to uncover novel drug targets in cancers. In this context, the kinome is often chosen because pharmacologic inhibitors targeting kinases identified from the screens are often available, providing the highest chance of clinical implementation. Using an arrayed kinome-focused siRNA screen, Lang and colleagues showed sensitivity of SCCOHT cell lines in culture and in xenografts, as well as PDX models to the clinically available multi-targeted tyrosine kinase inhibitor ponatinib (63). They also implicated a dependence upon FGFR signaling as the underlying mechanism for this sensitivity (56). These results coincide with similar observations in rhabdoid tumors where reexpression of SMARCB1 resulted in decreased expression of FGFR1 and FGFR2, as well as the relative *in vitro* and *in vivo* sensitivity of rhabdoid tumor cell lines to receptor tyrosine kinase inhibitors ponatinib and BGJ-398 (64, 65). Ponatinib is FDA-approved for the use in leukemias and warrants further investigation in SCCOHT.

Using a pooled short hairpin RNA screening approach also targeting human kinome, Xue and colleagues found that SCCOHT cells are highly sensitive to cyclin-dependent kinase4/6 (CDK4/6) inhibition (66). They showed that SMARCA4 loss causes down-

regulation of cyclin D1, limiting CDK4/6 kinase activity in SCCOHT cells and leading to *in vitro* and *in vivo* susceptibility to CDK4/6 inhibitors. Thus, their findings indicated that CDK4/6 inhibitors, approved for a breast cancer subtype addicted to CDK4/6 activation, could be repurposed to treat SCCOHT. They also observed this synthetic lethal interaction between SMARCA4-loss and CDK4/6 inhibition in SMARCA4-deficient NSCLC despite their differences in tissue of origin and mutation landscape (67). Given that SMARCA4 loss occurs in a variety of other cancer types, this common druggable vulnerability, shared by SCCOHT and NSCLC, may also be effective for targeting other SMARCA4-deficient tumors. Furthermore, patients may also benefit from the antitumor immunity triggered by CDK4/6 inhibition as recently shown by others (68, 69). The Canadian Profiling and Targeted Agent Utilization Trial (NCT03297606), a pan-Canadian phase II basket trial matching patients with cancer with different genetic variants to appropriate targeted treatments, has recently approved a new match to treat SMARCA4-mutant tumors with the CDK4/6 inhibitor palbociclib based on the above findings (66, 67). Patients with SCCOHT will be included in this new trial arm.

### Immunotherapies

Although the low mutation burden of SCCOHT would not predict responsiveness to immune checkpoint blockade (ICB) based on neoantigen burden alone, programmed cell death protein 1 (PD-1) inhibitors including pembrolizumab have shown substantial and durable responses in selected patients with recurrent SCCOHT after prior treatment with cytotoxic chemotherapy and also immediately following radiation treatment (70). In addition, 1 patient, known to these authors, showed near complete treatment response to CDK4/6 inhibition in combination with ICB (see comment above). Furthermore, preclinical data from SWI/SNF-mutant melanoma (71) and clear cell renal carcinoma (72) models demonstrate a causal connection between loss of SWI/SNF components such as PBRM1 and sensitivity to ICB. Although these reports focus upon loss of the PBRM1 subunit, Pan and colleagues showed loss of this subunit in SCCOHT cells (73). Rhabdoid tumors, also with low mutation burden, have recently been shown to have high infiltration of immune cells; this

immunogenicity is linked to endogenous retrovirus expression induced by SMARCB1 loss (74). Indeed, several recent reports support the efficacy of these inhibitors in patients with rhabdoid tumors (75, 76). Checkpoint blockade responses in SWI/SNF-mutant cancers may be associated with overexpression of immunostimulatory genes (71, 72). Given the similarity between SCCOHT and rhabdoid tumors, similar mechanisms may be in place underlying the response of SCCOHT to PD-1 inhibitor. A French phase II basket trial AcSé program with pembrolizumab (NCT03012620) is currently open for women with rare ovarian tumors including relapsed SCCOHT. While further investigation will define the utility of checkpoint inhibitors in SCCOHT, mechanistic understanding remains limited on the basis of the complex nature of modeling immune cell interactions in the available SCCOHT models, where the cell of origin is not yet defined. A phase II trial including pembrolizumab in combination with initial chemotherapy for advanced disease (stage II to IV) is due to start in France in 2020.

As more clinical trials become available for patients with SCCOHT, we suggest that immunotherapy be the first choice for treatment when eligibility requirements permit. After initial therapy, as described previously, immunotherapy appears to be the most promising non-standard therapy based on activity in selected patients reported to date and data from other related tumor types. The addition of CDK 4/6 inhibitors and epigenetic therapies also have some favorable reported outcomes to date on the basis of very limited, and mostly unpublished, case reports. We hope that additional viable options will become available as more preclinical and translational research is reported.

## Conclusions

In the six years since the discovery of SMARCA4 mutations in SCCOHT, this cancer has been transformed from being a little studied, poorly understood cancer for which there was no rational therapeutic options, to a tumor which is now the focus of much research. This is leading to the discovery of multiple potential treatments, meaning that there is now a need to carefully evaluate and prioritize the best candidate drugs for future trials. The rarity of SCCOHT creates challenges in the identification and management of affected patients. The true number of women affected worldwide remains unknown, creating barriers to rapidly and systematically identify eligible individuals for new treatments or clinical trials. We have begun establishing an international registry of well-characterized patients with, or at-risk for, SCCOHT. The collation of high quality clinical and epidemiologic data will allow us to better understand this disease and act as a catalyst to improve translational research and the overall outcome for patients with SCCOHT.

Females with germline PVs in *SMARCA4* likely have a clinically important risk of SCCOHT up to the age of approximately 60 years, particularly in the context of a positive family history. Genetic testing for germline *SMARCA4* PVs is recommended for all affected individuals with SCCOHT with cascade testing of at-risk family members

upon identification of germline PVs. Because surveillance is unproven, we recommend RRBSO for unaffected adult females with germline PVs in the context of a positive family history. Given the lack of defined guidelines for the management of women with SCCOHT, we recommend aggressive cytoreductive surgery followed by adjuvant combination therapy with a cisplatin- and etoposide-based regimen. HDC with stem cell rescue for individuals who have a complete clinical response may be considered (36, 48). Patients with progressive or recurrent disease should enroll in a clinical trial or consider nonstandard therapy based on the latest data that may come from case reports and limited source material.

SCCOHT is an excellent example of a cancer where the development of novel therapies targeting the cancer vulnerabilities induced by the driver mutation is possible. The key message for patients and family members is to remain in contact with disease experts who have knowledge of the latest clinical trials, seek consultation from academic referral centers, and request input from members of the ISC, <https://www.smallcellovarian.org/consortium.html>. The landscape of treatments for SCCOHT will continually change as we improve patient outcomes and work toward prevention and cure for this rare and aggressive malignancy. International prospective multicenter protocols with collection of data are urgently needed to be considered for both first-line and relapsed disease in this particularly rare condition.

## Disclosure of Potential Conflicts of Interest

S. Banerjee reports receiving speakers bureau honoraria from AstraZeneca, Tesaro/GlaxoSmithKline, Roche, and Seattle Genetics. No potential conflicts of interest were disclosed by the other authors.

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# Clinical Cancer Research

## Small-Cell Carcinoma of the Ovary, Hypercalcemic Type—Genetics, New Treatment Targets, and Current Management Guidelines

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