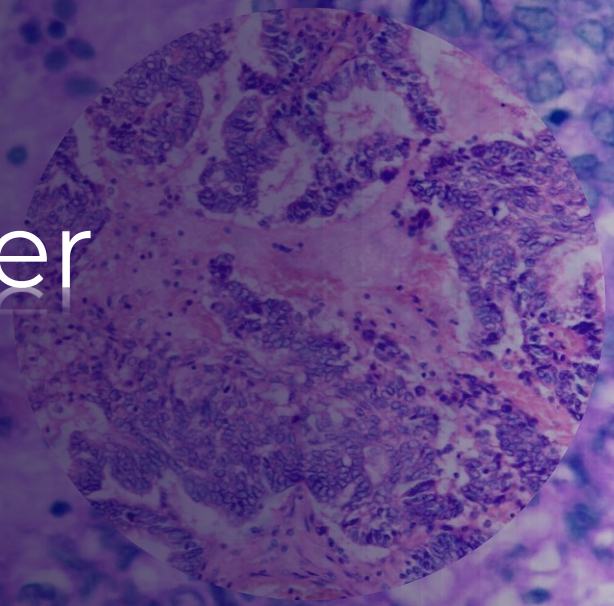
KIF18A inhibitors: novel therapeutics for platinum-resistant high-grade serous ovarian cancer



Ovarian cancer: „A silent killer”

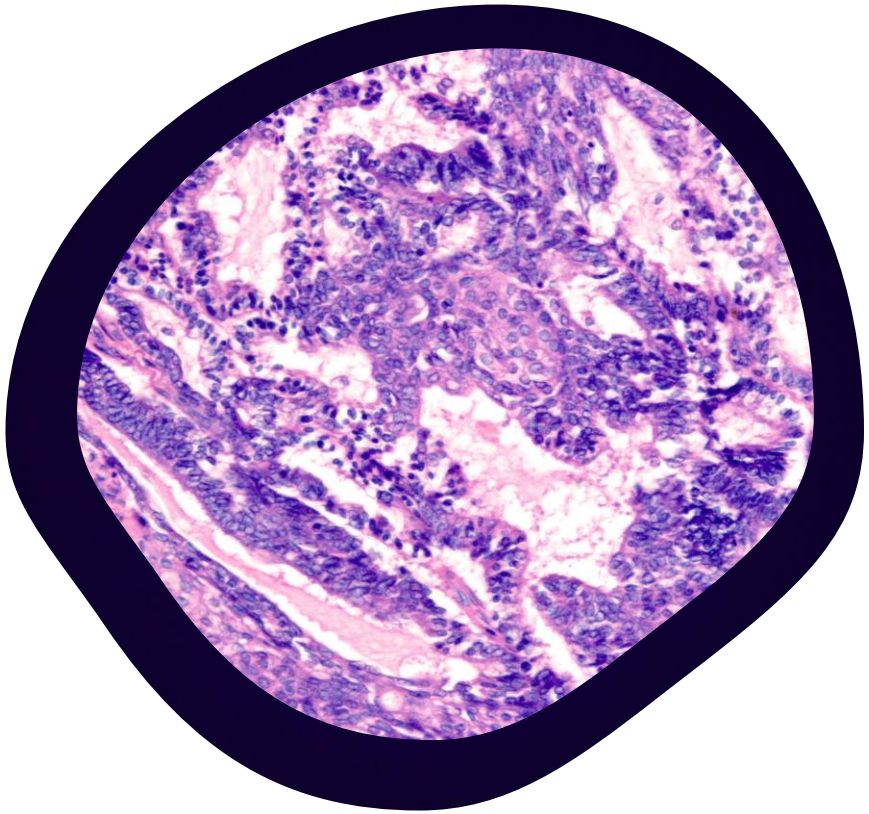
The deadliest of gynecologic cancers.[1,2]

Relative five-year survival rate is around 50%.[3]

2022		**2050** (projected)[4]
324,603 new cases		**503,448** new cases
206,956 deaths		**350,956** deaths

High-grade serous ovarian cancer (HGSOC)

- Accounts for **70% of all ovarian cancer cases** and **nearly 80% of deaths.**[5]
- Has a unique pattern of metastasis along the peritoneal cavity and on the surface of abdominal organs.[6]
- Characterized by ascites accumulation driven by vascular endothelial growth factor (VEGF).[7]
- More than 95% of HGSOC tumors harbor a TP53 mutation.[5]
- Approximately half of HGSOC tumors harbor genomic features of homologous recombination deficiency (HRD), most commonly associated with BRCA1/2 mutations.[8]
- All HGSOC tumors exhibit severe chromosomal instability (CIN).[9]



Standard treatments

1. Tumor cytoreductive surgery, often involving the removal of gynecologic organs, lymph nodes, and omentum.[5]

2. Platinum (Pt)/taxane-based chemotherapy (most commonly carboplatin and paclitaxel).[5]

3. A humanized anti-VEGF antibody (bevacizumab) or Poly (ADP-ribose) polymerase (PARP) inhibitors (such as olaparib or niraparib) as concomitant or maintenance therapies.[10,11,12,13]

Issues with standard treatments

1. Up to 80% of patients relapse within 24 months, especially those with stages III-IV who failed to have optimal surgery.[10,14]

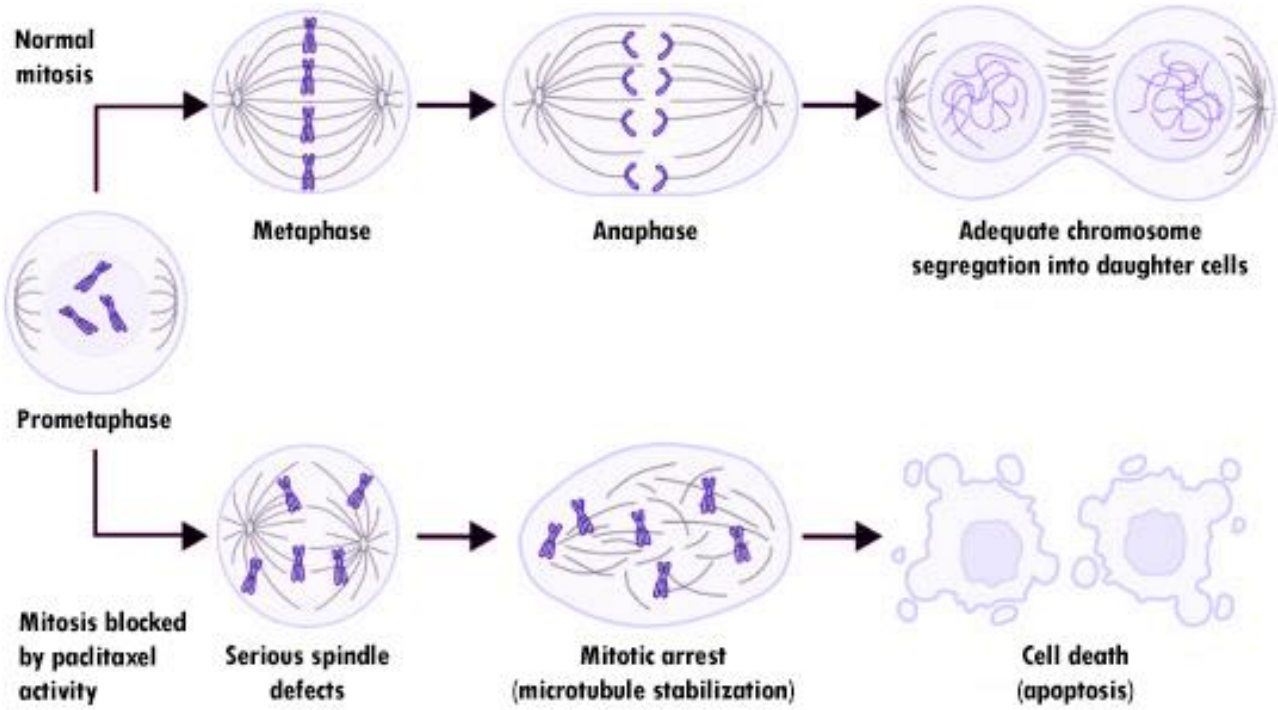
2. Most patients develop drug resistance and experience treatment-related toxicity.[10]

3. With increasing lines of therapy, toxicity increases, while progress-free survival and quality of life decrease.[10]

4. There are limited therapeutic options for women with HR proficient cancers.[5]

Targeting mitosis via microtubules

Mitosis (somatic cell division)[15]



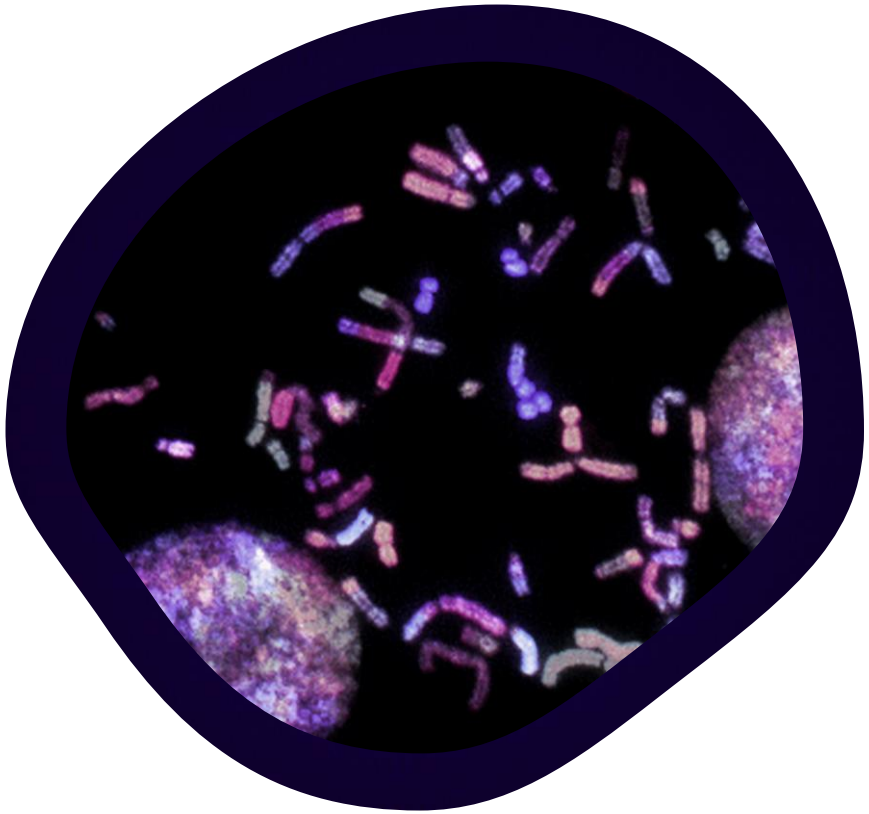
As an **anti-mitotic drug** that stabilizes microtubules, paclitaxel stood the test of time as a first-line treatment.[11]

However, it is **highly unspecific**. Besides cancer cells, it also affects[16,17]:

- All rapidly dividing cells within the body, including healthy ones, which leads to hair loss, nausea, and vomiting.
- Microtubules within neurons, which leads to peripheral neuropathy.

Targeting mitosis: chromosomal instability

- **Chromosomal instability (CIN)** refers to an increased and continuous chromosome mis-segregation that is a hallmark of cancer cells.[18]
- CIN leads to an abnormal number of chromosomes in daughter cells, termed aneuploidy.[18]
- Aneuploidy can be numerical (loss or gain of whole chromosomes) or structural (loss or gain of parts of chromosomes).[18]
- Aneuploidy has been detected in approximately 90% of solid cancers.[19]



CIN & HGSOC

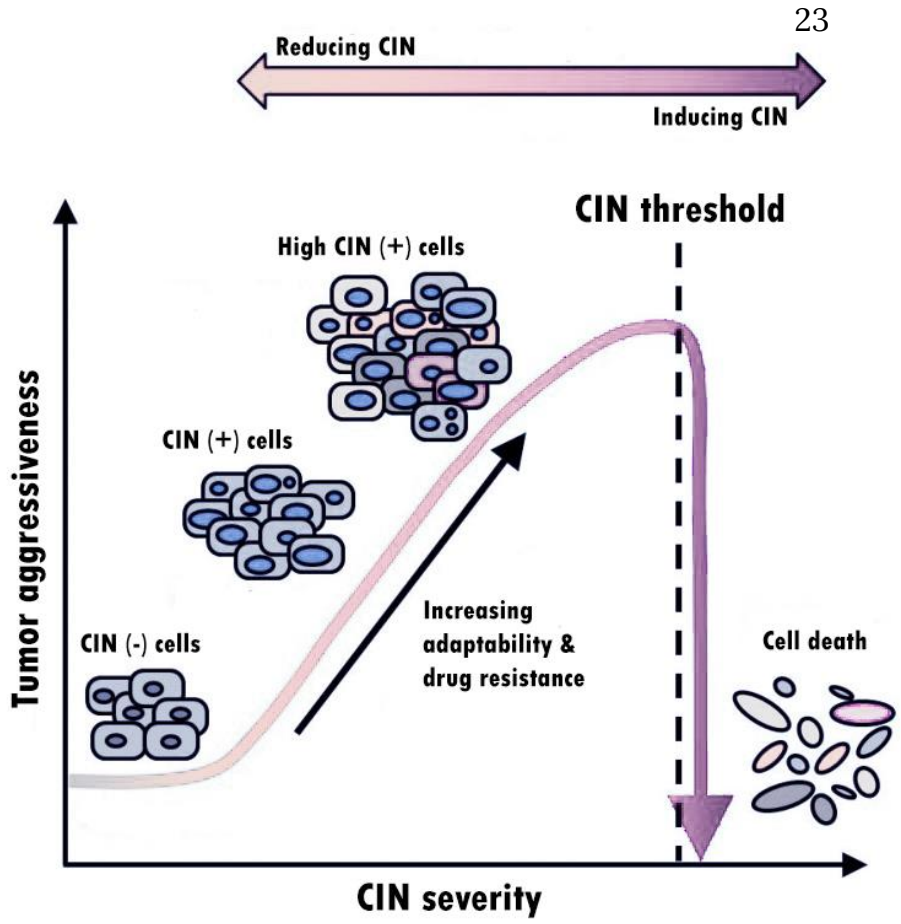
1. CIN occurs in 100% of solid HGSCOC tumors and 90.9% of ascites samples regardless of age, stage, chemotherapy, or BRCA status.[20]

2. Chemoresistant disease shows higher levels of CIN than chemosensitive disease.[20]

Could targeting CIN be an effective approach for treating drug-resistant HGSOC?

Targeting CIN via mitotic regulators

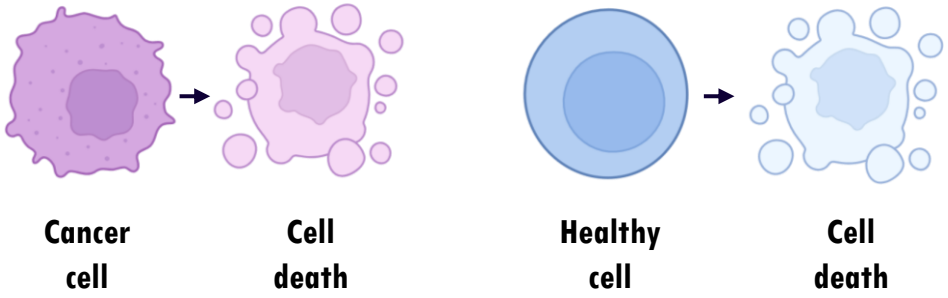
- Moderate levels of CIN help cancers develop heterogeneity, drug resistance, and growth advantage, but extreme levels of CIN can have an opposite effect and cause cancer cell death.[21,22]
- Drugs that target mitotic regulators and induce high levels of CIN, such as Eg5 or Plk1 inhibitors, have shown limited success in clinical settings so far.[23]
- Similar to drugs that target microtubules, drugs that target mitotic regulators are relatively non-selective, affecting both healthy and cancer cells.[17]



Targeting CIN: could it be selective?

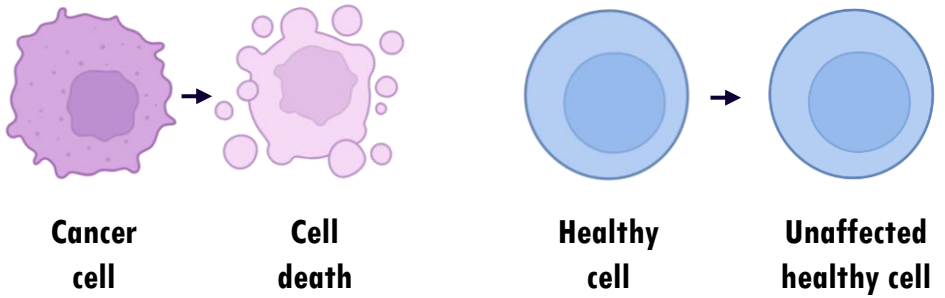
Traditional anti-mitotic therapies

They target microtubules or mitotic regulators in both healthy and cancer cells.[17]



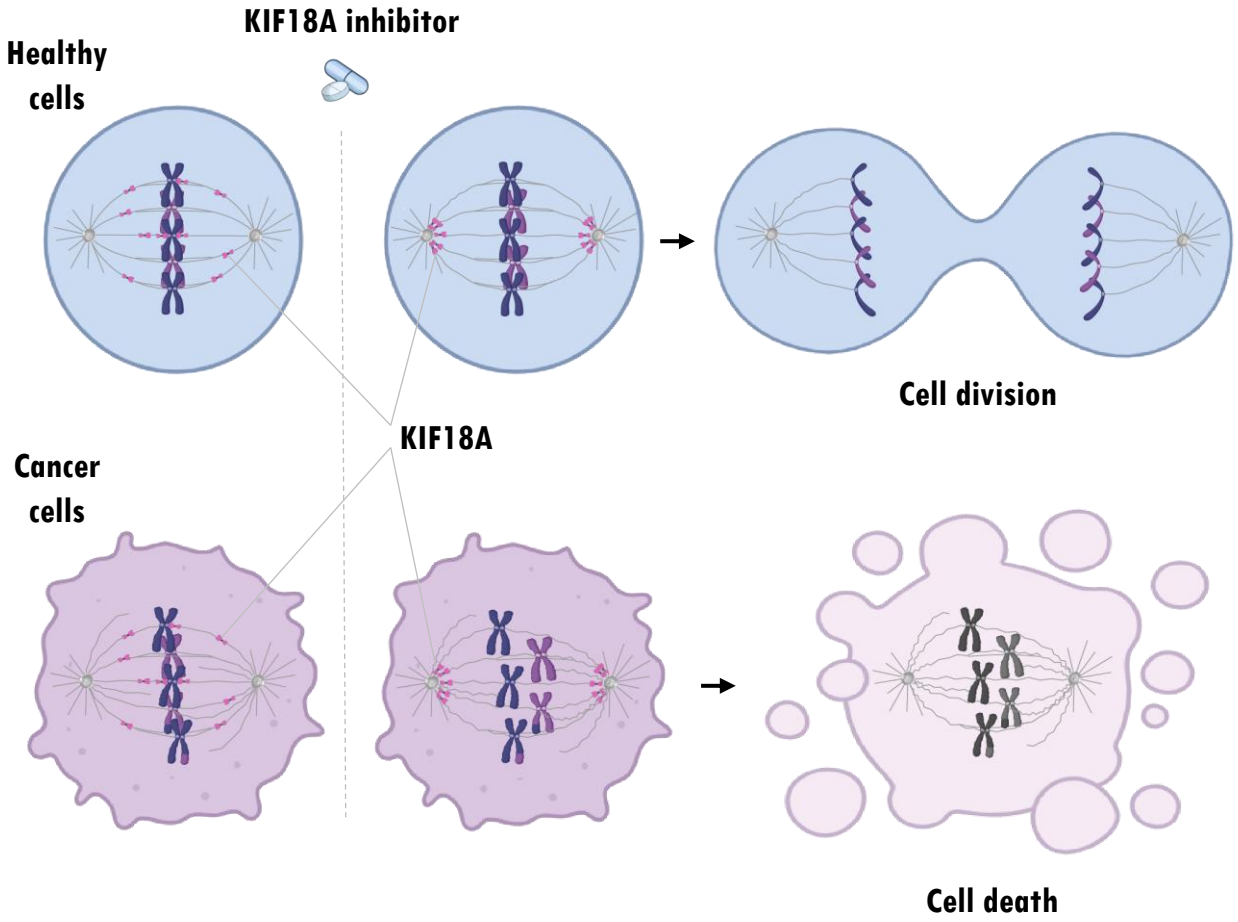
Selective anti-mitotic therapies

They would ideally target **vulnerabilities specific to CIN (+) cancer cells**, without affecting mitosis in healthy cells.[17]



Targeting CIN via KIF18A

- KIF18A is a motor protein with microtubule depolymerizing activity.[24]
- It ensures proper kinetochore-microtubule interactions during mitosis and helps chromosomes align at the equator.[25,26]
- Without KIF18A, chromosomes oscillate around the equator and form a wider metaphase plate.[26]
- Healthy cells can tolerate these changes and normally progress through mitosis.[17,27,28,29]
- **CIN (+) cancer cells, which often have abnormal spindles and difficulties aligning their chromosomes, depend on KIF18A to ultimately ensure successful mitosis.**[17,27,28,29]



KIF18A inhibitors in clinical trials

Volastra Therapeutics	VLS-1488	Phase I/II
Volastra Therapeutics *licensed from Amgen	Sovilnesib *formerly AMG-650	Phase Ib
Accent Therapeutics	ATX-295	Phase I/II
Changchun GeneScience Pharmaceuticals Co.	GenSci122	Phase I
Volastra Therapeutics	VLS-1272	Preclinical
Insilico Medicine	ISM9682	Preclinical
Apeiron Therapeutics and the University of Vermont	N/A	Preclinical

volastra

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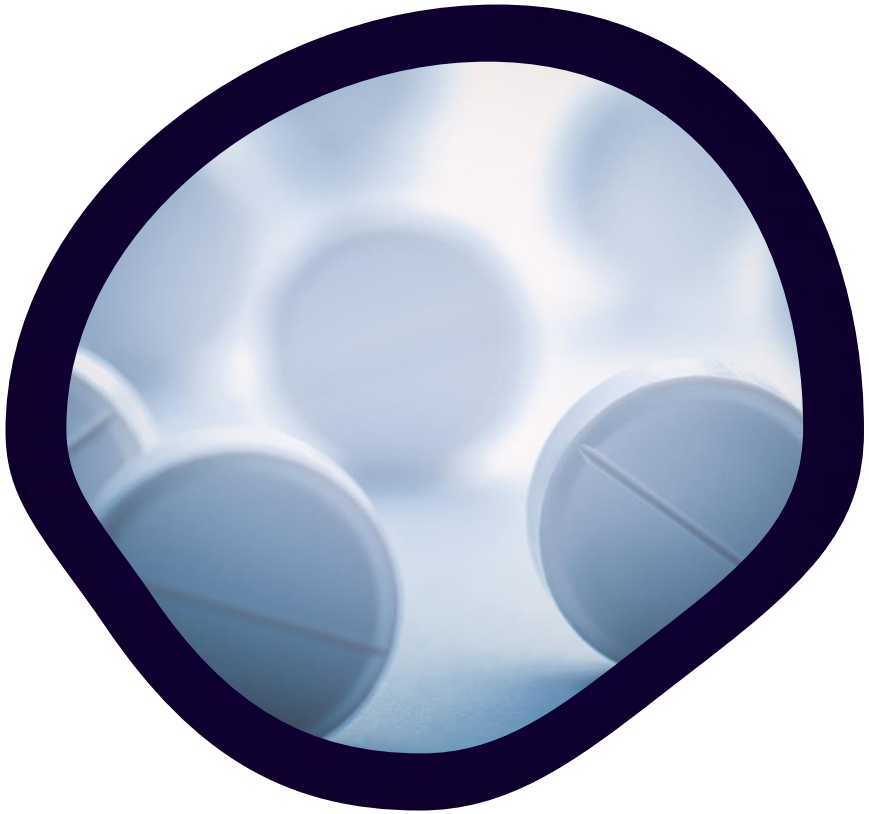
KIF18A inhibitors: results from early trials

- **The first, ongoing, in-human trial includes a once-daily oral KIF18A inhibitor (VLS-1488).**
- The inhibitor showed a highly favorable safety profile at clinically active doses.
- It also demonstrated tumor reduction in 7 of 17 advanced ovarian cancer patients enrolled in dose escalation, most of whom were platinum resistant and heavily pretreated with a median of 5 lines of therapy.
- There is currently an ongoing enrollment in dose expansion.



Source: *Volastra's preliminary data announcement*

KIF18A inhibitors: future perspectives

1. Collect and review additional data from the ongoing studies to better inform the conclusions and help guide the next phase of decision-making.

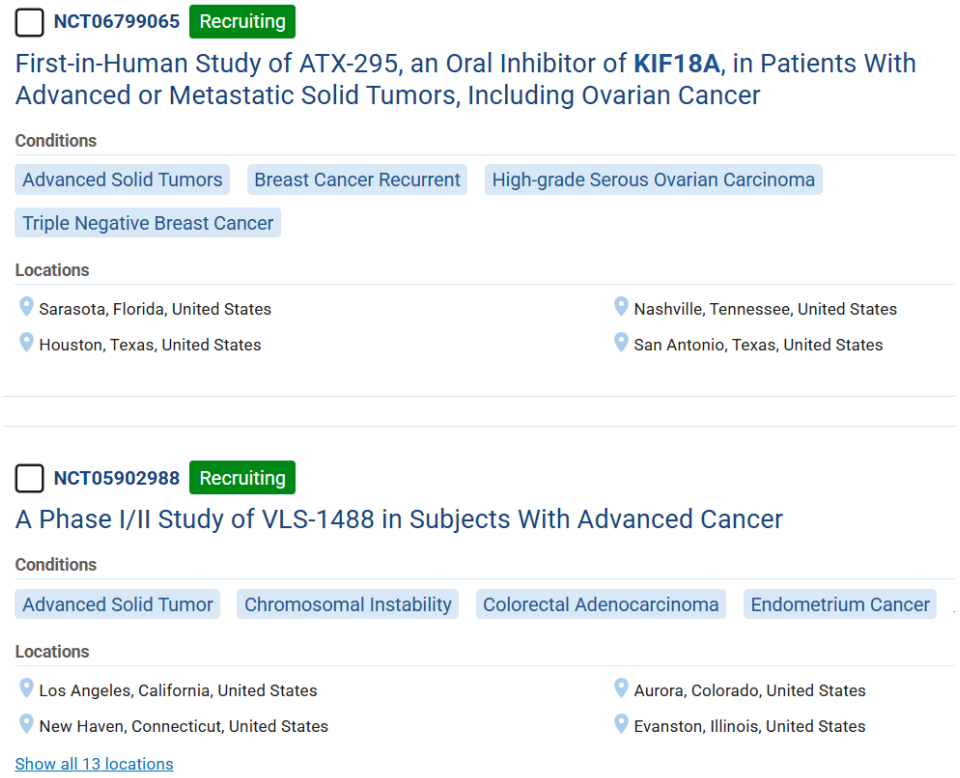
2. Explore the combinations of KIF18A inhibitors with standard-of-care therapies that also target CIN through their own mechanisms.[17]

3. Test the effects of KIF18A inhibitors on other types of cancer characterized by high levels of CIN.[17]

Key takeaways

- **KIF18A is a promising therapeutic target for hard-to-treat HGSOC**.
- There are currently four ongoing clinical trials of KIF18A inhibitors.
- If proven successful in the ongoing trials, KIF18A inhibitors may be used alone or in combination with other agents to treat advanced HGSOC and other CIN (+) cancers with unmet medical needs.

To learn more about the ongoing trials, visit ClinicalTrials.gov.



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