# KIF18A Inhibitors — Clinical Evidence for Anti-Aging and Dual-Purpose (Aging-Disease + Oncology) Development

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Trial/dataset identifiers verified against retrieved sources; other figures are as reported by the curated skill and were not number-gated.

**Prepared for:** Insilico Medicine — KIF18A anti-aging program **Date:** 2026-08-13 **Scope:** Review of the two internal background dossiers (KIF18A anti-aging biology; KIF18A indication prioritization), then an evidence assessment of whether selective KIF18A inhibitors — or same-mechanism drugs — provide **solid human clinical evidence of safety, efficacy and robustness** for an anti-aging or dual-purpose (aging-related disease + oncology) strategy. **Grounding note:** Every registry ID, phase and status below was returned this session by the internal trials dataset and/or ClinicalTrials.gov. Every PMID was returned by PubMed this session. Efficacy figures that originate from your uploaded dossiers (e.g., the ASCO 2025 VLS-1488 abstract) are attributed as such and were **not** independently re-verified against a primary source by a tool this session.

## 1 Bottom line / Verdict

**There is currently NO direct human clinical evidence — of safety, efficacy, or robustness — for KIF18A inhibition as an anti-aging intervention.** All KIF18A inhibitors in humans are early-phase (Phase I / I-II) **oncology** programs in chromosomally unstable (CIN) solid tumors, none of which enrolls an aging or senescence population or uses a geroscience endpoint. The anti-aging thesis in your dossier is mechanistically coherent (aneuploid-selective clearance → reduced senescence/ inflammaging) but rests entirely on **preclinical and associational** evidence; the single most important gap — a direct KIF18A-inhibitor lifespan/healthspan experiment — remains unfilled, as your own biology report states.

**What the human data DO support today, and with what confidence:**

| CLAIM | VERDICT | CONFIDENCE |
|---|---|---|
| **KIF18A inhibitors are being tested in humans and are tolerated enough to advance** | **Yes** — ⩾6 distinct programs, one Amgen Phase I completed (NCT04293094) | High |
| **Early single-agent anti-tumor activity in CIN-high tumors (HGSOC)** | **Emerging / immature** — signals reported in your ASCO 2025 dossier, not yet mature tool-verifiable readouts | Low–Moderate |
| **The mechanism has a built-in patient-selection axis (CIN/aneuploidy) that de-risks it vs. older anti-mitotics** | **Plausible** — this is the key differentiator, but a locked companion-diagnostic CIN cutoff is not yet established | Moderate |
| **"Aneuploidy-selective senolytic" works in humans for aging** | **Unproven** — zero human data; closest precedent is a different senolytic class (D+Q) | Very Low |

**Recommendation in one line:** Pursue KIF18A as an **oncology-first, aging-bridged** ("dual-purpose") asset — let the CIN-high cancer programs generate the safety/PD and biomarker package, then bridge to a geroscience biomarker study — rather than positioning it as a standalone anti-aging therapeutic today.

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## 2 Trial landscape — selective KIF18A inhibitors in humans

The field is entirely **early-phase, oral small-molecule monotherapy**, concentrated in **high-grade serous ovarian cancer (HGSOC)** and other CIN-high tumors (TNBC, NSCLC). Registry IDs below were confirmed this session by the internal trials dataset and ClinicalTrials.gov.

| DRUG | SPONSOR | REGISTRY ID | PHASE | STATUS | LEAD INDICATION(s) |
|---|---|---|---|---|---|
| **VLS-1488** | Volastra Therapeutics | NCT05902988 | I/II | Recruiting | Advanced solid tumors; HGSOC, sq-NSCLC, TNBC, HNSCC, carcinosarcoma |
| **Sovilnesib (AMG 650)** | Volastra Therapeutics | NCT06084416 | Ib (dose-opt) | Active, not recruiting / Closed | HGS ovarian, fallopian tube, primary peritoneal |

| DRUG | SPONSOR | REGISTRY ID | PHASE | STATUS | LEAD INDICATION(s) |
|---|---|---|---|---|---|
| **Sovilnesib / AMG 650 (original)** | Amgen | NCT04293094 | I | **Completed** | Advanced solid tumors (breast, ovarian, endometrial, fallopian tube) |
| **ATX-295 (ACNT-2)** | Accent Therapeutics | NCT06799065 | I (CT.gov) / I-II (internal) | Recruiting | Solid tumors incl. HGSOC, TNBC/breast, NSCLC |
| **MEN2501 (ISM9682)** | Menarini Group / Stemline (Insilico Medicine origin) | NCT07226427 | I | Recruiting | Platinum-resistant ovarian cancer |
| **HS387** | Zhejiang Hisun Pharmaceutical | NCT07092748 | I | Open/Recruiting (China; CTR20252636) | NSCLC, ovarian, solid tumors |
| **GenSci-122** | Jiangsu Gensciences | NCT06772415 | I | Open | Solid tumors |
| **GH-2616** | (developer per dataset) | NCT06329206; NCT07260513 | Ia/Ib; I | Open; Closed | Solid tumors |
| **HW-221043** | (developer per dataset) | internal ID only (no NCT) | I | Planned | Solid tumors |

**Aggregate phase/status mix (internal dataset, KIF18A-titled/targeted records):** predominantly Phase I with several Phase I/II; a mix of Recruiting/Open, one Completed (Amgen NCT04293094), and closed dose-optimization cohorts. This is a **crowded, fast-moving early-stage field** — at least ~9 distinct clinical assets from US, EU and Chinese sponsors — but **no asset beyond Phase II and no approval**.

> Data caveat: ClinicalTrials.gov lists NCT06084416 (Volastra sovilnesib) as ACTIVE_NOT_RECRUITING while the internal dataset marks it "Closed" — the same state under two vocabularies (no longer enrolling).

### Reported clinical readouts

**From tools this session:** the trial records returned **design and primary-outcome measures only** (DLTs, MTD/RP2D, TEAE/SAE frequency, ORR by RECIST v1.1). **No response rates, tumor-shrinkage figures, or adverse-event counts were returned** — i.e., mature efficacy/safety readouts are not found in available tool sources.

**From your uploaded background dossier** (attributed, not independently re-verified by a tool this session):

- **VLS-1488** (ASCO 2025, Abstract #3012): 7/17 (41%) evaluable HGSOC patients with tumor reduction; 3 partial responses; 6 with stable disease; **no dose-limiting toxicities** at any dose level in a heavily pre-treated, platinum-resistant population; FDA Fast Track (Oct 2024).
- **ATX-295**: FDA Fast Track (Apr 2025); "best-in-class" preclinical claims only.

**Interpretation:** the human dataset today shows KIF18A inhibitors are **advanceable and apparently tolerable** (Amgen Phase I completed; no DLTs reported for VLS-1488), with **early, immature efficacy signals** in the highest-CIN indication (HGSOC). This is genuine proof-of-tolerability and preliminary proof-of-activity in oncology — but it is **not** yet robust, controlled efficacy evidence, and it says nothing directly about aging.

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## 3 Same-mechanism (MoA) precedent — what the anti-mitotic class teaches us

KIF18A is a kinesin-8 mitotic motor. The most informative human precedent comes from other **spindle/kinesin/chromosome-segregation** agents. The class base rate is a **cautionary tale**, which is exactly why KIF18A's differentiation matters.

| CLASS | EXAMPLE DRUG | FURTHEST VERIFIED PHASE | KEY OUTCOME | SOURCE (this session) |
|---|---|---|---|---|
| **KSP/Eg5 kinesin** | Ispinesib (SB-715992) | Phase II (multiple; **no Phase III**) | Broad single-agent Ph II (HCC, CRC, melanoma, breast); stalled, no approval | NCT00095992, NCT00103311, NCT00095953, NCT00089973; review PMID 35043768 |
| **KSP/Eg5 kinesin** | Filanesib (ARRY-520) | **Phase III — Terminated** (FACTOR, +carfilzomib) | Activity only in biomarker subsets (AAG-low; t(11;14)/1q21) in myeloma | EudraCT 2014-001052-39; NCT02092922, NCT01248923, NCT01989325; PMIDs 34921527, 32501528, 31575851 |
| **Aurora A kinase** | Alisertib (MLN8237) | Phase II/III | Many Ph I–II combinations; **no registration** | NCT02187991, NCT02038647, NCT02560025 |
| **PLK1** | Volasertib (BI 6727) | **Phase III (AML) — negative** | Added toxicity/early-mortality concern in unfit AML | NCT01121406, NCT01023958; PMIDs 34350385, 29882583 |

| CLASS | EXAMPLE DRUG | FURTHEST VERIFIED PHASE | KEY OUTCOME | SOURCE (this session) |
|---|---|---|---|---|
| **CENP-E** | GSK923295 | not reported this session | not reported | — |
| **KIF18A (index)** | AMG 650 / ATX020 series | Early clinical | CIN-selective mitotic lethality enriched in aneuploid tumors | PMIDs 39747049, 38151625, 41543111, 41369352 |

**Base-rate narrative.** Un-selected anti-mitotics have a **poor** track record: the KSP/Eg5 leader ispinesib generated a broad Phase II panel but never reached registration; the one KSP agent to reach Phase III (filanesib) was **terminated**; the adjacent PLK1 agent volasertib **failed** Phase III in AML with added toxicity; Aurora A (alisertib) accumulated combinations without approval. The recurring failure mode is **lack of single-agent efficacy in unselected solid tumors**, compounded by **myelosuppression/ neutropenia** as the canonical dose-limiting toxicity (class reviews PMID 35043768, 33310050).

**Why KIF18A could break the pattern.** Filanesib's only durable signals were **biomarker-restricted** (AAG-low; t(11;14)/1q21). KIF18A's thesis puts that enrichment axis into the mechanism itself — dependence on chromosomal instability/aneuploidy (PMIDs 39747049, 38151625). The precedent therefore predicts that KIF18A's odds hinge on **prospectively enriching for CIN-high tumors**, not repeating all-comer designs. This is consistent with your indication-prioritization report placing HGSOC (~100% CIN) first.

**Safety-signal comparison — important honesty flag.** The class's canonical DLT is marrow suppression (PMIDs 35043768, 33310050; volasertib toxicity PMID 34350385). Your background dossier reports KIF18A inhibitors **spare bone marrow** and that KIF18A-knockout mice are viable (Payton et al., Nat Cancer 2024; Cohen-Sharir et al., Nature 2021, PMID 33505028). However, an explicit, **tool-verified quantitative marrow-sparing comparison in humans was NOT confirmed** this session. Treat "bone-marrow-sparing / wide therapeutic index" as a **preclinically-rationalized hypothesis pending mature clinical safety readouts**, not established human fact.

## 4 Biomarker & patient-selection strategy

Patient selection is the pivot on which KIF18A's whole differentiation (and its aging rationale) turns.

| BIOMARKER | ROLE | EVIDENCE (this session) |
|---|---|---|
| **CIN-high status** | Core enrichment — KIF18A dependence is enriched in chromosomally unstable/aneuploid cells; diploid cells spared | Preclinical PMID 39747049; ATX020 in CIN-high HGSOC PMID 41369352; review PMID 41543111 |
| **Aneuploidy score / genome instability** | Proposed stratifier | PMID 41942602 (early vs late genome-instability profiles); PMID 38588415 (CIN metrics inconsistent across methods) |
| **CIN gene-expression signature (CIN4/ CIN70-type)** | Predictive-biomarker precedent in a real RCT | PMID 27056899 (CIN4 predicted taxane benefit, NCIC-CTG MA21) |
| **Whole-genome doubling (WGD)** | Hypothesized enrichment marker | Not directly validated for KIF18A (hypothesis-only) |
| **TP53 mutation** | Hypothesized aneuploidy-tolerance marker | Not directly validated for KIF18A (hypothesis-only) |

**Caveats that matter.** CIN is **not universally predictive** — it failed as an immune-checkpoint response predictor (PMID 33171596) — and CIN quantification is **method-dependent** (PMID 38588415). A **locked companion-diagnostic CIN cutoff** for KIF18A response in humans is **not yet reported**; today's oncology trials enrich mostly by **histology** (ovarian/HGSOC as a CIN-near-universal proxy), not a validated CIN score. For a dual-purpose/aging use, this is the crux: the aging thesis needs a validated marker of aneuploid-cell burden in normal-aged tissue, which does not yet exist as a clinical assay.

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## 5 Anti-aging & dual-purpose translational assessment

**The aging case, as your dossiers frame it, is mechanistically strong but experimentally unproven:**

- Genetic proof-of-principle (analog, not KIF18A): reducing aneuploidy (BubR1 overexpression) extends healthy lifespan, and clearing $p16^{+}$ senescent cells extends median lifespan ~25% in mice (your dossier; Baker et al., PMIDs 23242215, 26840489). This validates the upstream logic (aneuploidy/senescence clearance → healthspan), not KIF18A specifically.

- Human senolytic precedent (different class): the closest in-human design analogue is dasatinib+quercetin reducing senescent-cell burden (p16, SA-β-gal, SASP) in a disease-of-aging population (PMID 31542391; corrigendum 31982828; strategy review PMID 34699859). This proves the senolytic-in-humans paradigm and its PD/biomarker endpoints — but not the aneuploidy-clearance mechanism.
- KIF18A-specific aging data: **none in humans.** KIF18A is HOA_count = 0, absent from GenAge/geroprotector/ClinicalTrials.gov aging lists, and present in 4 aging clocks but not as a top feature (your indication-prioritization report). The strongest direct KIF18A-aging link — oocyte aneuploidy (Biswas et al. 2024, PMID 39475646) — actually argues that KIF18A is **protective** in oocytes, so an inhibitor would be **contraindicated for reproductive aging**. The aging value is somatic (clearing aneuploid/senescent cells), not germline.

**Dual-purpose logic (the realistic path).** The oncology indications your prioritization report ranks — HGSOC (9.2/10), TNBC/basal-like (8.5), CIN-high CRC (7.8), HCC (7.2) — are themselves **age-related diseases of accumulated genomic instability**. The cleanest way to build human evidence relevant to aging is therefore to **run the oncology programs with embedded geroscience biomarkers** (senescence/SASP/aneuploidy PD readouts), then bridge. A first-in-human aging study would most plausibly borrow the D+Q template: Phase 1 primary = safety + PD target engagement (reduction in senescent/aneuploid-cell burden: p16INK4A, SA-β-gal, SASP IL-6/IL-8 in serial skin/adipose biopsies); enrichment = a validated CIN/aneuploidy score + circulating SASP; exploratory = physical function (gait speed, 6-min walk) and biological-age clocks (inferred from PMIDs 31542391, 34699859 — **not** from any KIF18A trial).

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## 6 Risks & unknowns

1. **No aging efficacy data, and none coming soon** — every KIF18A trial is oncology; a dedicated aging readout would take years and a validated biomarker that does not yet exist.
2. **Class base rate is unfavorable** — prior anti-mitotics (KSP/Eg5, PLK1, Aurora) largely failed in the clinic (PMIDs 35043768, 34350385; EudraCT 2014-001052-39). KIF18A's escape hatch is CIN enrichment, still to be proven prospectively.
3. **Marrow-sparing is hypothesis, not verified human fact** — the differentiating safety claim lacks a tool-verified quantitative human comparison this session.
4. **Biomarker not locked** — no validated companion-diagnostic CIN cutoff; CIN is method-dependent and not universally predictive (PMIDs 38588415, 33171596).
5. **Chronic-dosing safety unknown** — anti-aging use implies chronic/intermittent dosing in non-cancer subjects, a far higher safety bar than late-line oncology; no data address this.
6. **Efficacy readouts are immature and single-source** — the encouraging VLS-1488 numbers come from your dossier's ASCO 2025 abstract, not a mature tool-verified primary source.

**What would change the verdict:** (a) a controlled oncology readout showing durable single-agent efficacy enriched by a validated CIN score; (b) demonstrated marrow-sparing/wide therapeutic index in humans; (c) a preclinical KIF18A-inhibitor healthspan/lifespan experiment (the missing keystone); (d) a PD study showing an inhibitor reduces aneuploid/senescent-cell burden in normal aged tissue.

## 7 Recommendation

1. **Position KIF18A as oncology-first, aging-bridged ("dual-purpose"), not standalone anti-aging.** The human safety/efficacy package will and should come from the CIN-high cancer programs (HGSOC lead), consistent with your indication prioritization.
2. **Design for enrichment now.** The MoA precedent is unambiguous: prospectively select CIN-high/aneuploidy-high populations and invest in a **validated, method-robust CIN companion diagnostic** — this is the single biggest de-risking lever.
3. **Embed geroscience biomarkers into oncology trials** — serial senescence/SASP/aneuploidy PD endpoints in on-treatment biopsies — to accumulate aging-relevant human PD data at low incremental cost, using the D+Q senolytic template (PMID 31542391) as the design analogue.
4. **Fill the keystone preclinical gap** — commission a direct KIF18A-inhibitor aged-mouse healthspan/lifespan study; without it the anti-aging thesis cannot mature past "mechanistically plausible."
5. **Track competitors closely** — this is a crowded early field (Volastra, Amgen-origin, Accent, Menarini/Stemline, and multiple Chinese sponsors); differentiation will come from selectivity, chronic-dosing tolerability, and biomarker strategy, not from being first into CIN cancers.
6. **Do not pursue reproductive-aging indications with an inhibitor** — KIF18A is protective in oocytes; inhibition is contraindicated there (Biswas et al., PMID 39475646).

## 8 Sources

**Verified trials (internal trials dataset + ClinicalTrials.gov, this session):** NCT05902988 (VLS-1488), NCT06084416 & NCT04293094 (sovilnesib/AMG 650), NCT06799065 (ATX-295/ACNT-2), NCT07226427 (MEN2501/ISM9682), NCT07092748 (HS387; CTR20252636), NCT06772415 (GenSci-122), NCT06329206 & NCT07260513 (GH-2616). MoA-precedent trials: NCT00095992,

NCT00103311, NCT00095953, NCT00089973 (ispinesib); EudraCT 2014-001052-39, NCT02092922, NCT01248923, NCT01989325 (filanesib); NCT02187991, NCT02038647, NCT02560025 (alisertib); NCT01121406, NCT01023958 (volasertib).

**Literature (PubMed, this session):** KIF18A CIN-selectivity — 39747049, 38151625, 41543111, 41369352. Anti-mitotic class — 35043768, 33310050, 34350385, 29882583, 34921527, 32501528, 31575851. Biomarker — 27056899, 41942602, 38588415, 33171596. Senolytic/aging — 31542391, 31982828, 34699859. Reproductive aging (KIF18A protective) — 39475646.

**Background dossiers (user-provided, this session):** `kif18a_anti_aging.md` (biology/aging mechanism, ASCO 2025 VLS-1488 abstract #3012, aging-clock and GTEx analyses); `kif18a_indication_prioritization_base_pandaclaw.md` (13-indication scoring, HGSOC 9.2/10, TNBC 8.5, CRC 7.8, HCC 7.2; aging-relevance assessment). Efficacy figures sourced from these dossiers are attributed and were not independently re-verified by a tool this session.

This analysis supports research and portfolio decisions and is not medical advice. Associational/trial-level base rates are distinguished from predictive per-patient claims throughout; where evidence was thin it is labeled as such rather than filled.