mTOR Non-Oncology Analysis

Sleuth

Modern decision intelligence for the bioeconomy

Project Scope and Key Questions

Key Questions the Company Needed Answered

- Which non-oncology mTOR-pathway modulators align with the company's strategic priorities in cardiometabolic and neurodegenerative disease? This included understanding therapeutic indications, mechanistic rationale (insulin sensitivity, lipid metabolism, autophagy), and where pathway modulation is most compelling?
- What is the full mechanistic and translational profile of these assets across the broader mTOR network? Specifically, the company sought clarity on molecular targets within the pathway, biomarker support, human evidence of target engagement, and the strength of translational validation supporting each program.

What We Delivered Using Sleuth

- Built an AI-augmented dataset of non-oncology mTOR-pathway assets with pathway-level resolution. Sleuth captured direct mTOR inhibitors as well as upstream and downstream regulators, mapped by target node, indication focus, mechanistic hypothesis, and originating company context.
- Delivered a stage- and partnership-ready strategic landscape to inform build vs. buy decisions. Assets were classified with granular development staging (discovery, lead optimization/selection, IND-enabling tox, Phase I–III), and partnership readiness was assessed to support decisions between acquiring mature programs versus pursuing internal discovery of emerging mTOR effectors.

Executive Summary

mTOR Non-Oncology Asset Landscape

1. **LANDSCAPE SCOPE:** Identified 144 mTOR pathway assets targeting non-oncology indications (expanded from direct mTOR to full pathway: PI3K/AKT upstream, TSC1/2-Rheb, mTORC1/2, downstream effectors). 84 preclinical, 36 clinical (Phase I-III), 17 approved.

2. **PATHWAY POSITIONING:** PI3K/AKT upstream dominates with 60 assets (42%), reflecting hypothesis that upstream modulation provides superior metabolic control. Direct mTORC1/mTOR inhibitors represent 31 assets. TSC1/2-Rheb axis shows 21 assets as emerging node.

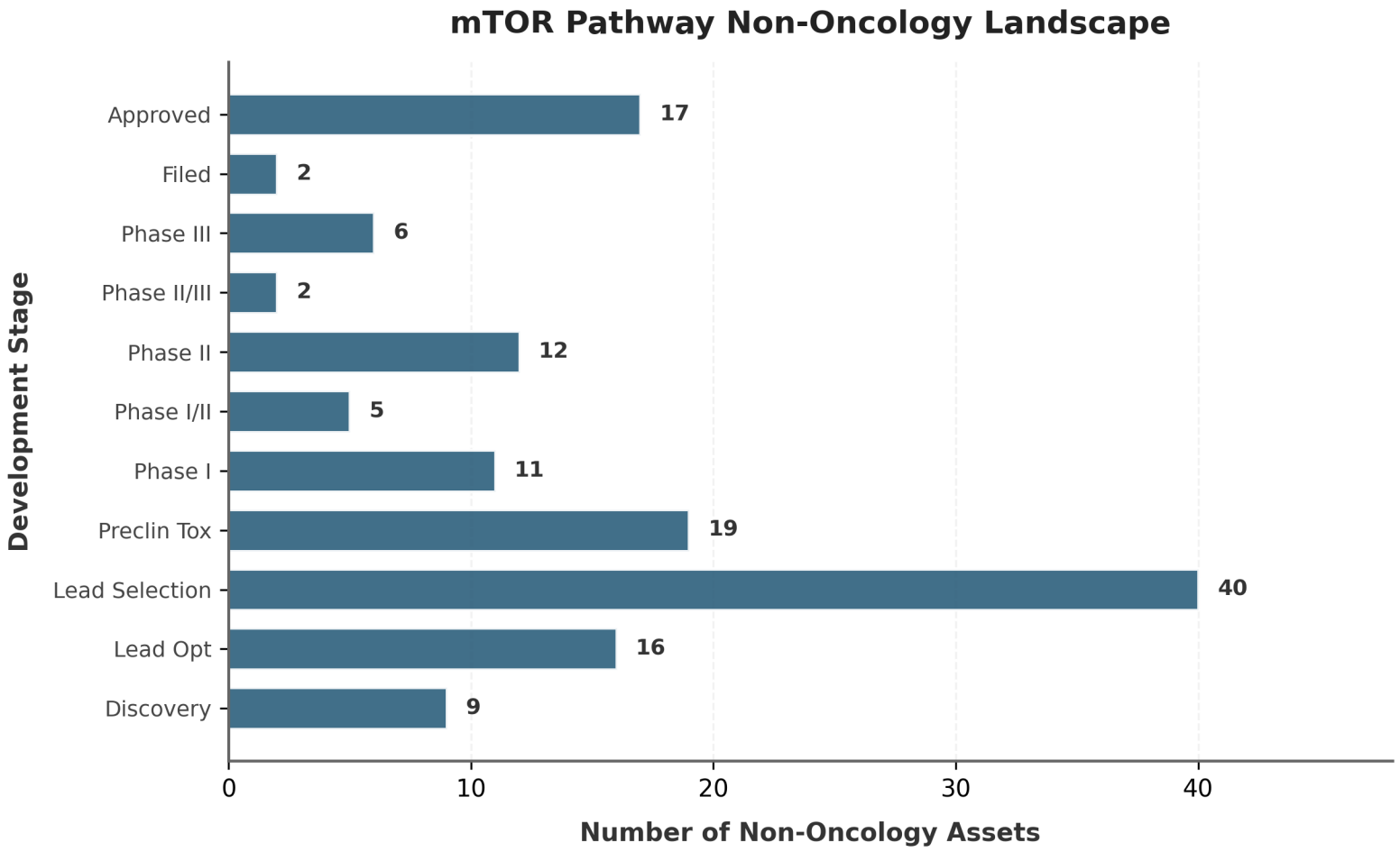
3. **PARTNERSHIP OPPORTUNITY:** 67% of clinical assets (24 of 36) remain unpartnered despite Phase II-III maturity. Advanced unpartnered assets offer near-term acquisition opportunities with clinical validation complete. 4 research collaborations provide upgrade potential.

4. **VALIDATION GAP:** 26 of 36 clinical assets (72%) have human evidence, but quality varies by node. mTORC1/mTOR shows 70% evidence rate (historical rapalog experience). PI3K/AKT upstream relies on mechanistically indirect measurements.

5. **PRECLINICAL MATURITY:** 40 assets in lead selection and 19 in preclinical toxicology indicate near-term IND potential. PI3K/AKT upstream contains 56% of preclinical pipeline. 25 early-stage assets (discovery/lead optimization) signal sustained innovation.

mTOR pathway non-oncology landscape spans 144 assets

Preclinical stages show granular breakdown—84 assets before Phase I with detailed staging



- 144 mTOR pathway assets target non-oncology indications (expanded from direct mTOR to full pathway: PI3K/AKT upstream, TSC1/2, mTORC1/2, downstream effectors)
- 84 preclinical assets with granular staging: 9 discovery, 16 lead optimization, 40 lead selection/candidate nominated, 19 preclinical toxicology/IND-enabling
- 36 clinical-stage assets across Phase I through Phase III, with 17 approved products (primarily device coatings like sirolimus-eluting stents)
- All assets are pure non-oncology focused—oncology co-development programs excluded per stakeholder request for metabolic /neurodegeneration focus

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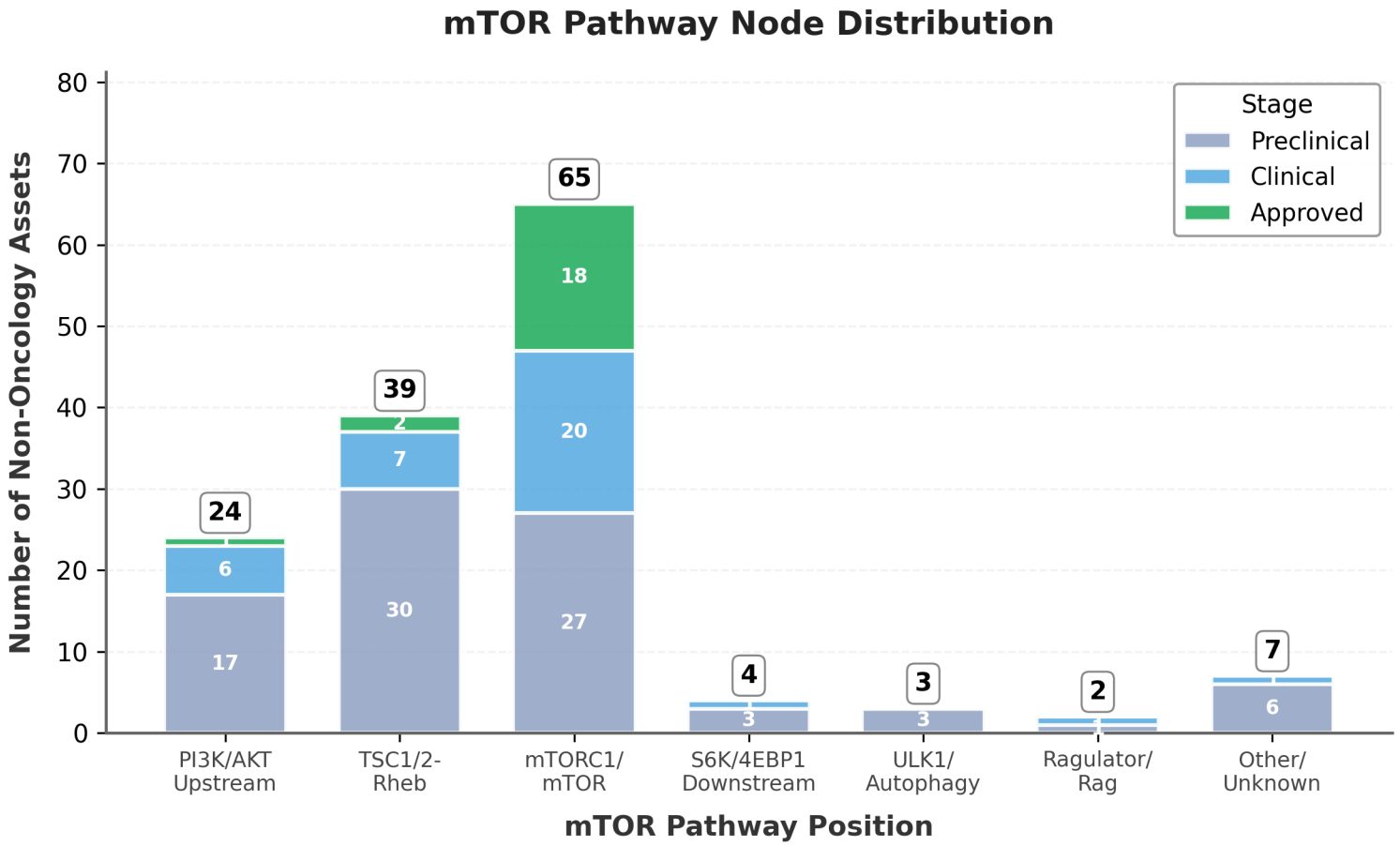
mTOR pathway modulation analysis; 301 total assets, 144 non-oncology; Q4 2024 data

PI3K/AKT upstream leads non-oncology mTOR pathway with 60 assets

Direct mTORC1/mTOR inhibitors represent minority—pathway positioning reveals innovation spread



- 60 assets (42% of landscape) target PI3K/AKT upstream of mTOR complex. Reflects therapeutic hypothesis that upstream modulation offers better metabolic control than direct mTOR inhibition.
- 31 assets directly target mTORC1 or mTOR complex. Includes approved rapalogs and clinical dual inhibitors concentrated in clinical and approved stages.
- 21 assets target TSC1/2-Rheb axis showing emerging regulatory node interest. Split between preclinical (13 assets) and clinical (8 assets).
- Preclinical assets outnumber clinical 2:1 across all pathway nodes. Substantial early-stage innovation has not yet progressed to human testing.

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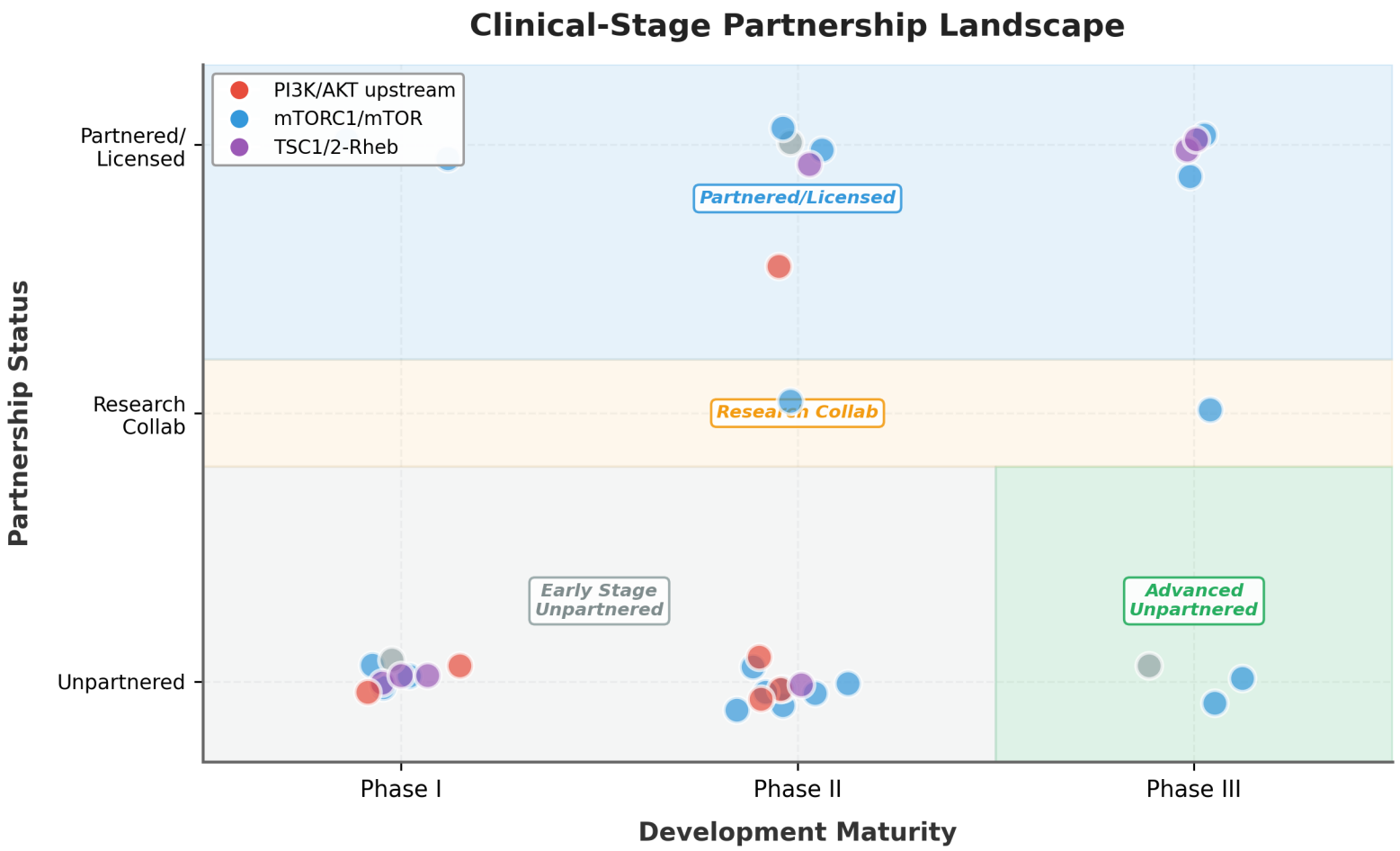
Non-oncology assets by mTOR pathway position; stage breakdown (preclinical/clinical/approved)

67% of clinical assets remain unpartnered despite Phase II-III maturity

Partnership status reveals licensing opportunities for advanced assets



- 36 clinical-stage assets mapped by partnership readiness: 24 unpartnered (67%), 8 partnered or licensed, 4 research collaborations.
- Phase II-III unpartnered assets represent near-term acquisition opportunities. Clinical validation complete with no competitive deal structures to navigate.
- Research collaboration zone indicates early partnership interest without full commitment. Potential for company to upgrade existing relationships.
- PI3K/AKT upstream assets show mixed partnership status reflecting mechanism uncertainty
- mTORC1/mTOR assets in Phase II represent highest-conviction targets.

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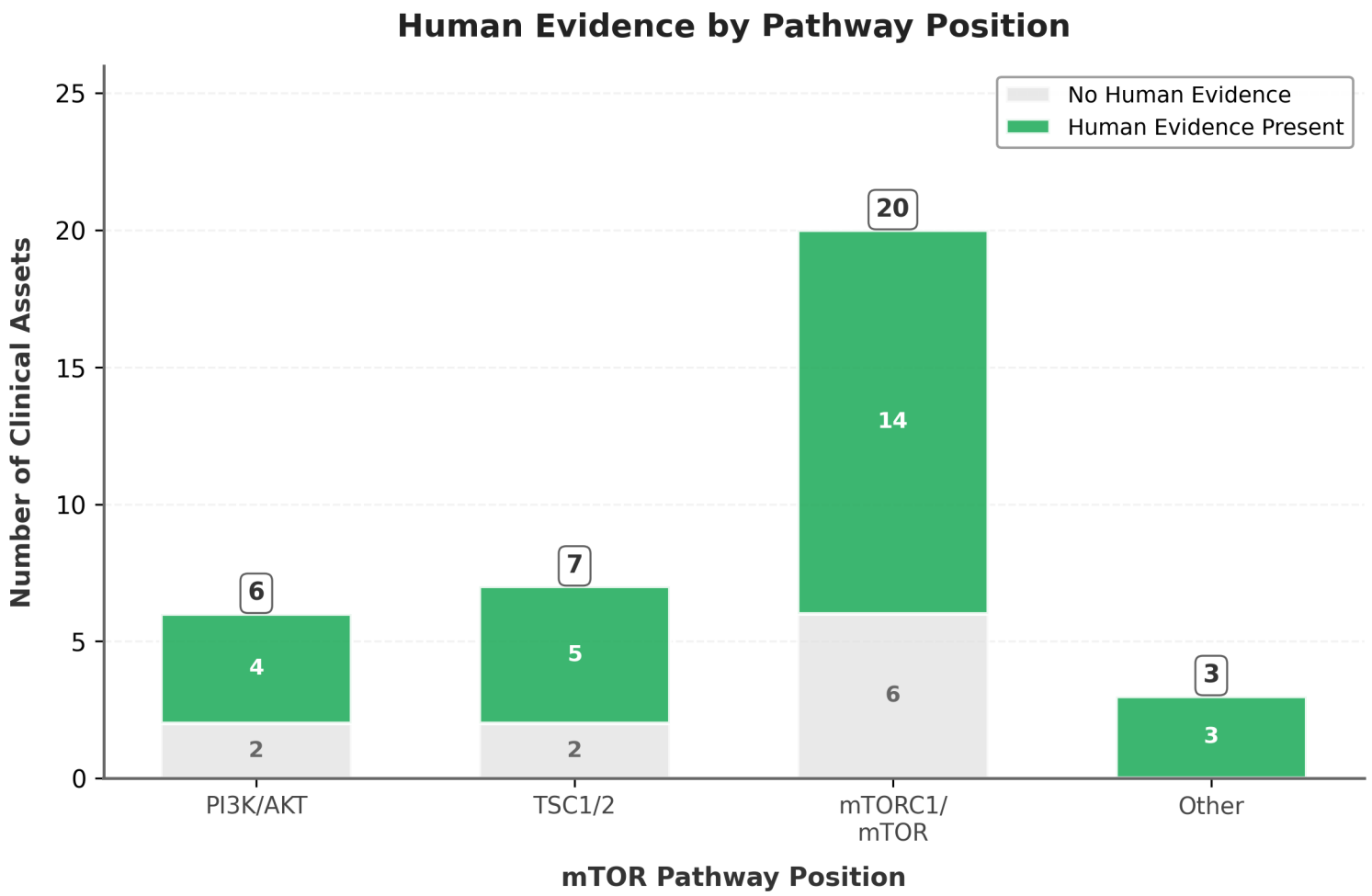
Clinical-stage assets only; partnership status Q4 2024; pathway node indicated by dot color

Human evidence present in 26 of 36 clinical mTOR pathway assets

Evidence concentrates in mTORC1/mTOR direct inhibitors



- 26 of 36 clinical assets (72%) have disclosed human evidence of target engagement or functional readouts. Includes patient data or healthy volunteer studies.
- mTORC1/mTOR direct inhibitors show highest evidence rate at 70% (14 of 20 assets). Historical rapalog clinical experience provides validation template.
- PI3K/AKT upstream programs show 67% evidence rate (4 of 6 assets). Upstream pathway measurements are mechanistically indirect.
- TSC1/2-Rheb axis shows 71% evidence rate (5 of 7 assets). Emerging node with growing clinical validation despite smaller asset count.

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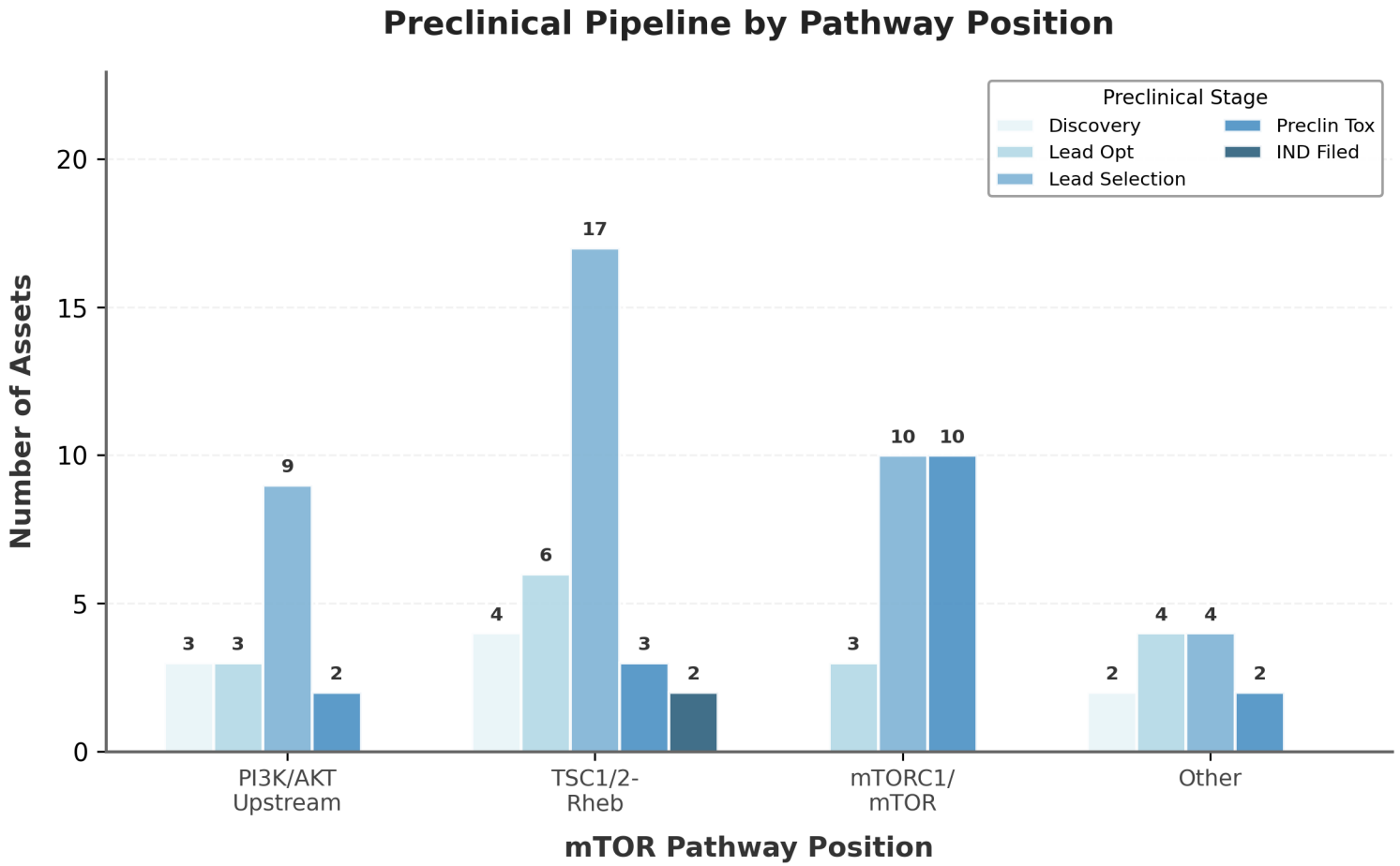
Human evidence = patient data or healthy volunteer studies; clinical-stage assets only (n=36)

84 preclinical assets concentrate in lead selection and optimization

PI3K/AKT upstream dominates early pipeline with 56% of assets



- 84 preclinical assets with granular breakdown: 9 discovery, 16 lead optimization, 40 lead selection / candidate nominated, 19 preclinical toxicology / IND-enabling.
- PI3K/AKT upstream contains 47 preclinical assets (56% of preclinical pipeline); heavy concentration in lead selection stage indicates near-term IND potential.
- mTORC1/mTOR direct inhibitors have 18 preclinical assets distributed more evenly across stages and reflects sustained innovation in established target class.
- TSC1/2-Rheb axis shows 13 preclinical assets concentrated in early stages; discovery and lead optimization focus indicates emerging target

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Preclinical-stage assets only; granular staging per development milestones; n=84 total