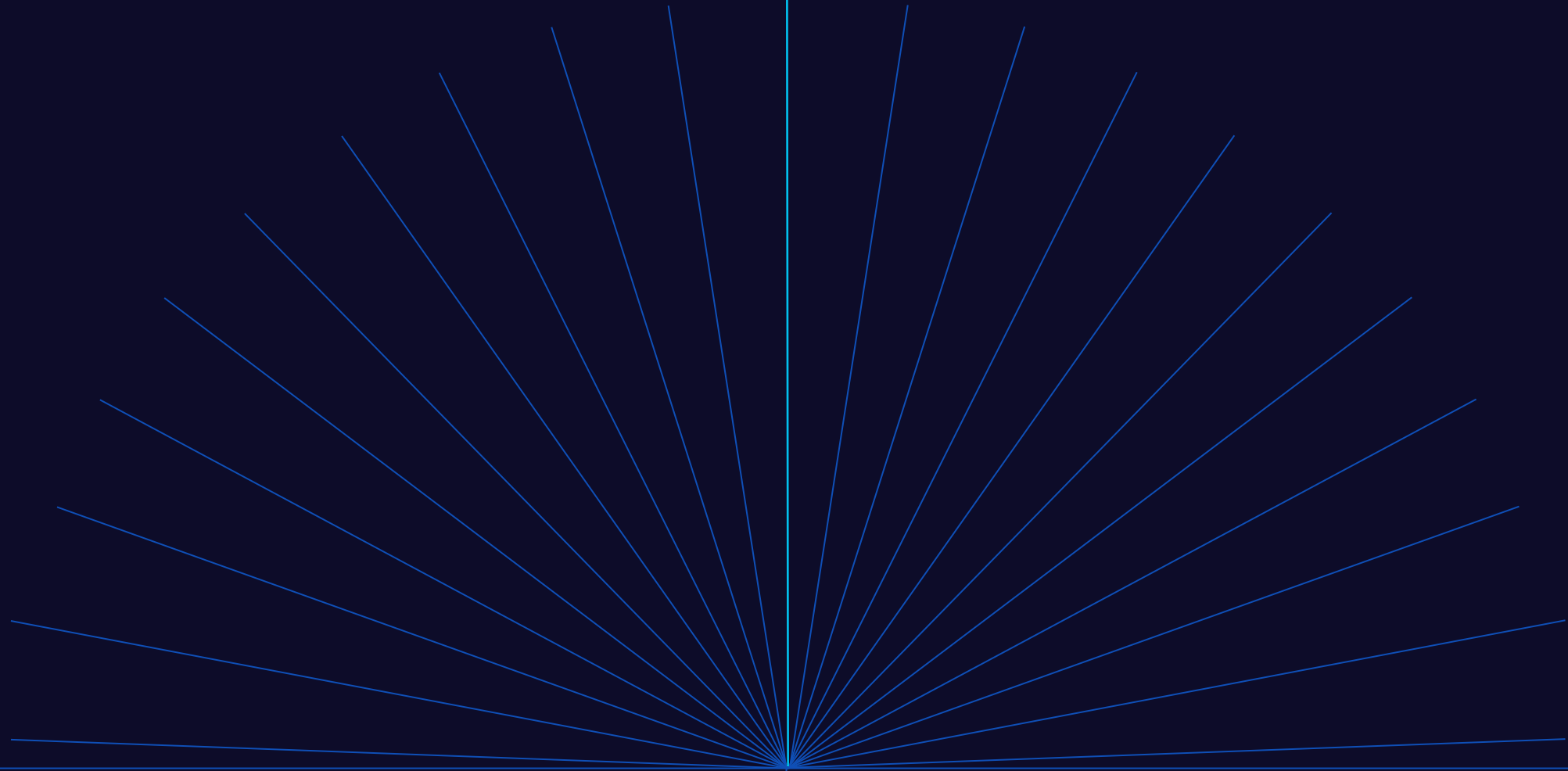




Sleuth

Sleuth Intel Hub
Protein Degraders Intelligence Report
Q3 2026

Table of Contents

Section 1: The Data

- Pipeline and landscape
- Mechanisms
- Degradation targets
- Where degraders have won
- Degradation deals

Section 2: Sleuth Perspectives

- Degraders and resistance
- Catalysts through 2027
- DAC deep dive
- CRBN glues vs new E3 ligases
- Sleuth predictions

+ **How Sleuth can help**

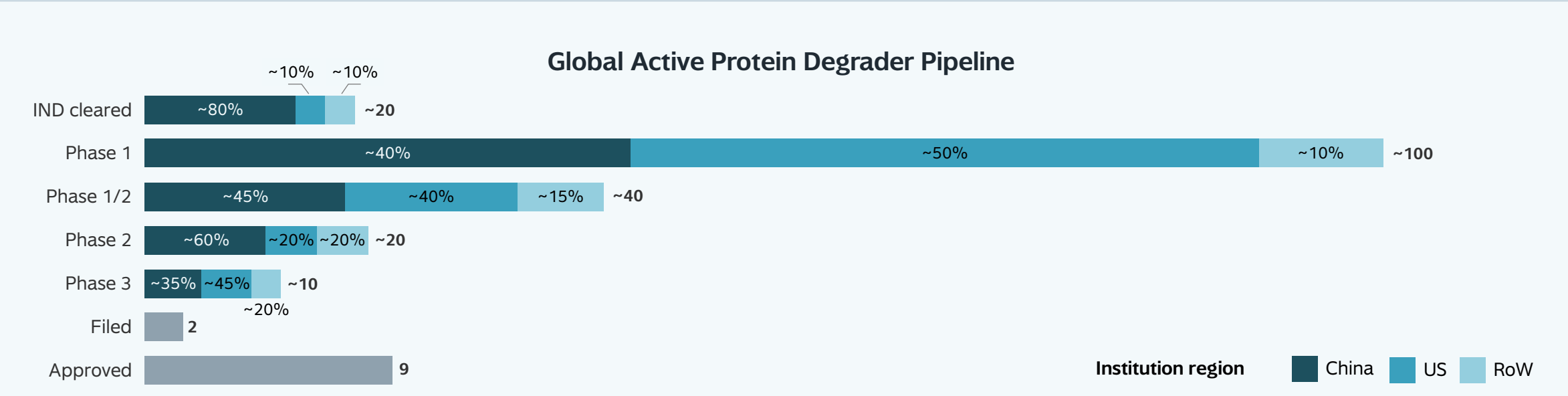


Section 1: The Data

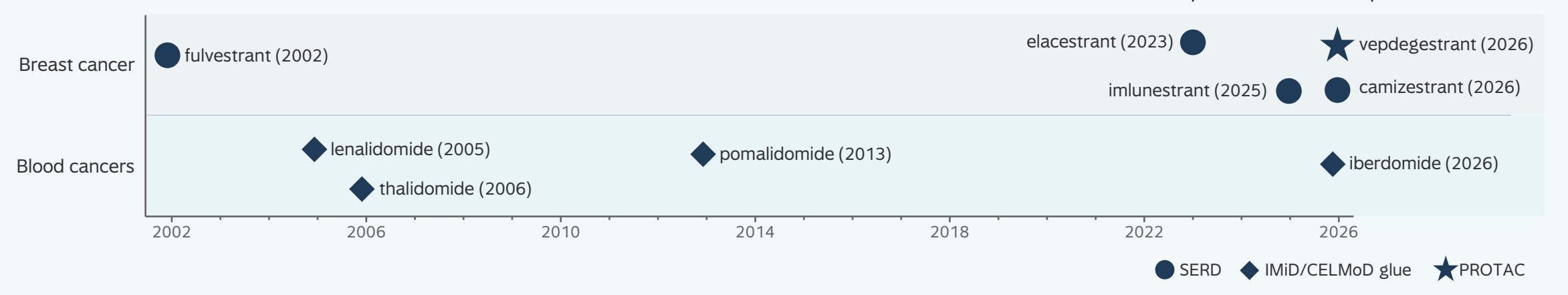


Of ~200 clinical degraders, approvals are centered in breast and blood cancers

SERDs and IMiDs came first; 5 of 9 cancer approvals came since 2023; PROTACs now lead cancer trials



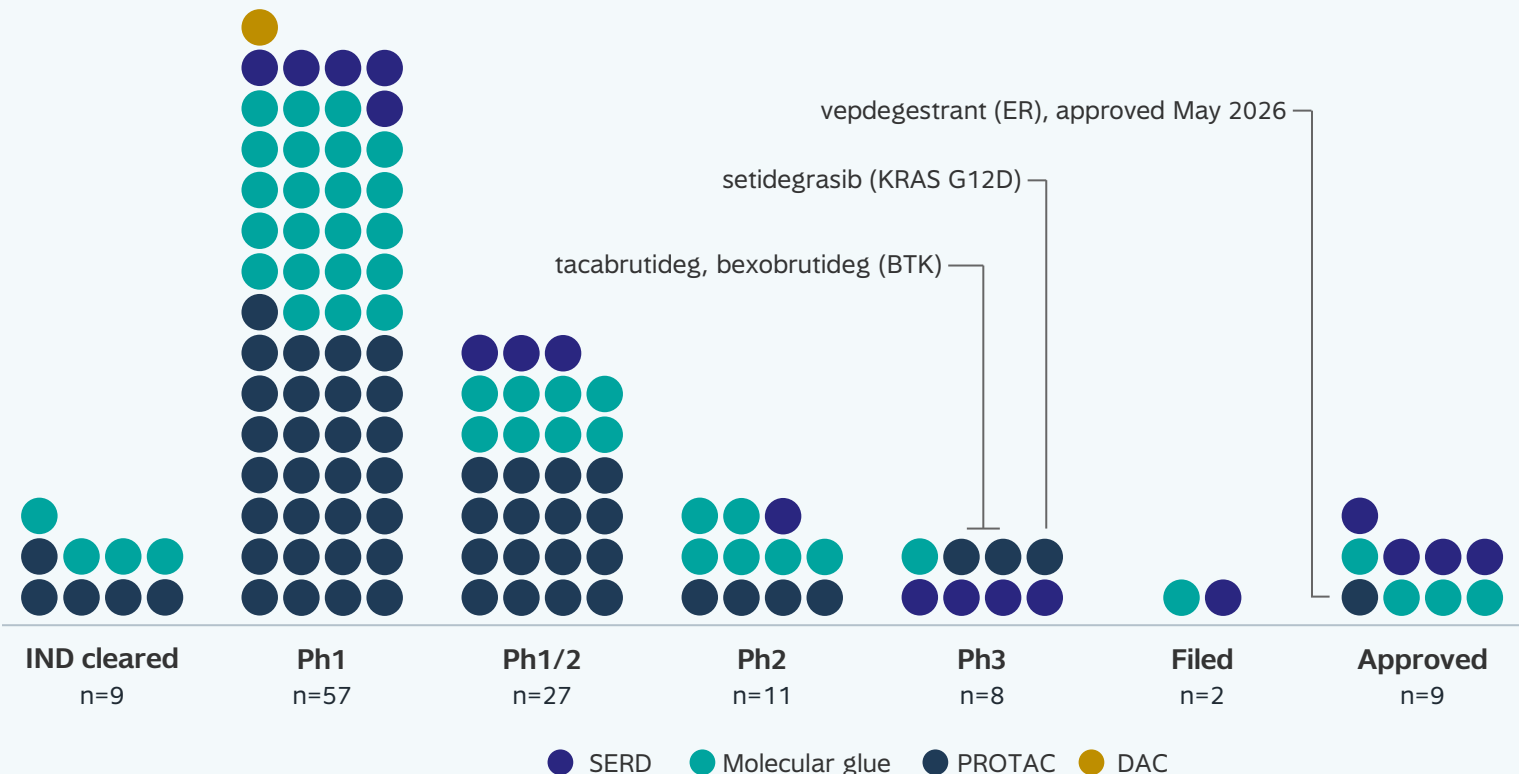
Approved degraders by year of first cancer approval



The first approved PROTAC brings catalytic degradation to ER, where SERDs led

Vepdegestrant is cancer's only approved PROTAC; 3 more PROTACs are in Phase 3 (BTK and KRAS G12D)

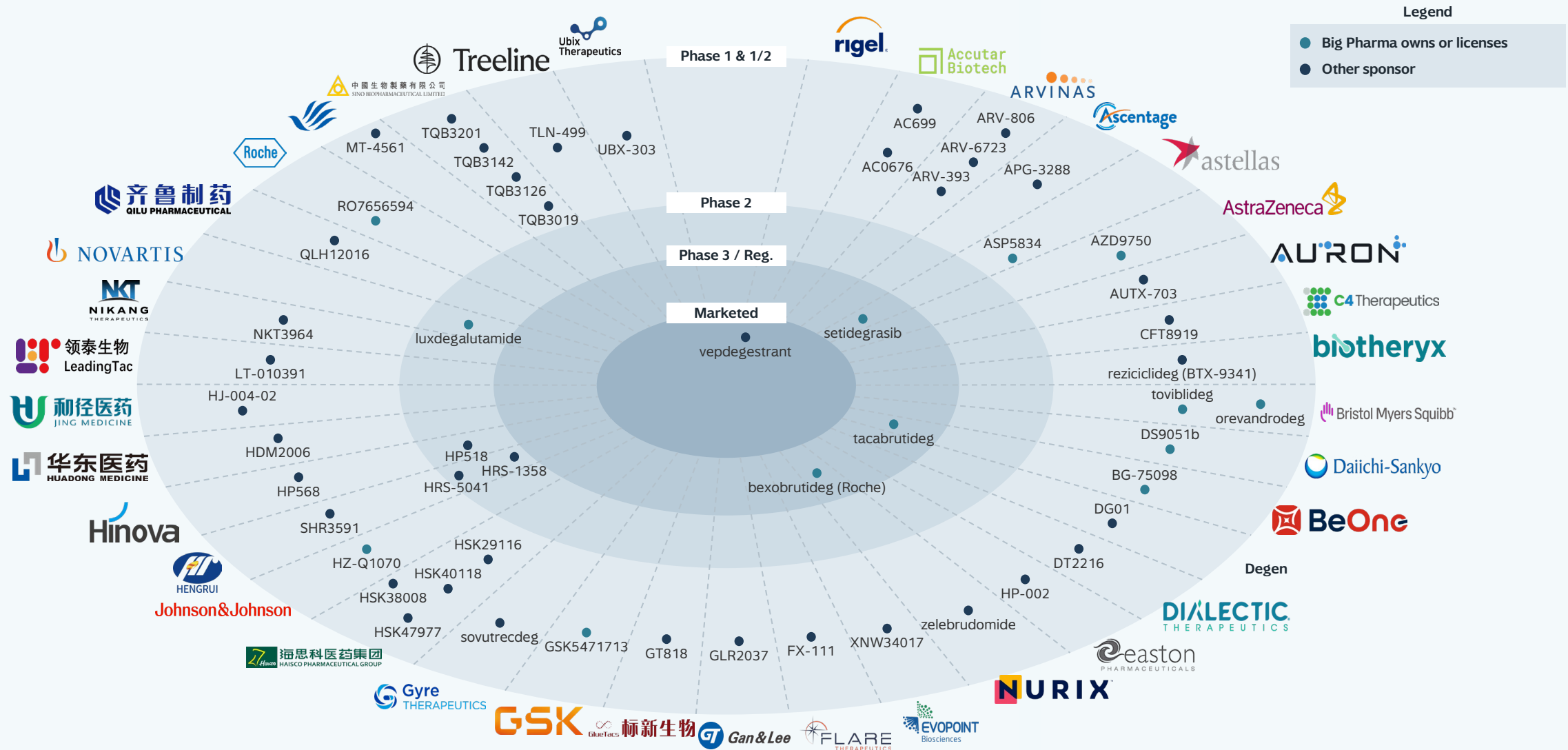
Key Degradation Mechanisms Across Clinical Development Stages



- Each SERD molecule breaks down one ER; all 3 oral SERDs won approval only in ESR1-mutant breast cancer (HR 0.44 - 0.62)
- IMiD glues aim cereblon at IKZF1/3 (myeloma, lymphoma) and CK1 α (del(5q) MDS); the 2 drugs filed are a SERD and a glue
- Vepdegestrant, recycled to clear many ER copies, beat SERD fulvestrant head-to-head only in ESR1-mutant tumors (HR 0.57)

Oncology PROTACs remain early, with 45 of 53 clinical assets in Phase 1 or 1/2

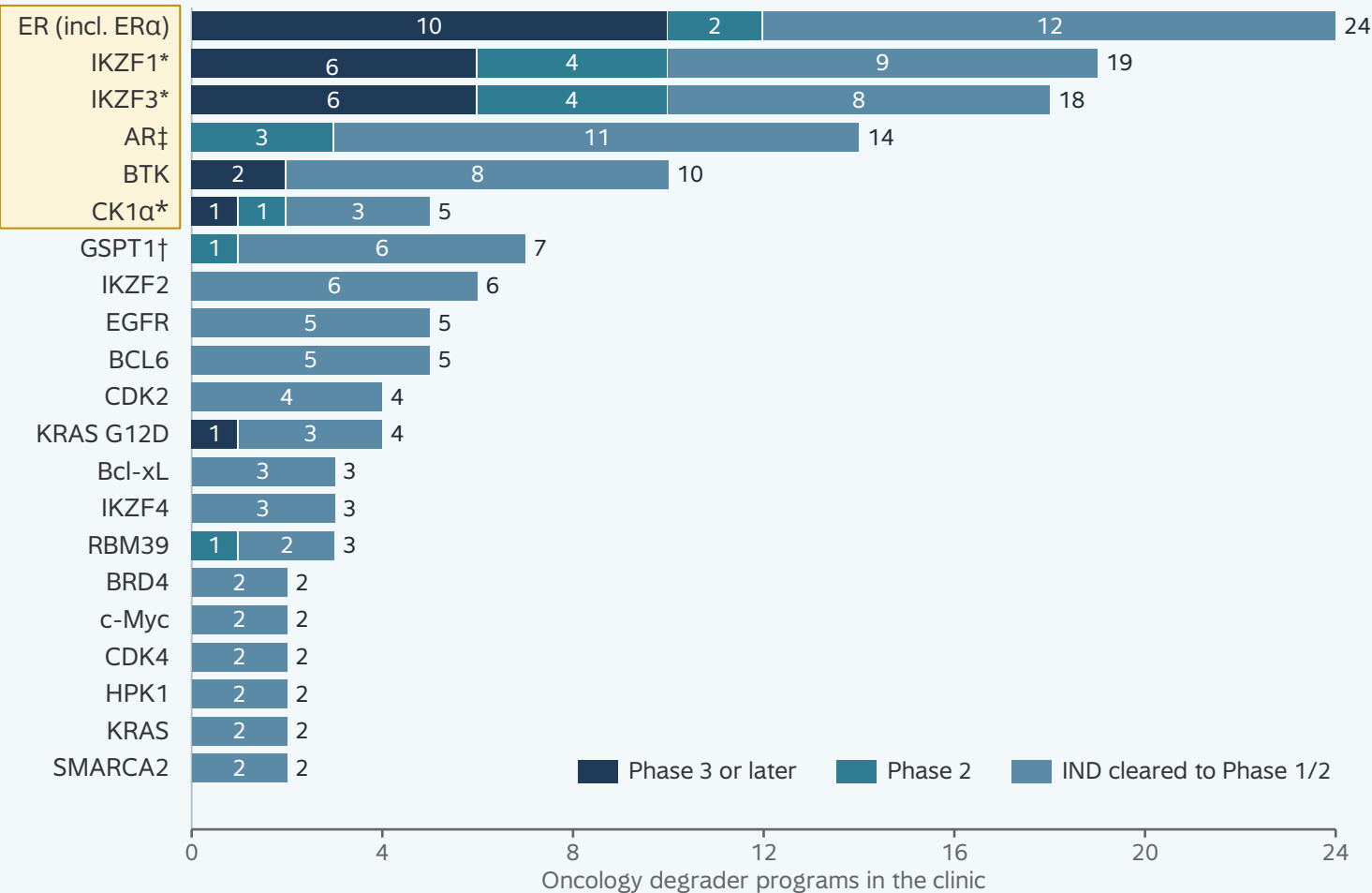
Only 4 have reached Phase 3 or market, all at BTK, ER or KRAS G12D, and Big Pharma holds 13 of the 53



Late-stage degraders cluster in four target families where resistance is proven

ER, IMiD targets, AR and BTK hold 45% of the 150 cancer degraders, where removal can bypass resistance

Clinical-stage oncology degraders by target and phase



- Mutations keep ER, AR and BTK working despite inhibitors; degraders remove the protein, though the first AR PROTAC missed L702H¹
- Blocked BTK still signals as a scaffold; bexobrutideg removes the whole protein: 83% ORR in CLL/SLL (median 4 prior lines)²
- All 4 approved drugs at IKZF1/3 and CK1α are glues (no approved inhibitor for these targets); some tumors resist by losing cereblon³

¹ Tumors resist AR drugs through mutations where the drugs bind, and BTK drugs through the mutations C481S, L528W and T474I. The first AR PROTAC, bavdegalutamide (ARV-110), broke down AR with the L702H mutation poorly. ² BTK passes on B-cell growth signals partly as a scaffold, so BTK with a blocked enzyme keeps signaling. Bexobrutideg Phase 1a: 39 of 47 patients (83%) with relapsed CLL/SLL responded after a median of 4 earlier treatments; median PFS 22.1 months (EHA 2026). ³ All 4 approved drugs at IKZF1/3 and CK1α are glues (thalidomide, lenalidomide, pomalidomide, iberdomide); tumors resist them by weakening cereblon. * The same glues hit IKZF1, IKZF3 and CK1α, drugs are counted uniquely in the 45% calculation. Active cancer degraders in the clinic, Sep 2026; a drug with several targets appears in each of its rows. † Includes ORM-1153, an antibody that delivers a degrader. ‡ Includes orevandrodeg (BMS-986460) and HSK38008 (hits AR-V7).

Degrader approvals are concentrated in validated targets

Of the other 9 validated targets, none has positive Phase 3 data yet; BTK and KRAS G12D are closest

How far the furthest degrader has got at each target

	Approved non-degrader?	Degrader in the clinic	Demonstrated response	Positive Phase 3	Still in development
Degrader approvals					
ER	✓	●	●	Positive	✓
IKZF1/3 and CK1α‡ (IMiD targets)	✗	●	●	Positive	✓
Validated targets without positive Phase 3 degrader data					
BTK	✓	●	●	Underway	✓
KRAS G12D†	✓	●	●	Underway	✓
AR	✓	●	●	Stopped before results	✓
CDK4/6	✓	●	●	P3 not reached	✓
BRAF V600	✓	●	●	P3 not reached	✗
EGFR, TRK, EZH2	✓	●	○	P3 not reached	✓
RET	✓	○	○	P3 not reached	✓
Targets without approvals					
BCL6	✗	●	●	P3 not reached	✓
GSPT1	✗	●	●	P3 not reached	✓
IKZF2	✗	●	●	P3 not reached	✓
SMARCA2	✗	●	●	P3 not reached	✓
STAT3, MDM2	✗	●	●	P3 not reached	✗
BRD9	✗	●	●	P3 not reached	✓

● Reached ○ Not yet reached
Responses in patients = a degrader has disclosed tumor responses (partial or complete; a 50% PSA fall in prostate cancer)
Positive Phase 3 = a degrader met its main goal in a Phase 3 trial
Still in development = an active company program, clinical or preclinical

- A proven target is not enough: 3 oral ER degraders missed first-line Phase 3 goals, and BMS stopped its AR Phase 3
- BTK leads drugged targets: 83 - 85% responded after BTK inhibitors, and 2 degraders are in Phase 3; KRAS G12D is next (24%)
- No degrader is in Phase 3 at the 7 targets with no approved drug: 4 lost their lead, but BCL6’s BMS-986458 hit 65% in lymphoma

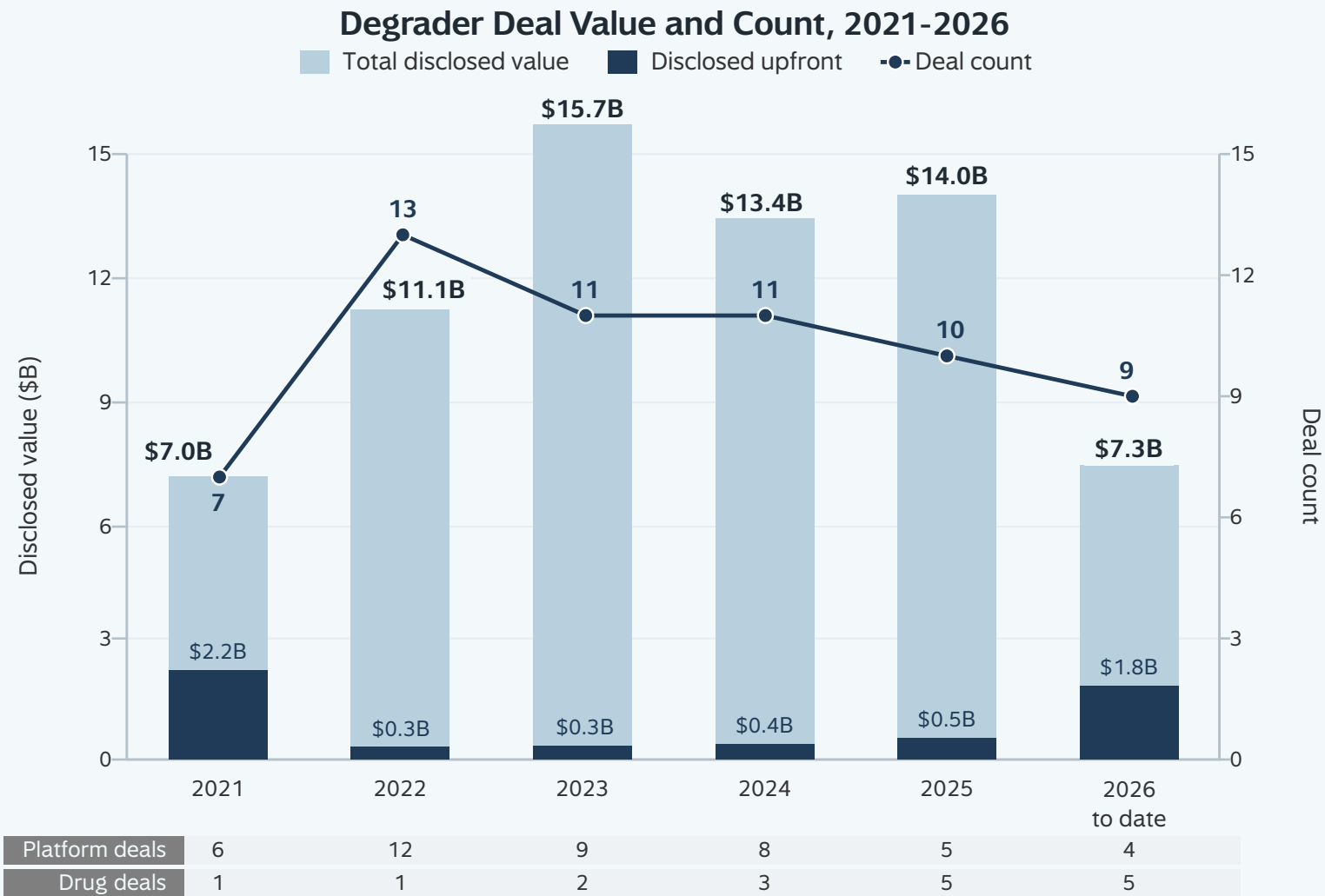


‡ Via lenalidomide in del(5q) MDS; newer CK1α degraders are earlier-stage. † KRAS G12D: the approved non-degrader drug is daraxonrasib, a RAS(ON) tri-complex inhibitor (a non-degrading molecular glue), approved Aug 2026 in metastatic pancreatic cancer after prior therapy.

Most degrader deals bought platforms, while upfront cash followed clinical proof

2 platform buyouts and 6 deals for clinical or approved drugs took 77% of the \$5.6B paid upfront

- Arvinas’s 2019 - 20 patient data validated designed degraders, and deal flow followed: 13 deals in 2022, 12 of them platforms¹
- Glues won 22 of 45 deals in 2022 - 25 on the IMiDs’ proof, but new glue targets must be found by screening, so upfronts stayed small (\$49.5M median)
- Platforms took 27 of 31 deals in 2021–23; as more degraders reached late-stage and approvals



¹ Arvinas reported PROTAC clinical data in Oct 2019 (safety and drug levels) and vepdegestrant ER-removal data in Dec 2020 (up to 90%, average 62%).

Section 2: Sleuth Perspectives



Degraders help resistant patients only when the tumor still needs the target

Of 10 degraders stopped where a drug is already approved, 6 had been tested in patients resistant to it

Target	Key degrader result	Tumor still needs it	Other drugs cannot reach it	Outlook
ER hormone receptor	4 oral degraders approved (ESR1-mutant)	Yes	Yes: aromatase inhibitors lose effect once ESR1 mutates	Won
BTK	83–85% response after BTK inhibitors; 2 in Phase 3	Yes	Yes: mutant BTK keeps signaling	Bet: approval by end-2027
BCL6	65% response (N=48), Phase 1/2	Yes	Yes: every BCL6 drug in trials is a degrader	Bet: a second degrader confirms
KRAS G12D	24% response, later-line pancreatic; 2 Phase 3 trials started	Yes	No: daraxonrasib approved	Watch
GSPT1	MRT-2359: 2 of 5 partial responses (1 confirmed); early programs stopped ¹	Yes, but so do healthy cells	Yes	Watch
AR hormone receptor	43% PSA response (n=47) ² ; BMS Phase 3 stopped	Often, but some tumors stop needing AR	Mixed; most AR degraders miss AR-V7 (HSK38008 targets it)	Watch

- Mutant ER still drives ESR1-mutant breast cancer, so removing it works (HR 0.57); late prostate tumors can grow without AR
- **Sleuth Insight:** BD teams focus on degraders where the tumor still needs the protein and current drugs fail: mutant BTK escapes inhibitors yet keeps signaling, and BCL6 has no approved inhibitor; KRAS G12D is a weaker bet in pancreatic cancer where daraxonrasib already blocks active RAS in later-line



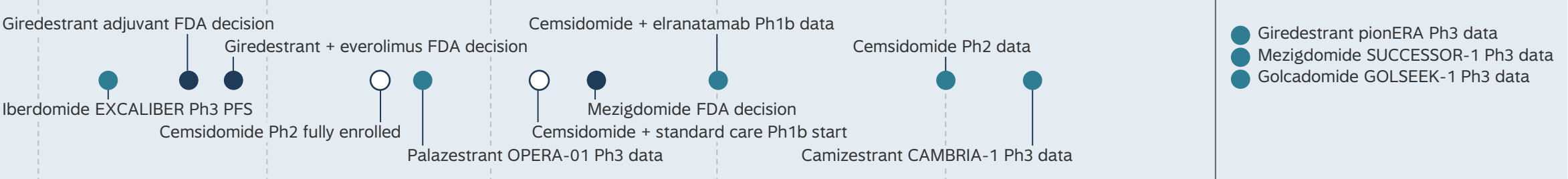
¹ GSPT1: the lead degrader stopped in AML and in both dosed antibody-conjugate programs. MRT-2359 is now developed only in AR-mutant prostate cancer; its responses shown are with enzalutamide (ASCO GU 2026). ² Luxdegalutamide, in men whose tumors carry AR mutations (ASCO 2024). KRAS G12D: setidegrasib, 5 of 21 (NEJM 2026); 36% in lung. BTK: bexobrutideg 83% (39 of 47; median PFS 22.1 months) and tacabrutideg 85% (57 of 67), both EHA 2026. 6 of 10: disclosed degrader stops at targets with an approved cancer drug; 5 were tested after an approved inhibitor and 1 in a group selected for resistance mutations. Response rates are single-arm and from separate trials. As of Sep 2026.

Through 2027, BTK is the only new target in reach of a first degrader approval

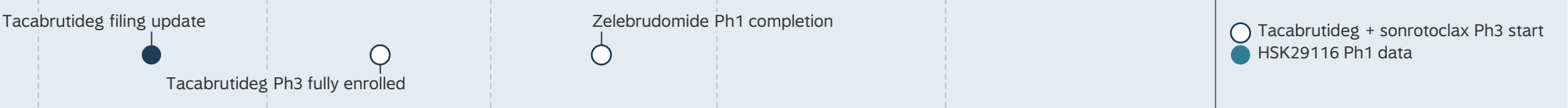
Of 29 key oncology degrader events, all 3 FDA decisions and all 6 Phase 3 readouts are in ER or IKZF1/3

Key Degrader Catalyst Calendar

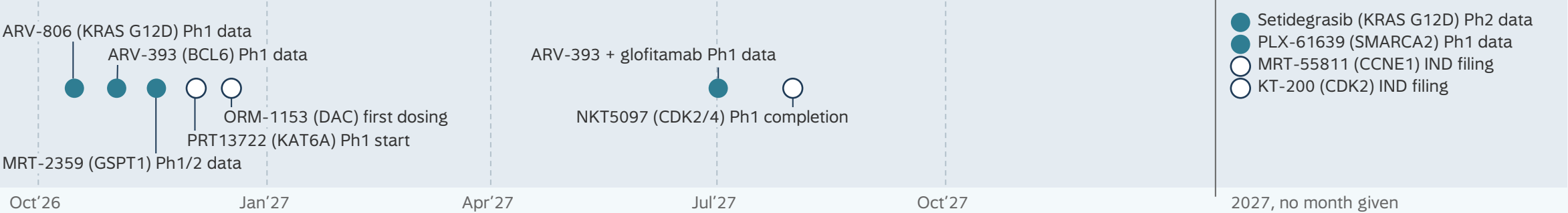
ER & IKZF1/3: Targets with an approved degrader



BTK: Could get its first approved degrader



Early-stage events only: KRAS G12D, BCL6, GSPT1, CDK, DACs and other targets

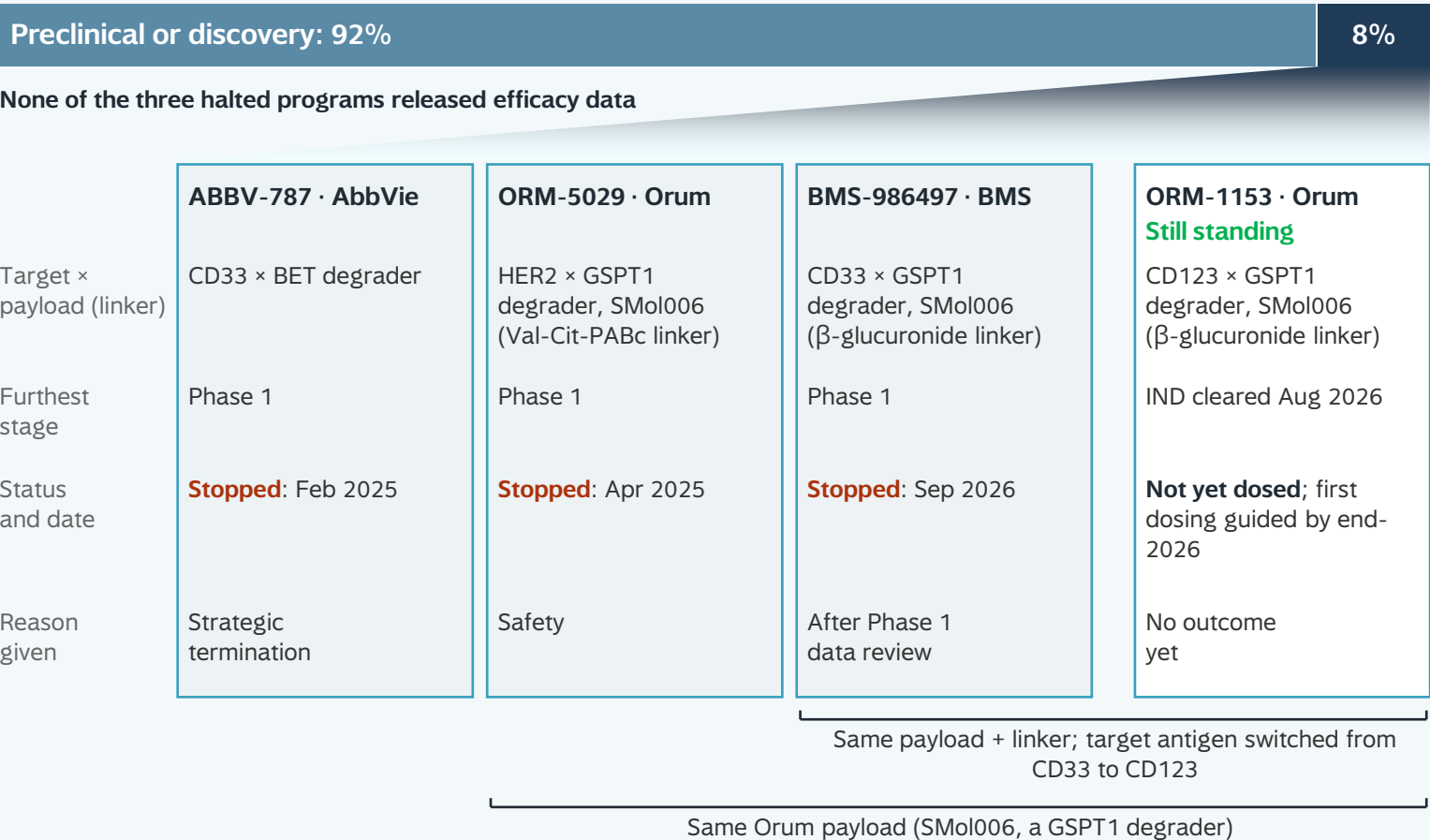


● Data readout (15) ● Regulatory / FDA (4) ○ Trial or IND milestone (10)

Degrader-antibody conjugates (DACs) are unproven, tested mostly on one payload

Of ~50 DAC programs, only 4 have reached the clinic and all 3 dosed stopped with no efficacy disclosed

Clinical Development of DAC Programs



- DAC thesis: an antibody carries a degrader too toxic to dose freely, like a GSPT1 glue, only into tumor cells with its antigen
- In the lab, ORM-6151 beat CC-90009 against AML cells at picomolar doses yet spared normal blood cells; BMS paid \$100M upfront
- **Sleuth Insight:** GSPT1 stalled as a free drug in AML and in both dosed DACs that carried it, so the stops may reflect the payload. J&J paid \$1B for Firefly’s KRAS-degrader DACs, yet BD teams should keep GSPT1 DAC deals to options with small upfronts until ORM-1153 shows patient benefit.



In myeloma, stronger CRBN glues are the main answer to IMiD resistance so far

Most IMiD resistance leaves CRBN intact, and no active new-ligase degrader has shown a response yet

How often CRBN itself breaks in myeloma		What works: stronger CRBN glues after IMiDs		Alternative, early bet: degraders on a new E3 ligase (all cancers)					
At diagnosis	Rare ($\leq 2\%$)	mezigdomide · BMS		Drug	Sponsor	Ligase	Target	Stage	Patient data
		Phase 3 SUCCESSOR-2, n=479		Active (7)					
After lenalidomide fails	~1 in 5	76% lenalidomide-refractory		REC-1245	Recursion	DCAF15	RBM39	Phase 1/2	Safety only, n=16
		Median PFS 18.0 vs 8.3 months (HR 0.48)		ST-01156	SEED	DCAF15	RBM39	Phase 1	None disclosed
After pomalidomide fails	Almost 1 in 3	vs carfilzomib + dex alone		PLX-61639	Plexium	DCAF16	SMARCA2	Phase 1	None disclosed
		Filed, FDA goal date May 13, 2027		MT-4561	Tanabe	IAP	BRD4	Phase 1/2	None disclosed
		iberdomide · BMS		AMX-883	Amphista	DCAF16	BRD9	IND cleared	None disclosed
		Phase 3 EXCALIBER-RRMM, first 420 of 939		VVD-130037	Vividion	KEAP1	NRF2	Phase 1	None disclosed
		≥ 1 prior line, incl. a proteasome inhibitor and an IMiD		E7820	Eisai	DCAF15	RBM39	Phase 2	0 of 12, AML
		MRD-negative complete response 41% vs 21%		Older or stopped (2)					
		vs daratumumab + bortezomib + dex		indisulam	Eisai	DCAF15	RBM39	Phase 2	35% with chemo (AML)
		FDA accelerated approval, Aug 13, 2026		tasisulam	Lilly	DCAF15	RBM39	Phase 3, stopped	3% vs 4.8% on chemo

- Cells have ~600 E3 ligases yet most clinical degraders recruit CRBN (VHL is second), leaving every CRBN drug exposed if a tumor disables CRBN or its machinery
- Stronger glues degrade IKZF1/3 more potently and work after IMiDs fail: 26 – 41% of heavily pretreated patients responded
- Sleuth Insight:** In myeloma, a new-ligase degrader's clearest role is the late-line minority whose CRBN has broken. BD teams should license new-ligase platforms as discovery options with small upfronts, and judge any new myeloma glue against mezigdomide's Phase 3 result



Sleuth predictions

Our read when we look beyond the data

- 1. BTK extends PROTAC approvals beyond ER:** Tacabrutideg and bexobrutideg produced responses in 83 – 85% of patients after BTK inhibitors, as they remove mutant BTK that continues to signal. An approval is likely by the end of 2027.
- 2. DACs are unlikely to progress without a new payload:** 3 of the 4 DACs that reached the clinic use the same GSPT1 payload, whose lead free drug also stalled in AML. Future DAC deals are likely to favor other payloads, such as KRAS, ER or PI3K α degraders.
- 3. New E3 ligases fit myeloma patients whose CRBN has broken:** Stronger CRBN glues remain active after IMiDs fail, and CRBN is altered in almost 1 in 3 patients after pomalidomide stops working. New-ligase degraders therefore suit this subgroup better than a broad replacement of CRBN.



How Sleuth can help



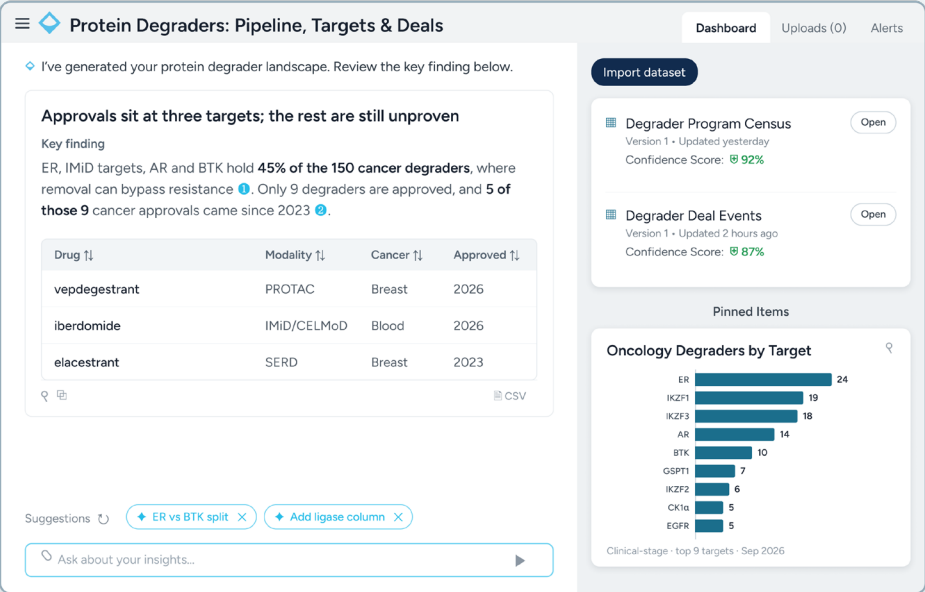
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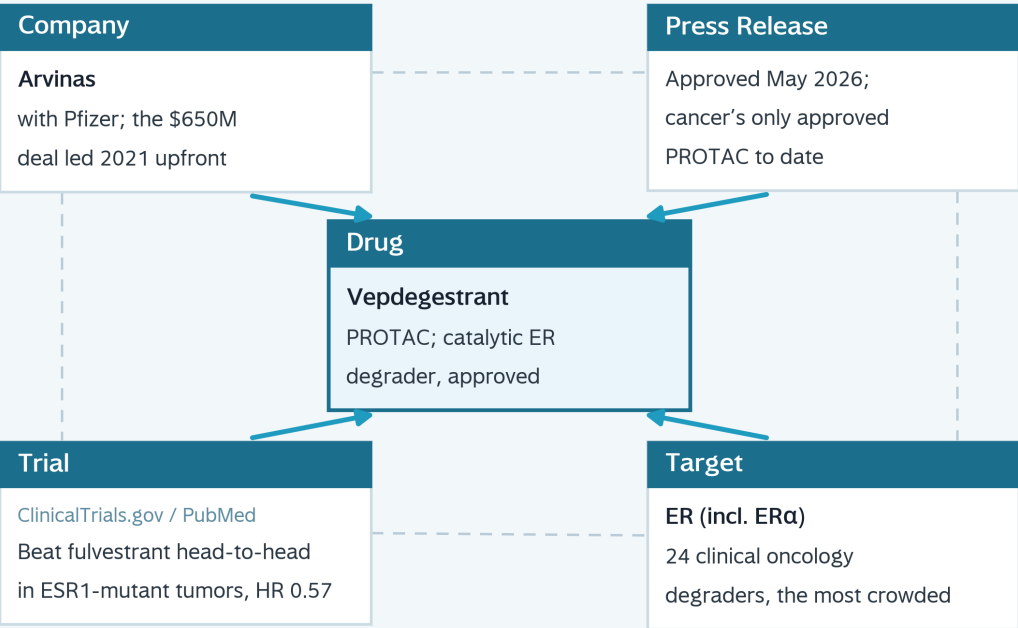
Main Takeaway: Degraders are proven at three targets and nowhere else yet. BTK is the next approval to watch, and it likely lands by the end of 2027.



Intelligence you can stand behind

Bring Sleuth your questions, and pre-connected intelligence surfaces automatically. Our knowledge graph connects data across the landscape, with full traceability.

Illustrative knowledge graph for vepdegestrant (ER)



Every claim traceable to source document



Case study: Epana Bio indication prioritization

What happens when you evaluate 167 indications with the same effort as six? [Read the full case here.](#)

Stakes: Epana Bio needed to make a high-stakes decision on which indications to pursue first for their targeted cell depletion therapeutics.

167 Indications evaluated

Challenge: Standard evaluation is often limited by bandwidth, forcing teams to choose from just a few familiar diseases.

25 Evaluated with a tailored Epana focus that most processes never reach

Approach: Epana ran a comprehensive evaluation of 167 indications, using an iterative framework to challenge scores and pressure-test every assumption.

4 Shortlisted for deep commercial diligence

Outcome: Leadership built the conviction needed to select lead indications and raise capital with an investor-ready narrative.

1 Optimized basket

“All the strategy that used to be proprietary to pharma — the ‘game within the game’ that actually drives strategic decisions — Sleuth made that accessible to a nine-person biotech. **I think it's the most disruptive, amazing thing for small organizations like ours.** A massive, massive unlock.”



Danny Wells, PhD
CEO, Epana Bio