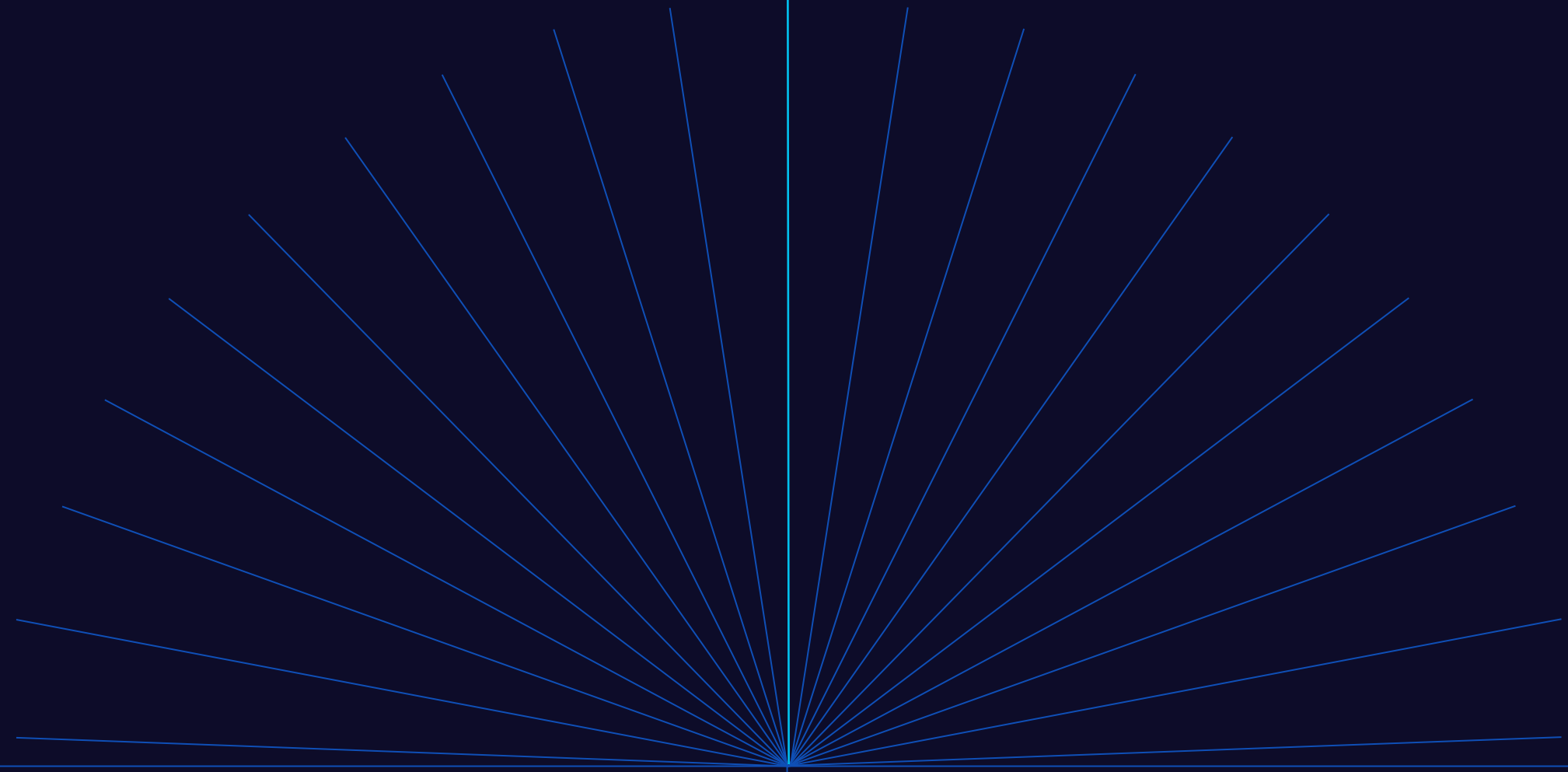
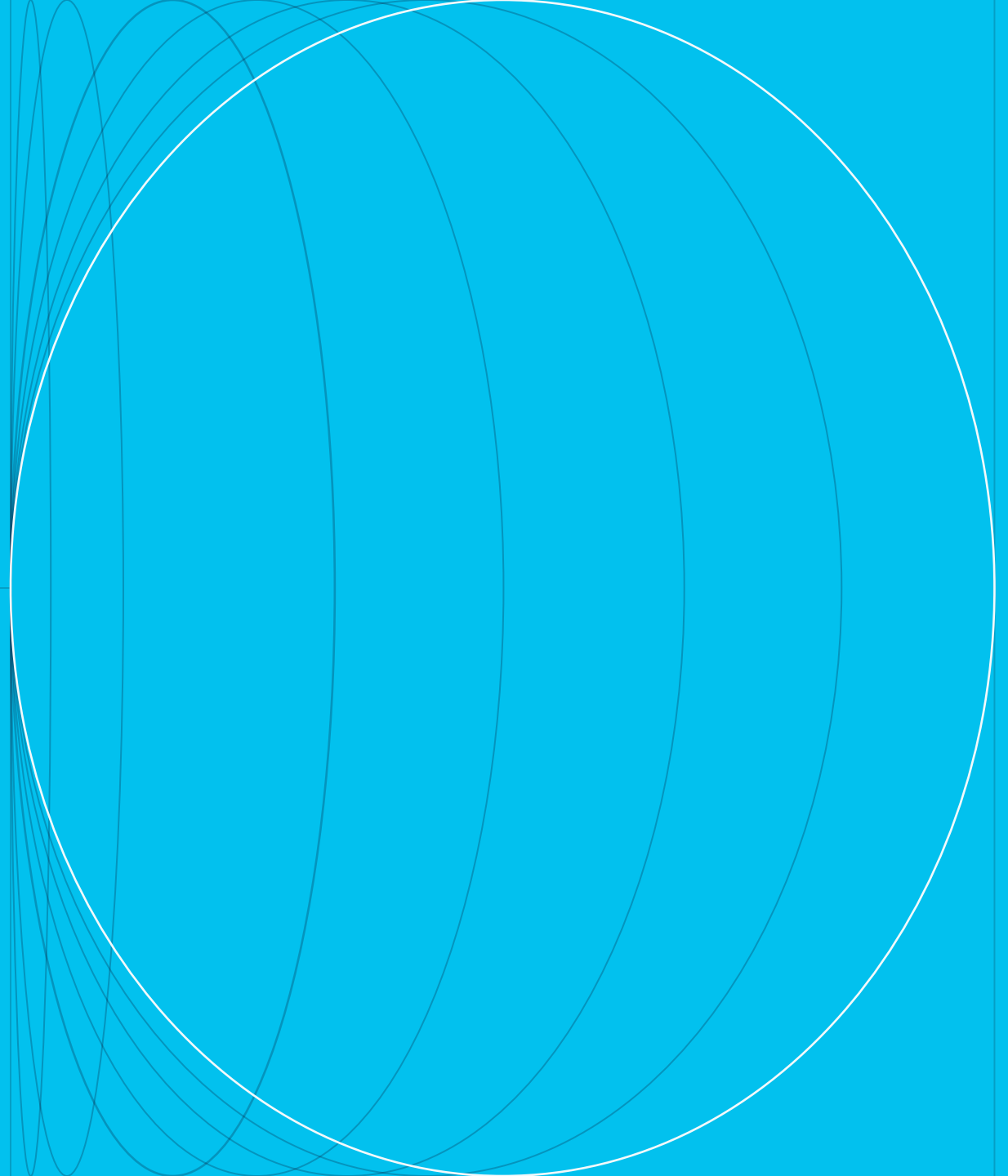


Sleuth

Sleuth Intel Hub
T-cell Engagers Intelligence Report
Q3 2026

Table of Contents

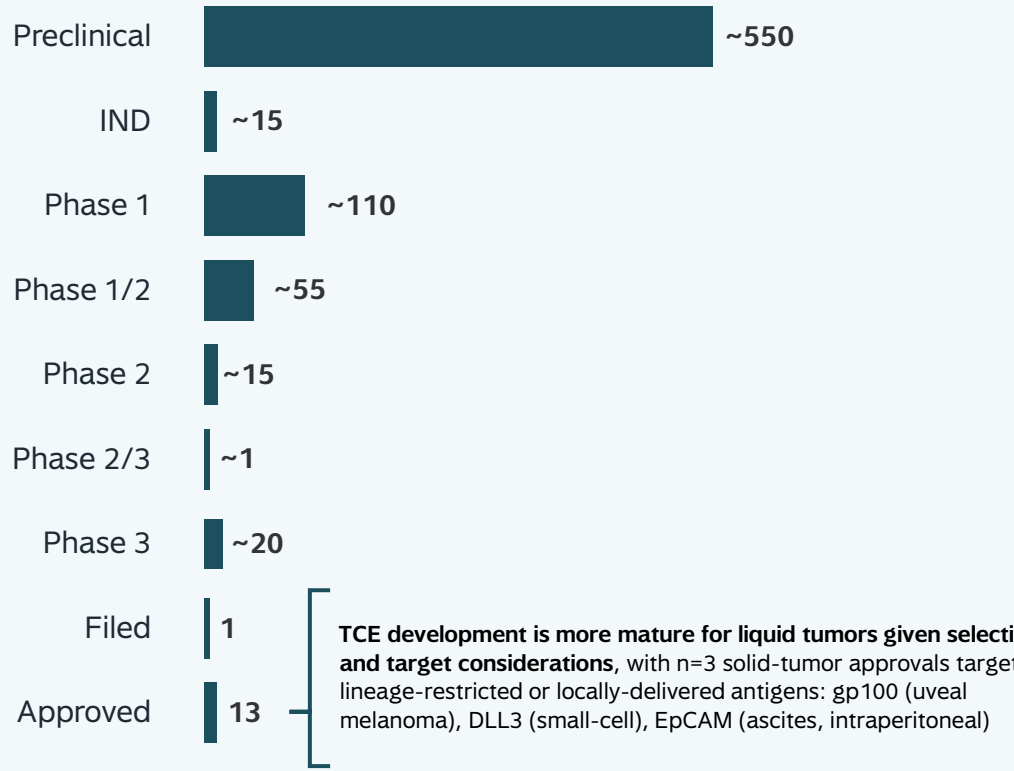
Section 1: The Data



Across ~770 TCE programs, 13 are approved but only 3 reach solid tumors

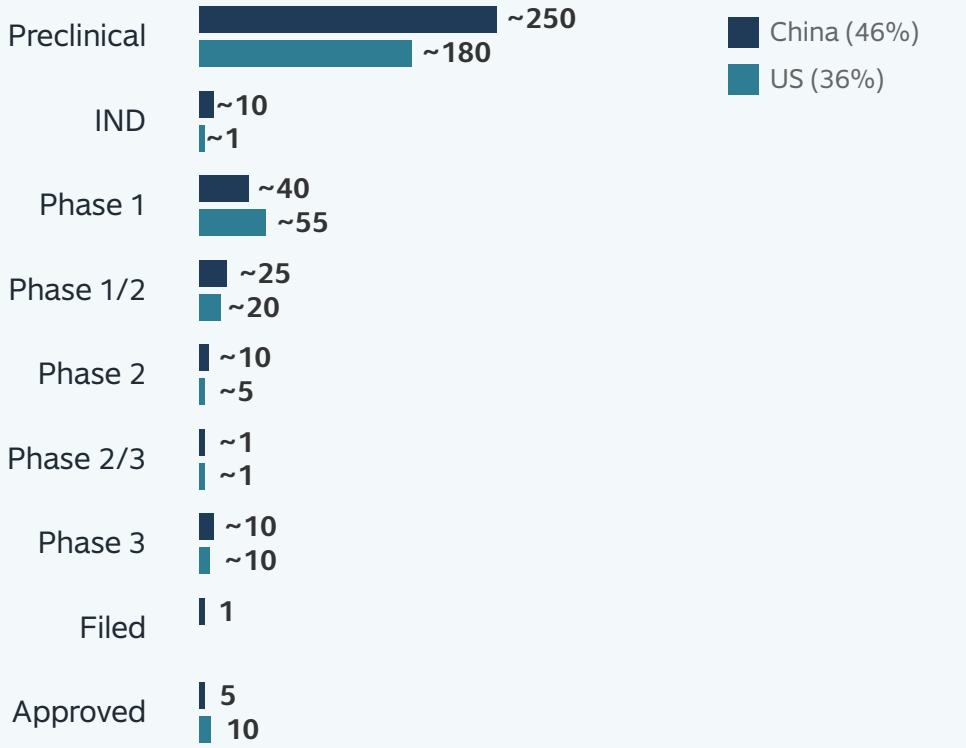
Approvals are heme-anchored: 10 of 13 are blood cancers, only 3 reach solid tumors

Global active pipeline (n=~770 programs)



TCE development is more mature for liquid tumors given selectivity and target considerations, with n=3 solid-tumor approvals targeting lineage-restricted or locally-delivered antigens: gp100 (uveal melanoma), DLL3 (small-cell), EpCAM (ascites, intraperitoneal)

China vs. US Clinical Volume



Bispecific ~500 : Trispecific ~160

~450 developers

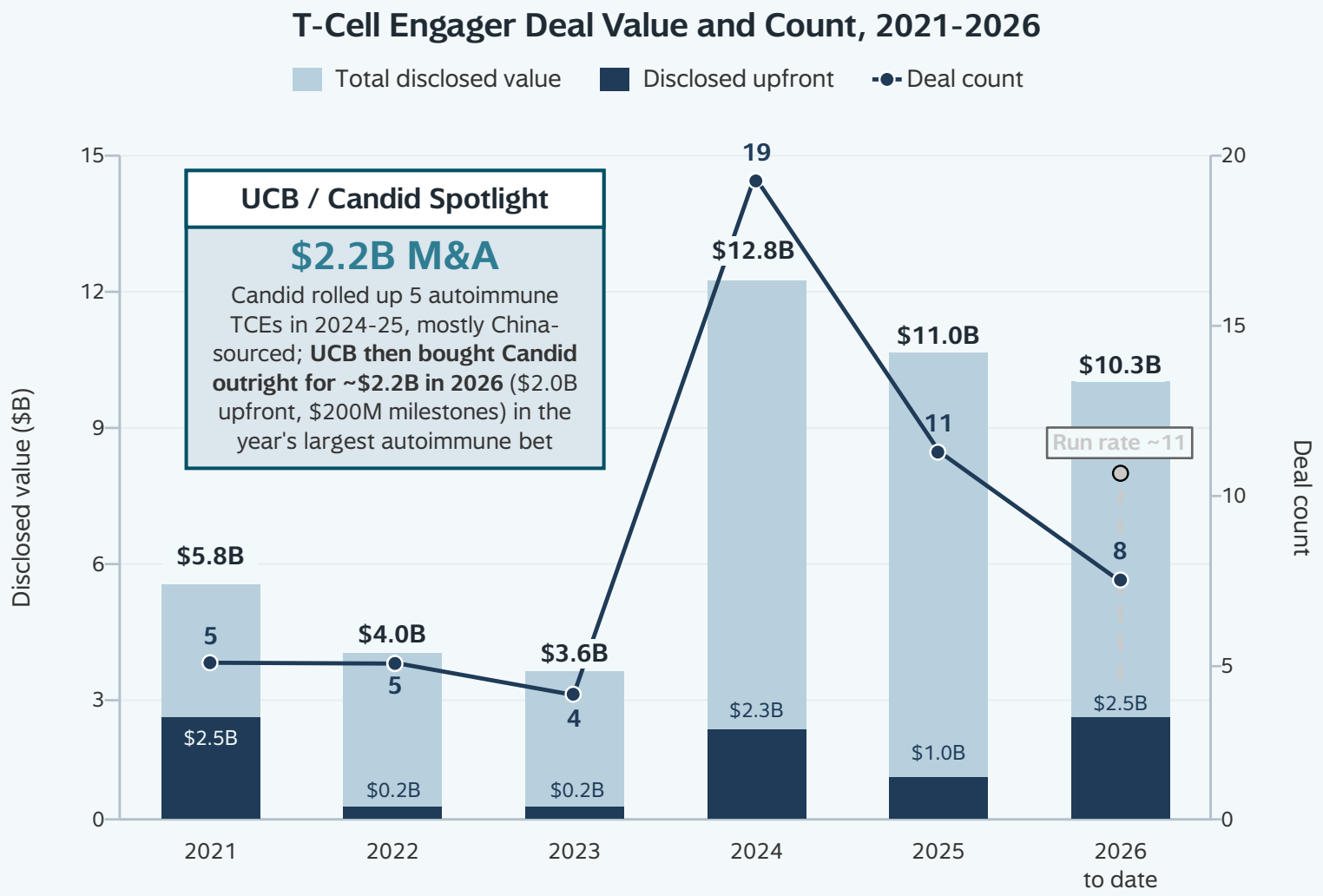
China ~360 / US ~280 / RoW ~130

T-cell engager pipeline as of Sep 2026.

Dealmaking peaked in 2024 as capital shifted to B-cell autoimmunity

Autoimmune went from zero deals before 2024 to the field's busiest new lane, 13 of 16 China-sourced

- Capital concentrated on B-lineage-depletion targets: BCMA (11), CD19 (8), CD20 (5) deals, well ahead of solid-tumor targets (PSMA / EGFR / DLL3 / HER2, 2-4 each)
- Autoimmune overtook heme: its 16 deals more than doubled heme's seven, with China-origin sellers accounting for 40% of activity
- Deal structure stayed mixed every year, with M&A recurring throughout (12 deals, 5 in 2024) rather than an acquire-early, license-late shift



Licensing and M&A deal-events, Jan 2021 to Sep 2026; disclosed upfronts and total consideration where reported; 2026 is year-to-date; GSK-Chimagen deal included.

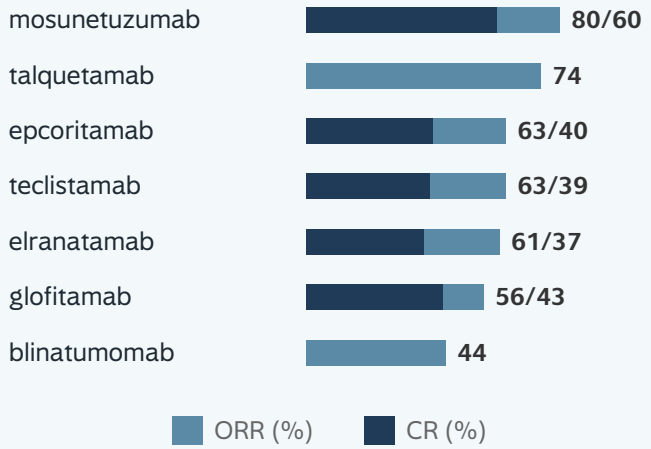
The clinical bar varies across heme, solid, and I&I based on targets & dev. maturity

Heme response is proven, solid wins only on clean targets, and immunology's deep B-cell reset is the open frontier

Representative Cross-trial Comparisons

Liquid tumors

TCEs drive strong response and up to ~2-year durability in heme, though tolerability poses the key barrier (e.g., cytokine storm, infections)



Key takeaway: TCEs set a high response bar in heme, shifting the next TCE's value story towards how their construct drives tolerable response

Solid tumors

TCEs reach solid tumors only on clean targets and win on survival, not response; shared antigens still stall conventional constructs (e.g., off-tumor toxicity)

tarlatamab (DLL3)

HR 0.60, ORR 35%

tebentafusp (gp100)

HR 0.51, ORR 9.1%, mOS 21.7mo

Key takeaway: solid-tumor is a construct question: masking shows early responses where unmasked failed (PSMA 82% vs 30%), none durable yet

Immunology

TCEs are early but show early signs of deep, CAR-T-like B-cell depletion / response; safety remains a key question for non-fatal disease (i.e., CRS, infections, hypogamm.)

Human data across five engagers:

CLN-978 (CD19)
SLE: 82% B-cell depletion, 71% response

Cizutamig (BCMA)
SSc: near-complete marrow plasma-cell depletion

A-319 (CD19)
SLE: DORIS remission 6/10, LLDAS 8/10 (12mo)

CC312 (CD19)
SLE: 100% CD19+ plasma-cell depletion (20µg); SRI-4 5/6 (wk36)

Velinotamig (BCMA)
Lupus nephritis: 2 of 2 renal response

Safety so far: CRS mostly grade 1*

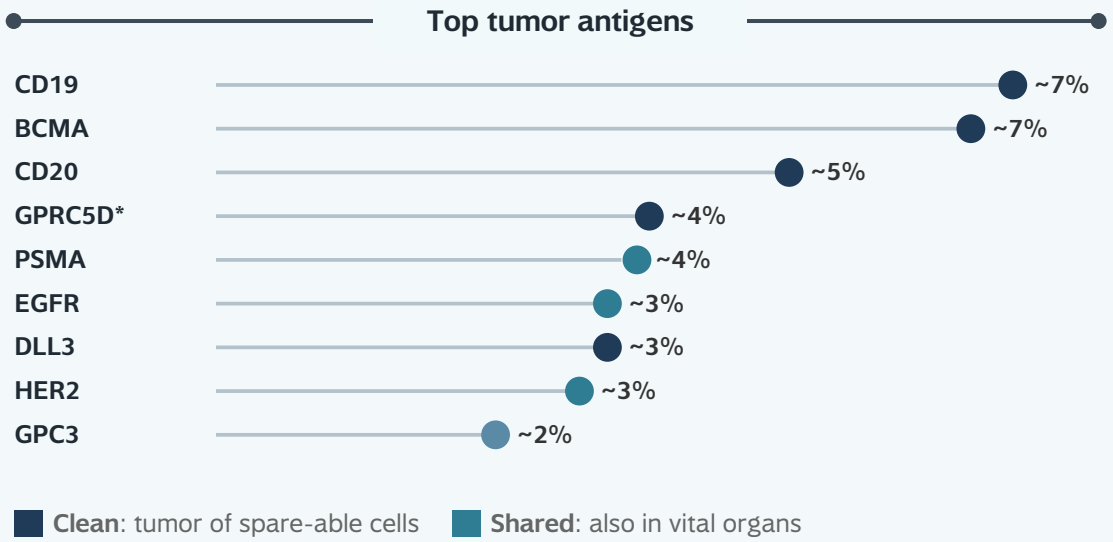
Key takeaway: the white space is off-the-shelf, drug-free reset; attenuated, SubQ, masked designs fit a non-fatal disease's safety bar, but durability stays unproven

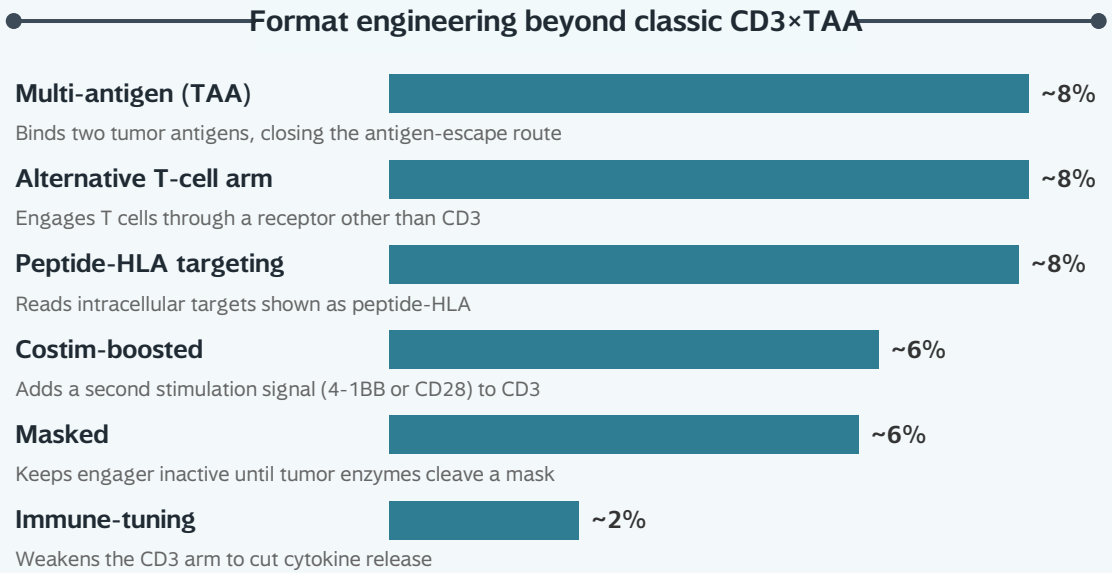
* Select CLN-978 case: most CRS events in SLE and RA trial results were Grade 1 and occurred following the first dose (10 ug); single case of Grade 3 CRS was observed following administration of the 45 ug dose; enrollment of the 45 ug cohort was later discontinued. Cross-trial, single-arm unless a hazard ratio is shown; CAR-T is a cross-modality literature benchmark; as of Sep 2026.

Programs crowd a few targets, and ~50% are engineered beyond CD3×TAA formats

The field crowds blood-cancer B-cell targets (CD19, BCMA), then solid-tumor targets (PSMA, HER2)

Target Clusters Across TCE Landscape (% of total field)





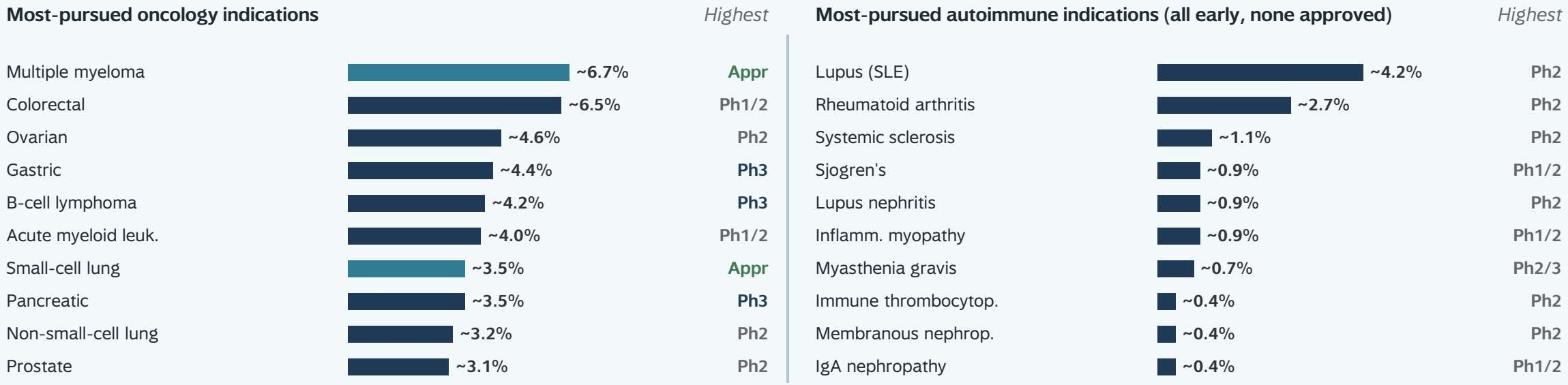
- CD3 is the effector arm in 79% of programs; ~50% add engineering beyond the plain CD3×TAA bispecific (masking, costimulation, extra targets) rather than dropping CD3
- No next-generation format exceeds ~8% of the active base, so novel formats are spread thin with no consolidating winner yet
- The crowd is nearing surface antigens: peptide-HLA targeting escape it by reading intracellular antigens

* GPRC5D: plasma-cell target, also on skin, nails and tongue (only partly clean). T-cell engager landscape as of Sep 2026; targets and mechanism labels are multi-assigned. TAA: Tumor-associated Antigen.

TCEs are beginning to move past onc. and early data is beginning to back the bet

Autoimmune is the fastest-growing non-cancer lane, still all early, while oncology holds the approvals

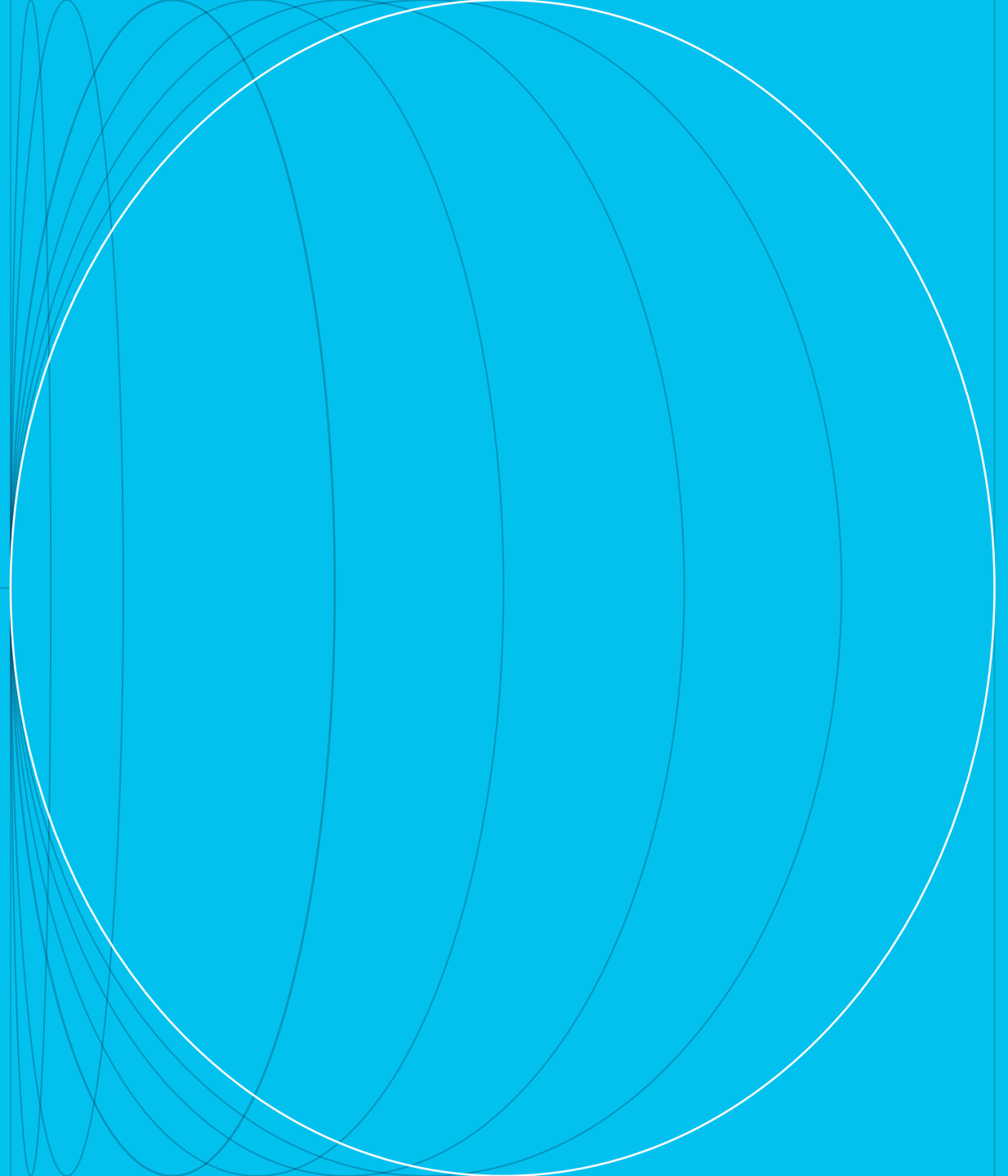
Approximately 190 Indications Pursued Across TCE Landscape (% of total field)



- Multiple myeloma crowds as the most-validated lane: clean, lineage-restricted targets (BCMA, GPRC5D*) and 5 global approvals (4 FDA approved)
- The off-the-shelf B-cell reset thesis is promising, early, and focused on SLE & RA: blinatumomab cleared B-cells and improved refractory RA (n=6), CLN-978 showed deep depletion, and n=5 SLE patients reached remission
- Solid-tumor proof exists only on clean, niche targets: tarlatamab (DLL3, small-cell) and tebentafusp (gp100, uveal melanoma) are approved; no systemically delivered shared epithelial-target TCE has cleared the bar

* GPRC5D: plasma-cell target, also on skin, nails and tongue (only partly clean). As of Sep 2026; a program can list several indications, so counts sum above the program base. Approximately ~2% programs target infectious disease (not shown).

Section 2: Sleuth Perspectives



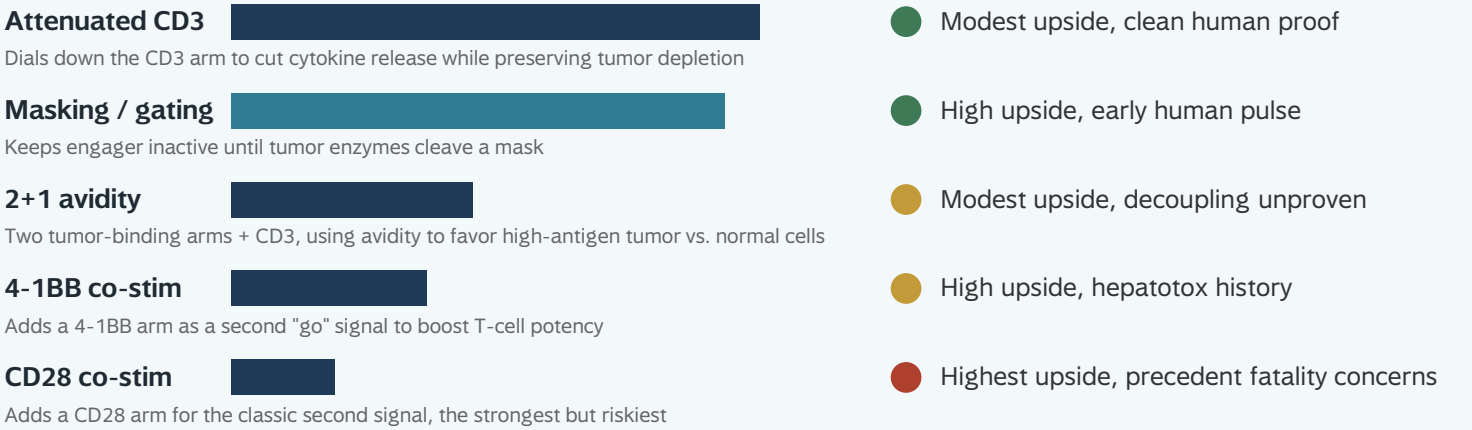
Proven window-widening levers are incremental; the high-upside ones unproven

Each lever is a different fix: masking confines activity to the tumor, attenuation lowers it globally

Representative Cross-trial Comparisons

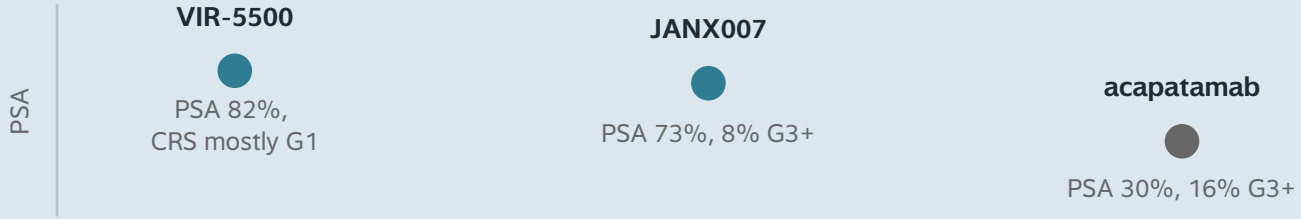
Next-generation Levers Ranked by Clinical Proof

Each lever is an engineering approach to improve beyond classical TCE constructs



Masking gradient on PSA (masked vs unmasked programs)

PSMA is a key target with masked and unmasked engagers in the clinic. Masked programs show higher PSA response (per program, PSA is from a dose subgroup and grade ≥3 CRS from the full safety set)



- Attenuated CD3 lowers T-cell activation, decoupling tumor-cell depletion from cytokine release: AZD0486 reached 96% response with no serious CRS
- Masking keeps the engager inactive until the tumor cleaves it: Vir's masked PSMA showed improved response vs. unmasked (cross-trial comparison: 82% vs. 30%)
- **Sleuth Insight:** The levers depend on indication. Masking is the solid-tumor rescue; attenuated CD3's gentler, global dial-down is the natural fit for non-fatal autoimmune, where safety is the bar, not depth. Watch attenuated CD3 for move into immunology.

Proof ranking is a qualitative read of mechanism and human evidence, not a measured score; response and safety figures are single-arm, early-phase and cross-trial, not head-to-head, per named subgroup or dose. PSA responses are from higher-dose/PSA-evaluable subgroups (VIR-5500 n=17 at ≥3,000µg/kg; JANX007 n=85 at ≥2mg); grade ≥3 CRS is each program's full safety population (VIR-5500 n=58; JANX007 n=109), so response and CRS denominators differ. acapatamab PSA and CRS are both from its n=56 RP2D expansion. As of Sep 2026.

'Trispecific' is four bets; only the myeloma dual-target bet shows early efficacy

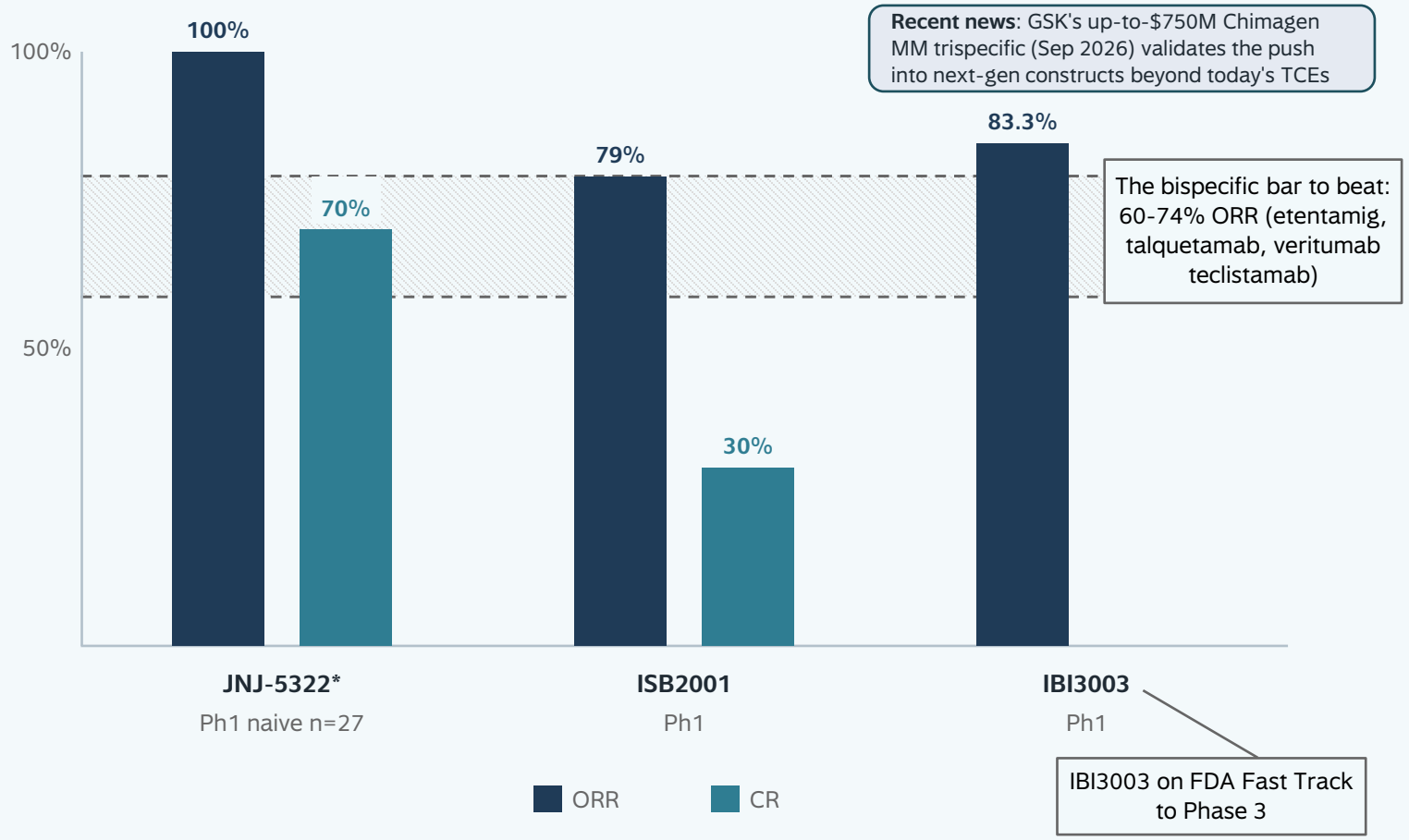
The third arm plays four roles: second antigen, costimulation, longer half-life, or a second B-cell target

- Only dual-target myeloma shows real efficacy: two antigens close the escape route that single-target bispecifics leave open
- The other three stay unproven: costimulation carries steep toxicity, the albumin arm only extends half-life, autoimmune reach into a second B-cell type is promising but early
- **Sleuth Insight:** Of the four bets, only dual-target myeloma shows early efficacy so far; the autoimmune second-B-cell arm is promising but unproven. Watch IBI3003's MM Phase 3 as a key confirmatory readout.

Representative Cross-trial Comparisons

Trispecific Response vs. Bispecific Bar To Beat (RRMM)

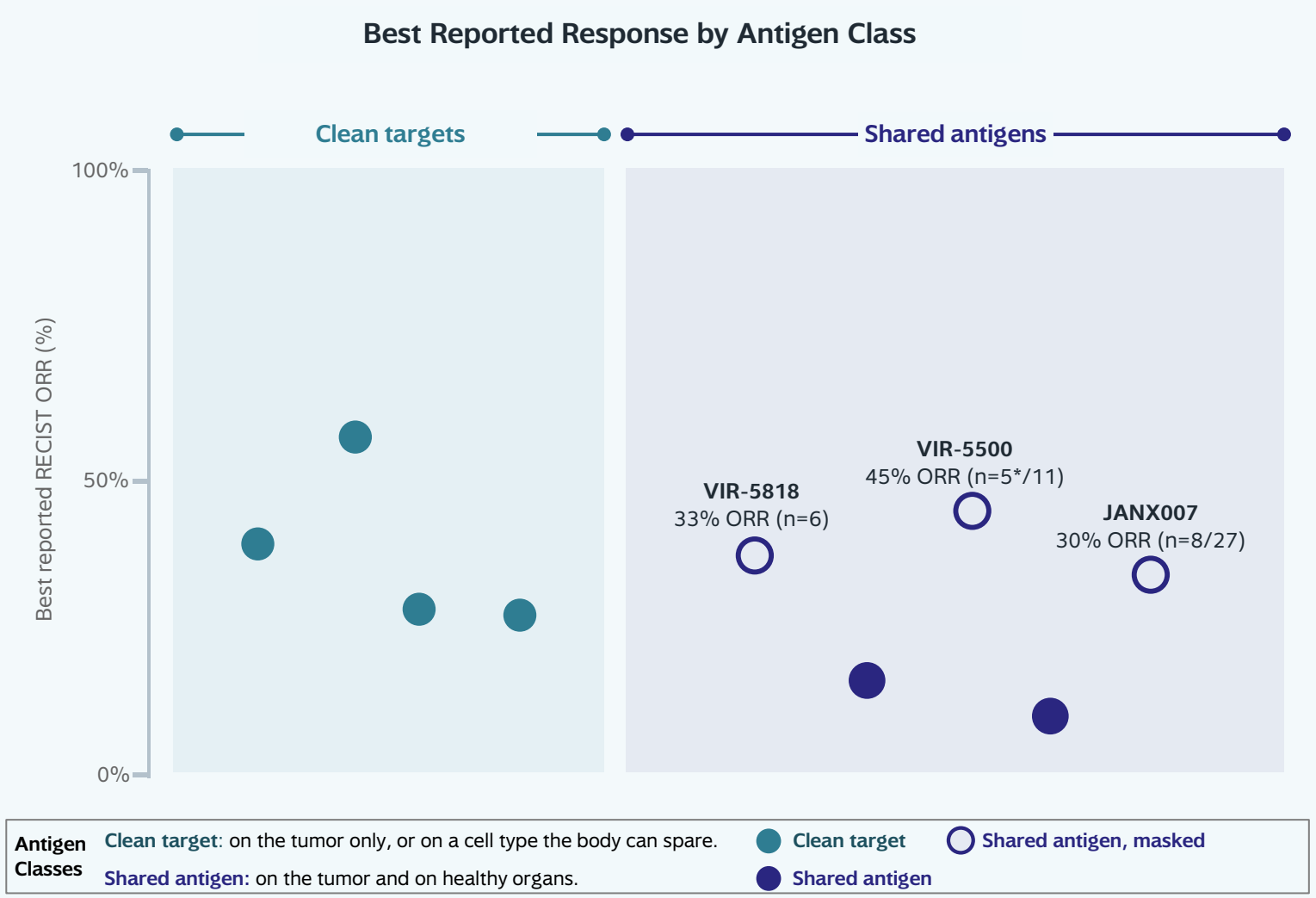
The space is early as no trispecific has a Ph2/3 readout



All figures are relapsed/refractory multiple myeloma, cross-trial and not head-to-head. Trispecifics are Phase 1: JNJ-5322 (100% is the naive subgroup, n=27), ISB2001 and IBI3003 (heavily pretreated). The 60-74% bar is myeloma bispecifics teclistamab (MajesTEC-1), talquetamab (MonumenTAL-1) and etentamig (ABBV-383). As of Sep 2026.

Clean targets set the bar; shared-antigen masking signal is positive but early

Shared-antigen response clusters below clean-target band; promising early masking examples have small sample



- On the hard endpoint, masked PSMA is modest: VIR-5500 45% and JANX007 30% RECIST ORR sit below the clean-target bar, both Phase 1, small-n, and unproven on durability; CX-904 was discontinued
- Both validated solid-tumor engagers sit on clean targets (tebentafusp, tarlatamab); no approved shared antigen has produced a lasting response†
- **Sleuth Insight:** Of ~80 clinical shared-antigen programs, none has passed validation; masked PSMA now produces measurable responses, shifting the question towards durability of these approaches

Audited clean-lineage responses vs company-reported shared-antigen data, cross-trial, not head-to-head. * ORR = 45%, 4 of 5 confirmed. † Catumaxomab (EpCAM, shared antigen) is approved but by local intraperitoneal delivery for malignant ascites; excluded here because this panel compares systemic tumor response. As of Sep 2026.

Masking is the shared-antigen rescue bet, yet no masked program has left Phase 1

Late stage belongs to the exceptions: unmasked CLDN18.2 on its wider window, EpCAM by local delivery

Shared-antigen Competitive Map by Class and Development Stage

Highest Stage of Development (by company, by class)

Shared antigen	Phase 1 & 1/2	Phase 2	Phase 3 / Reg.	Approved
PSMA	Johnson&Johnson, REGENERON, Crescendo biologics, Universitätsklinikum Tübingen, GSK, Janux, Vir Biotechnology™			
EGFR	东方百泰 EASTERN BIOTECH, Henlius, KANGABIO 康抗生物, trimerbody PHARMA, University of Virginia, Vir Biotechnology™, WuXi AppTec, YUHAN	CENTRIMED, REGENERON		
HER2	ablbio medicine for a better life, AP Biosciences 圆祥生技, ZBT 步長制藥 BUCHANG PHARMA, CHIMAGEN BIOSCIENCES, ExcelMab, HighField Biopharmaceuticals, sanofi, Vir Biotechnology™, YZY BIO 友芝友生物制药			
CLDN18.2	AstraZeneca, I-MAB BIOPHARMA, innovent, 鲁南制药 健康世界 KEEPING THE WORLD HEALTHY		astellas, 齐鲁制药 QILU PHARMACEUTICAL	
EpCAM	ABOGEN 艾博生物, bioatla, EVIVE, Genmab, ProMab Biotechnologies, Inc.		YZY BIO 友芝友生物制药	LINDIS BIOTECH †
GPC3	AstraZeneca, BeOne, CENTRIMED, Keymed Biosciences, METiS THERAPEUTICS, 齐鲁制药 QILU PHARMACEUTICAL			

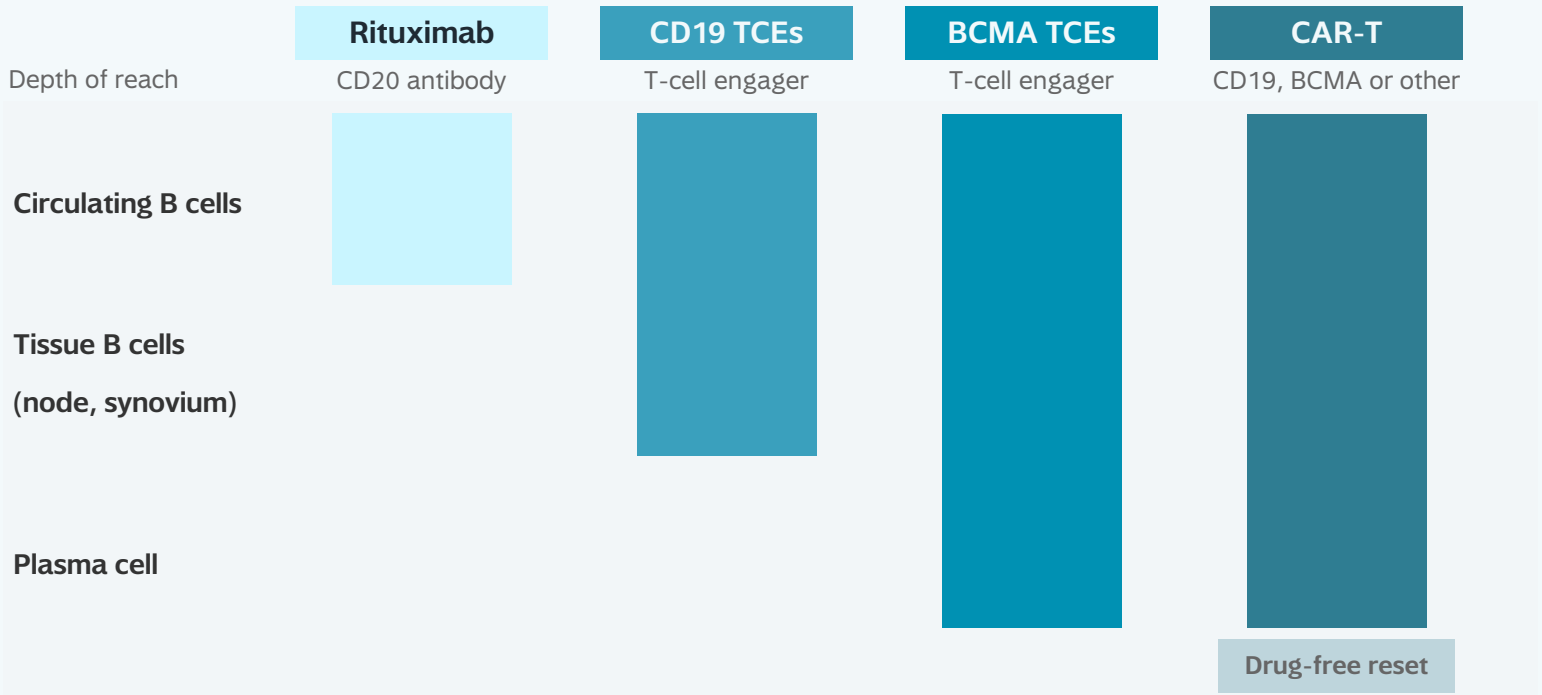
Clinical-stage only; one logo per lead company (current clinical sponsor), placed at highest stage reached; company count, not program count, not cross-summed with pipeline totals. Occupied late-stage cells are NOT rescues. † catumaxomab (Removab): EU marketing authorisation withdrawn 2017 for commercial reasons, re-approved in the EU 2025 (Lindis Biotech / Pharmanovia). M701 filed for local malignant-ascites control (systemic ORR 0%); CLDN18.2 Phase 3 includes ORR-0 programs. LAVA-1207 (PSMA, LAVA Therapeutics) discontinued Dec 2024, excluded. JY016 (Eastern Biotech) is shown in Phase 1 & 1/2 on the basis of a registered trial (NCT07510841) whose planned start date has passed without confirmed initiation. MSLN and other shared antigens (B7-H3, CEACAM5, MUC16, ROR1) not shown. As of Sep 2026.

Autoimmune is the frontier: a TCE can deplete the compartment rituximab missed

BCMA engagers reach the marrow plasma cell that sustains autoantibody, making durability the next question

- CD19 engagers reach tissue and BCMA engagers reach the marrow plasma cell, the depths rituximab misses, clearing blood but leaving tissue reservoirs
- Two engagers show reach in humans: CLN-978 cleared B-cells in lymph node and synovial tissue, and cizutamig (BCMA) is dosing into the marrow plasma-cell compartment
- **Sleuth Insight:** While positive, the depletion reads are early, and repurposed onc TCEs (blinatumomab, teclistamab) already show grade 3 CRS in autoimmune use. Purpose-built autoimmune candidates have potential to beat out repurposed TCEs

How Deep Each Class Empties the B-Lineage



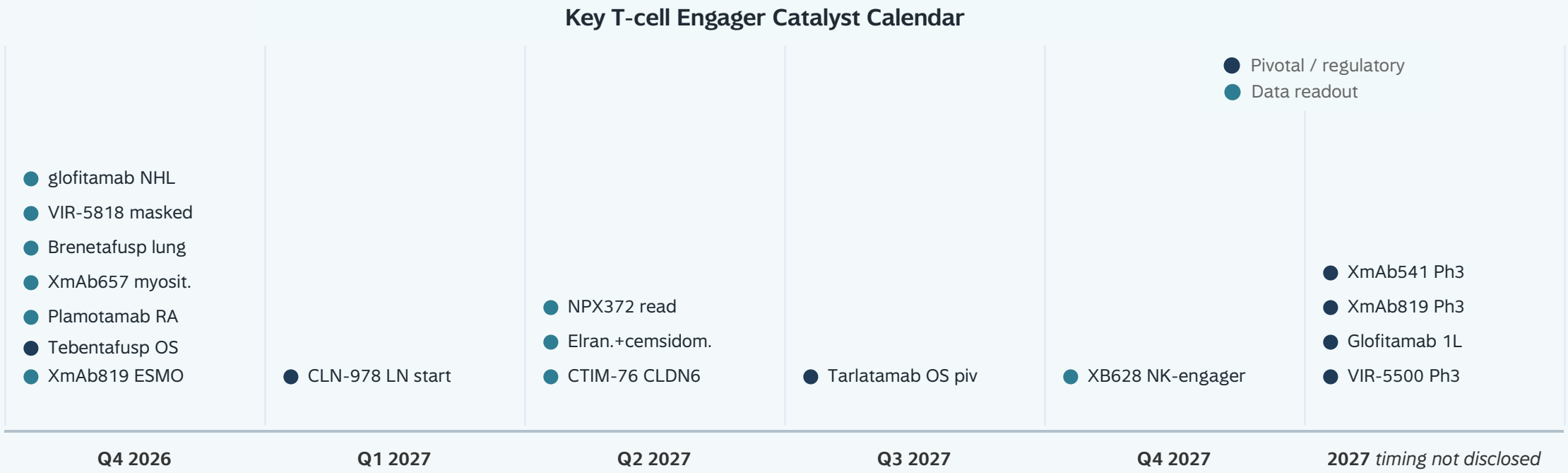
	Rituximab	CD19 TCEs	BCMA TCEs	CAR-T
Depth of reach	CD20 antibody	T-cell engager	T-cell engager	CD19, BCMA or other
Safety burden	Moderate	Moderate/High	Moderate/High	High
Logistics hurdles	Low Off-the-shelf	Low Off-the-shelf	Low Off-the-shelf	High Autologous, lymphodepletion

Depletion reads are Phase 1, small-n; CAR-T is a cross-modality literature benchmark; deepest tissue-depletion evidence is strongest for CD19 CAR-T. As of Sep 2026.

Q4 2026 gives early masking and autoimmune reads, but the verdicts wait for 2027

VIR-5818 tests masking on HER2, Plamotamab tests the B-cell reset, both early-phase in Q4 2026

Non-exhaustive



- Q4 2026 poses two early questions: does masking lift a second shared antigen (VIR-5818, HER2), and can a B-cell engager reset RA and SLE. 2026 provides early direction but key durability and survival pivotals will land in 2027
- **Sleuth Insight:** We expect the class to re-rate on the 2027 pivotal cohort, VIR-5500 masked-PSMA and XmAb819. Position ahead of those reads rather than on the Q4 signal.

Watchlist as of Sep 2026, non-exhaustive; quarter-level timing.

Sleuth predictions

Our read when we look beyond the data

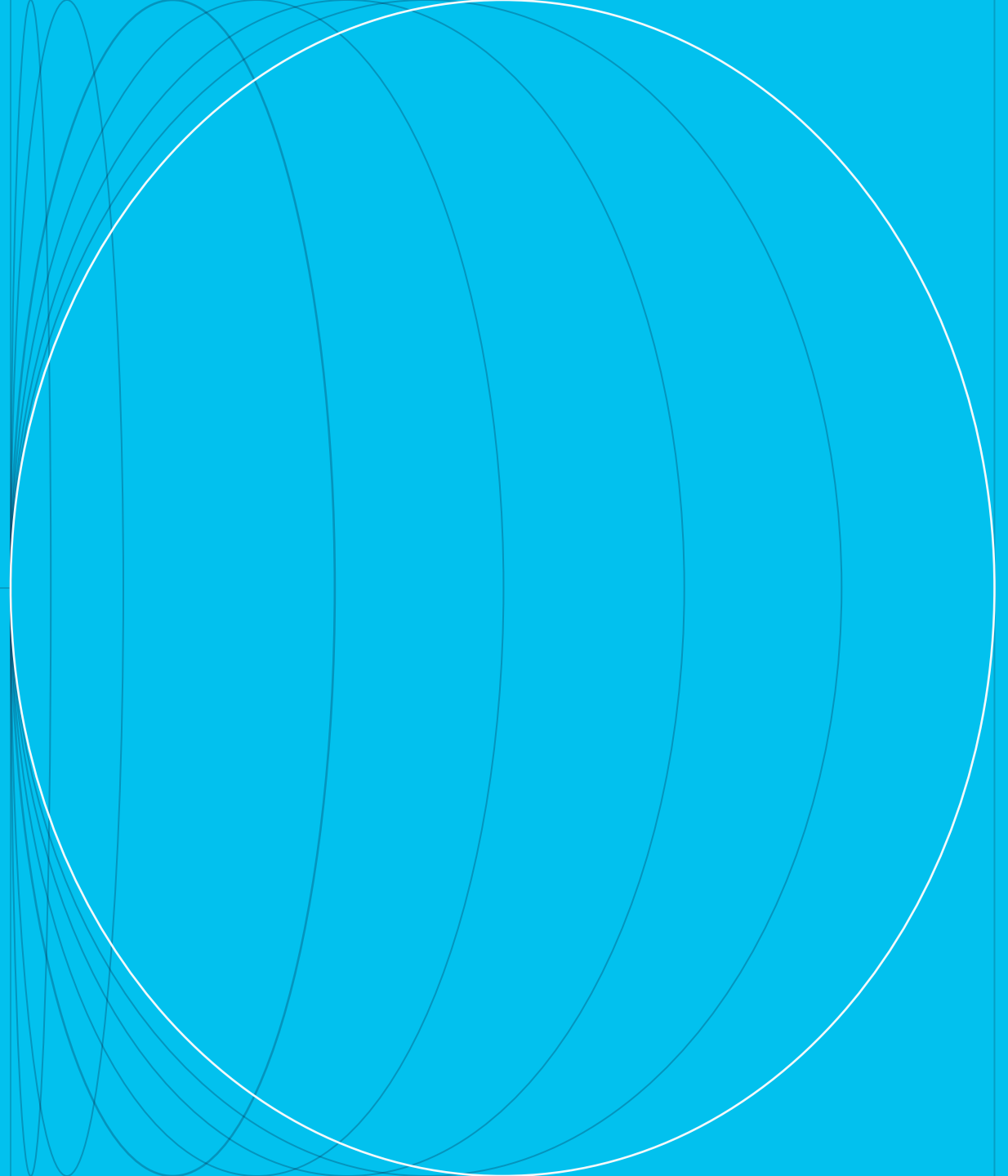
1. **No shared-antigen engager clears the bar before 2027:** swing read is VIR-5500's masked-PSMA pivotal: durable tumor shrinkage would validate the masking format that is currently in limbo given the modest ORR relative to benchmarks

2. **The trispecific premium is priced ahead of the clinical pay-off:** Phase 1 batches top the bispecific bar (JNJ-5322 100%, IBI3003 83.3% vs 60-79%), and IBI3003's Phase 3 won't post a durability edge worth its added safety risk.

3. **CD28-costimulated engager stays an open question throughout 2027:** Regeneron's nezastomig posted two grade-5 immune events and was pulled back to redesign, and CD28's potency and toxicity rise together, so the strongest second signal stays stuck in P1.

Forward reads, not outcomes; settling trials are ongoing, figures literature or document-cited. As of Sep 2026.

How Sleuth can help



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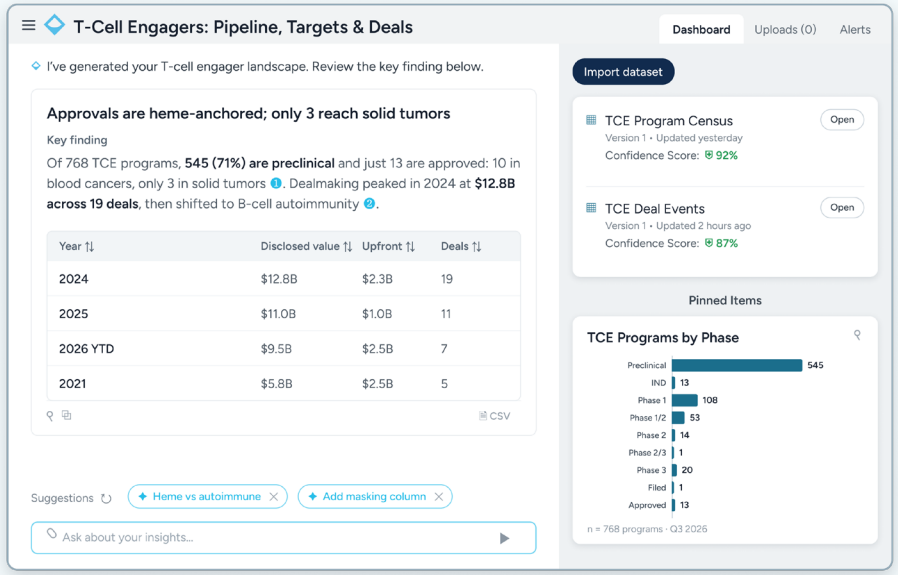
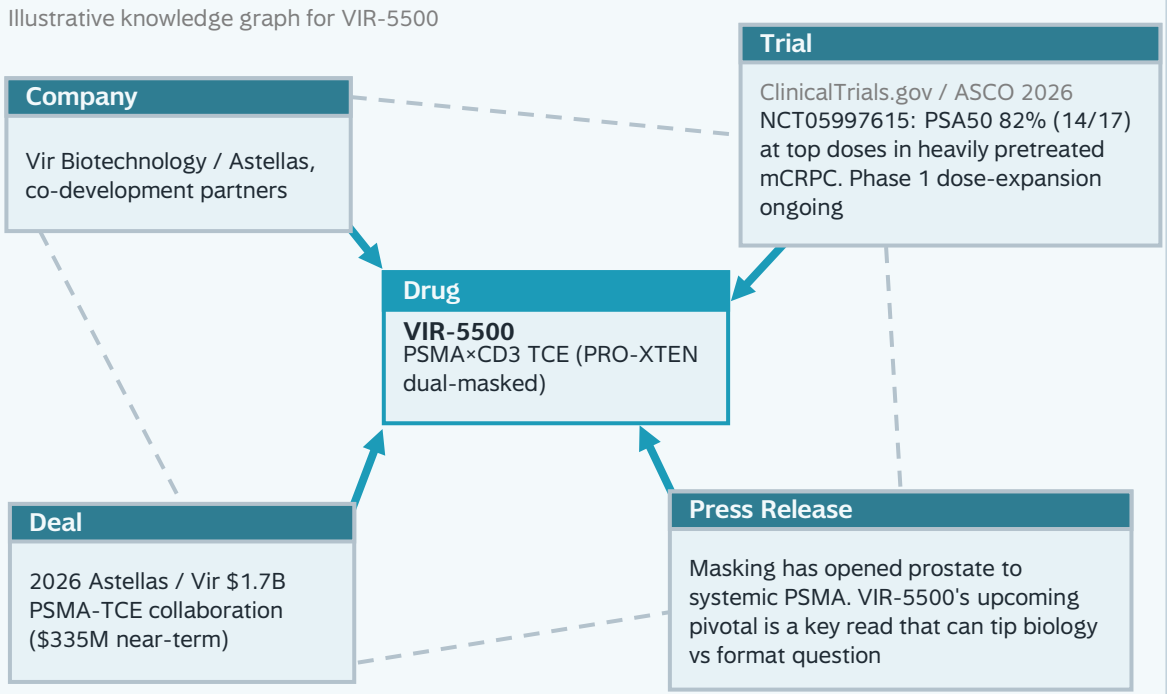
Main Takeaway: T-cell engagers are proven in blood cancers but not beyond. Masking is the shared-antigen rescue bet, and the verdicts land in 2027.



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.



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.

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

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

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

167	Indications evaluated
25	Evaluated with a tailored Epana focus that most processes never reach
4	Shortlisted for deep commercial diligence
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