

LEAD — THE BACKUP PATHWAY REACHES PHASE 2

Polθ and USP1: drugging the backup pathway

Two 2015 papers established that homologous-recombination-deficient tumors survive on Polθ-mediated end joining, a mutagenic route that anneals broken ends at short microhomologies.¹ A decade on, the class is in randomized testing: ART6043, an oral Polθ polymerase-domain inhibitor, showed tolerability and early clinical signals with olaparib at ESMO 2025, took FDA Fast Track in February 2026, and is now dosing in POLKA against olaparib alone in gBRCA-mutated HER2-negative breast cancer.² An earlier Polθ inhibitor, ART4215, completed Phase I in December 2025 but never opened its planned Phase IIa.³ USP1 runs parallel — KSQ-4279 regressed patient-derived PARP-resistant models and has finished Phase I under Roche⁴ — though Tango's TNG348 was dropped for grade 3/4 liver abnormalities.⁵

RESISTANCE IS A STATE, NOT A VARIANT

Both agents exploit a dependency that **appears under treatment** — which pathway the cell uses to resolve its breaks. Neither dependency represents a mutation, and neither is detected in the ~1.5% of the genome that codes for protein.¹⁰

IN BRIEF

Reversions arrive early

Plasma sequencing before rucaparib found *BRCA* reversions in 18% of platinum-refractory and 13% of platinum-resistant ovarian cancers, against 2% of platinum-sensitive.⁶ Multiple reversions per patient are common, indicating resistance is already multiclonal at baseline.

The scar end joining leaves

Polθ activity leaves a recognizable indel signature — deletions of five or more bases at junctions bearing short microhomology, catalogued as ID6 and associated with a single-base substitution signature that correlates with defective HRR.⁷ A record of repair history, not of current dependence.

Resistance with no variant to report

Restored fork protection confers resistance in *BRCA*-deficient cells even with the *BRCA* defect intact.⁸ Promoter methylation and expression shifts do the same, even as a sequencing panel returns the same mutational status before and after acquired resistance.

THE PIPELINE Backup-pathway targets in clinical development, October 2026.¹¹ Genotype and prior PARP exposure guides selection, although neither reports whether the backup pathway is load-bearing.

TARGET	AGENT	SETTING UNDER STUDY	STAGE
Polθ polymerase	ART6043 + olaparib	gBRCAm HER2-negative breast (POLKA)	Phase 2, randomized
Polθ polymerase	GSK4524101 ± niraparib	Advanced solid tumors	Phase I/II
Polθ ATPase	RP-3467 ± olaparib (Gilead)	HRD ovarian, breast, mCRPC, pancreatic	Phase I (POLAR)
USP1	KSQ-4279 / R07623066 ± olaparib	HRD, prior PARP inhibitor	Phase I complete
USP1	XL309 / ISM3091 · SIM0501 · HSK39775	Advanced solid tumors	Phase I

LIQUID BIOPSY

A resistance readout that arrives in time

Plasma can flag reversions before imaging does, and can capture subclones a single tissue biopsy would miss.⁶ What it cannot yet define is which repair route a tumor has switched to, which is one of the main questions the Polθ and USP1 programs are seeking to decipher.

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median progression-free survival on rucaparib with a reversion mutation detected in pretreatment plasma, compared to 9.0 months without.⁶

WHAT WE'RE READING

MECHANISM Polθ promotes alt-NHEJ Establishes Polθ as the engine of microhomology-mediated end joining, and shows it suppresses homologous recombination in the process. Mateos-Gomez et al., <i>Nature</i> 2015;518:254–257	THE DEPENDENCY HRD tumors depend on Polθ The companion paper: HR-deficient tumors upregulate <i>POLQ</i> and require it, making Polθ loss synthetically lethal with HR defects. Ceccaldi et al., <i>Nature</i> 2015;518:258–262	TRANSLATION USP1 inhibition after PARP A CRISPR screen identifies USP1 as an HRD dependency; the resulting inhibitor regresses PARP-resistant tumors under combination therapy. Cadzow et al., <i>Cancer Res</i> 2024;84:3419–3434
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FROM BREAKSIGHT

Mapping where the genome breaks

BreakSight enables discovery of novel DNA biomarkers of therapeutic response by tagging and localizing treatment-induced double-strand breaks across coding and non-coding sequence alike.

DDSITE
Capture and sequencing of break sites genome-wide, post-treatment or in a repair-deficient model.

DDINSIGHT
Reproducible break-site calling, treatment comparison, motif analysis and repeat enrichment at called sites.

WHERE THIS POINTS
Reversion panels report whether HR is restored. Mutation signatures report repair that has already occurred. Treatment-specific break landscapes speak to the question these programs turn to: which backup pathway is resolving breaks now, and where.

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TERMS USED IN THIS ISSUE

MMEJ / TMEJ End joining at short matching sequences, driven by Polθ — error-prone, and the fallback when HR is lost.¹	REVERSION MUTATION A second change that restores the reading frame of an inactivated <i>BRCA</i> allele, returning HR proficiency.⁶	USP1 The deubiquitinase that strips ubiquitin from PCNA and FANCD2; blocking it reduces protein experssion and stalls replication.⁹	ID6 A catalogued indel signature: deletions of ≥5 bp at junctions with short microhomology, which is the trace of MMEJ.⁷
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Chromatin context: why two tumors with the same genotype break differently under the same drug.

SOURCES

1. Mateos-Gomez et al., *Nature* 2015;518:254–257; Ceccaldi et al., *Nature* 2015;518:258–262.
2. Yap et al., ESMO 2025 (ART6043 Phase 1/2a, NCT05898399); Artios FDA Fast Track, 23 Feb 2026; POLKA Phase 2 dosing, 2026. 3. ART4215, NCT04991480 — completed 24 Dec 2025, no Phase IIa. 4. Cadzow et al., *Cancer Res* 2024;84:3419–3434. 5. Galgay, A. (2024, May 23) *Tango Therapeutics Announces Discontinuation of TNG348 Program*. BusinessWire. <https://www.businesswire.com/news/home/20240523266195/en/Tango-Therapeutics-Announces-Discontinuation-of-TNG348-Program>. 6. Lin et al., *Cancer Discov* 2019;9:210–219. 7. Alexandrov et al., *Nature* 2020;578:94–101. 8. Ray Chaudhuri et al., *Nature* 2016;535:382–387. 9. Li et al., AACR 2023, abstract 502. 10. Int. Human Genome Sequencing Consortium, *Nature* 2001;409:860–921; ENCODE Project Consortium, *Nature* 2012;489:57–74. 11. clinicaltrials.gov and sponsor disclosures, accessed 1 Oct 2026; RP-3467 POLAR, NCT06560632.