BREAKSIGHT, INC. — MONTHLY GENOME INTEGRITY BRIEF

THE BREAK REPORT

NOVEMBER 2026

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CHROMATIN CONTEXT · SWI/SNF · H3K27ME3 · METHYLATION · SLFN11 · BREAK LANDSCAPE

LEAD — THE VARIABLE THE PANEL DOES NOT REPORT

Same genotype, different break

Integrating a repair reporter at more than 1,000 genomic positions in one cell line established an important principle: the MMEJ-to-NHEJ balance varies more than five-fold amidst different chromatin features, with NHEJ biased toward euchromatin and MMEJ toward heterochromatin marked by H3K27me3, H3K9me2 and lamina association — one genome, one nuclease, and a repair route set by the local chromatin context.[1] The clinic uses this knowledge in its studies. A Phase 2 of the ATR inhibitor ceralasertib enrolled on a single chromatin-remodeler defect, ARID1A loss by IHC, returned a 14% confirmed response rate across 29 evaluable patients — but every response, three of them complete, fell in endometrioid endometrial carcinoma or ovarian clear-cell carcinoma, leading to an ORR of 33% with a median duration of 33.7 months in that subset.[2] The earlier ATARI cohorts, stratified on the same marker, found no association between ARID1A status and outcome in clear cell carcinoma, although it was a different story in certain rare non-clear cell carcinomas.[3]

THE GENOTYPE IS SHARED; THE CHROMATIN CONTEXT IS NOT

A variant list describes the genomic regions involved in any given phenotype. **Chromatin describes the site** — which regions are reachable, which route resolves damage, and where breaks land. Little of it is written in the ~1.5% of the genome that codes for protein.

IN BRIEF

One mark, two levers

EZH2 writes H3K27me3, and the mark does double duty: it tips local repair toward MMEJ, reversibly — EZH2 inhibition returns the balance to NHEJ[1] — and in small cell lung cancer it silences *SLFN11*, blunting platinum response.[8] One enzyme, two separable effects on the same drug.

Methylation as a dose, not a status

BRCA1 promoter methylation predicts rucaparib response only when every copy is silenced; heterozygous methylation predicts resistance, and methylation can be lost after chemotherapy.[5] A binary call on a methylated/unmethylated axis therefore reports the wrong variable.

Resistance written and unwritten

Work posted this year in HGSOC finds restoration of *BRCA1* expression after therapy occurs by local methylation loss and by promoter bypass — delineating additional ways by which homologous recombination is re-established in the absence of any reversion mutation to sequence.[7]

THE PIPELINE

Chromatin-directed programs in development, November 2026.[10] Each selects on a chromatin remodeler or writer defect, but none reads the state that defect produces.

TARGET	AGENT	SETTING UNDER STUDY	STAGE
ATR, in *ARID1A* loss	Ceralasertib	*ARID1A*-deficient solid tumors by IHC	Phase 2 reported 2026
SMARCA2 degradation	PRT3789 ± docetaxel	*SMARCA4*-mutated solid tumors	Phase I complete Oct 2025
SMARCA2 degradation	PLX-61639 (oral)	*SMARCA4*-mutated advanced solid tumors	Phase I, opened Feb 2026
EZH2	Zeprumetostat + fuzuloparib	Advanced or recurrent epithelial ovarian	Phase 2, from Jan 2026
EZH1/EZH2	HH2853 · tazemetostat	*SMARCA4*-mutant and -deficient tumors	Phase I/II

EXPRESSION READOUTS

The marker with no mutation to find

SLFN11 is lost to promoter hypermethylation and H3K27me3, not to any single mutation, and it separates outcomes independently of *BRCA* status: in advanced high-grade serous ovarian cancer, five-year survival ran 67% in SLFN11-positive tumors against 14% in SLFN11-negative.[9] This is an instance when no sequencing panel calls the prognostic biomarker.

19% of ovarian tumors carried a methylated *BRCA1* promoter (17 of 88), a group with significantly longer progression-free survival on a PARP inhibitor than unmethylated, HRD-negative tumors.[6]

WHAT WE'RE READING

MECHANISM

Chromatin sets the repair balance

A reporter read at >1,000 integration sites: MMEJ versus NHEJ swings five-fold with local chromatin, and EZH2 inhibition moves it back.

Schep et al., *Mol Cell* 2021;81:2216–2230

THE DEPENDENCY

Repair proteins are context-bound

Most repair factors act differently in heterochromatin than in euchromatin — a dependency marked by genomic coordinates and epigenetic features.

Vergara et al., *Nat Commun* 2024;15:5334

TRANSLATION

ATR inhibition in *ARID1A* loss

Synthetic lethality in action: durable complete responses in gynecologic histologies, based on the interactions between ATR and *ARID1A* loss.

Zhu et al., *Clin Cancer Res* 2026;32:1632–1640

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

If chromatin decides which route resolves a break, two tumors sharing a genotype could break in different places under the same drug — a difference a treatment-specific break landscape can measure directly.

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TERMS USED IN THIS ISSUE

CHROMATIN CONTEXT

The local state of the DNA — histone marks, compaction, position in the nucleus — and a factor influencing where a break may persist.[1]

SWI/SNF · ARID1A

The remodeling complex that moves nucleosomes; *ARID1A* is its most commonly lost subunit in gynecologic tumors.[2]

H3K27ME3 · EZH2

A repressive histone mark written by EZH2; it biases repair toward MMEJ and silences genes, including *SLFN11*.[1,8]

SLFN11

The replication-stress effector that halts forks under DNA damage; its loss is epigenetic, and it predicts response to platinum and PARP inhibitors.[9]

NEXT ISSUE · DECEMBER 2026 — Replication timing and fragile sites: where breaks concentrate when forks stall, and what that predicts.

SOURCES

1. Schep et al., *Mol Cell* 2021;81(10)2216-2230. **2.** Zhu et al., *Clin Cancer Res* 2026;32:1632-1640. **3.** Banerjee et al., *Int J Gynecol Cancer* 2021;31:1471-1475. **4.** Vergara et al., *Nat Commun* 2024;15:5334. **5.** Kondrashova et al., *Nat Commun* 2018;9:3970. **6.** Nougarede et al., *Clin Epigenetics* 2025;17:140. **7.** Xu et al., *bioRxiv* 2026; preprint. **8.** Gardner et al., *Cancer Cell* 2017;31:286-299. **9.** Akashi et al., *Mol Cancer Ther* 2024;23:106-118. **10.** Registry entries as of Nov 2026: NCT07339553, PRT3789 (Phase I complete Oct 2025), PLX-61639 (opened Feb 2026), NCT04390737, NCT03213665.