Supplementary Material

Manuscript: *Prior Sponsor Oncology Accelerated-Approval Activity and Post-Approval Regulatory Outcomes: A Retrospective Cohort Study*

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Supplementary Methods

This supplement preserves the frozen prespecified primary analysis and adds analyses motivated by a structured post-freeze methodological stress test. All numerical additions from that stress test were independently reproduced or verified against the frozen dataset. These additions were not used to redefine the primary exposure, outcome, cohort, or covariate set. They address differential follow-up, sponsor-cluster concentration, repeated regulatory decisions, construct validity of the binary sponsor-history exposure, and interpretation of competing regulatory outcomes.

The 5-year aligned sensitivity restricted the cohort to indications with at least 5 years of potential follow-up and then restricted the conditional verification-versus-withdrawal model to indications that had resolved within the first 5 years after accelerated approval. This estimand is distinct from the probability of verification by 5 years among all mature indications.

Sponsor concentration was evaluated using cluster-size summaries, leave-one-sponsor-out refits of the primary adjusted model, and joint exclusion of Merck Sharp & Dohme and Bristol Myers Squibb. The frozen coefficient was also evaluated with a t distribution using 35 degrees of freedom as a small-cluster reference.

For duplicate-decision sensitivity, product–indication rows representing the same combination regulatory action were collapsed in post-freeze review-motivated groupings. This does not replace the product–indication pair as the main cohort unit; it tests dependence that sponsor- or drug-level clustering cannot fully absorb.

Competing regulatory outcomes were displayed descriptively using Aalen–Johansen cumulative incidence functions, treating verification and withdrawal as competing events and ongoing status as censoring at the administrative cutoff. No Fine–Gray or cause-specific Cox model was used.

Supplementary Table S1. Targeted corporate-family sensitivity reclassifications

This was a targeted conservative sensitivity rather than an exhaustive reconstruction of every ownership lineage. Confidence reflects the directness of the ownership and historical-AA linkage used for the sensitivity definition.

AA ID	Product	Applicant	Applicant exposure	Family exposure	Lineage confidence	Rationale
AA009	Zydelig	Gilead Sciences	0	1	High	Gilead acquired NeXstar in 1999; NeXstar's DaunoXome had a 1996 FDA oncology approval reported as accelerated approval.

AA ID	Product	Applicant	Applicant exposure	Family exposure	Lineage confidence	Rationale
AA019	Darzalex	Janssen Biotech	0	1	Moderate	Janssen Biotech was a wholly owned Johnson & Johnson subsidiary; J&J had acquired ALZA in 2001, and ALZA had acquired Sequus/Doxil, which received oncology accelerated approval before the index AA.
AA022	Venclexta	AbbVie	0	1	High	AbbVie completed acquisition of Pharmacyclics in May 2015; Pharmacyclics had obtained the 2013 Imbruvica oncology AA before the 2016 Venclexta index AA.
AA086	Tecartus	Kite Pharma	0	1	High	Gilead completed acquisition of Kite in October 2017; Gilead had prior oncology accelerated-approval experience before the 2020 Tecartus index AA.
AA110	Exkivity	Takeda Pharmaceuticals USA	0	1	High	Takeda integrated Millennium Pharmaceuticals in 2008; Millennium's Velcade was submitted and approved under FDA accelerated-approval provisions before the 2021 Exkivity index AA.

Supplementary Table S2. Five-year aligned status among indications with at least 5 years of potential follow-up

Sponsor activity group	Status at 5 years	N	Percent	Denominator
Pathway-naive	verified	9	33.3%	27
Pathway-naive	withdrawn	5	18.5%	27
Pathway-naive	unresolved	13	48.1%	27
Prior-activity	verified	44	54.3%	81
Prior-activity	withdrawn	11	13.6%	81
Prior-activity	unresolved	26	32.1%	81

Among the 69 indications that had resolved within 5 years, the unadjusted OR for verification versus withdrawal was 2.22 (Fisher P=.287), and reapplication of the primary adjustment specification yielded aOR 1.16 (95% CI 0.29–4.70; P=.832). Only 16 withdrawals were available for the four-parameter adjusted model. Among all 108 mature indications, the adjusted OR for verification within 5 years was 1.59 (95% CI 0.46–5.48; P=.466), and the adjusted OR for withdrawal within 5 years was 0.93 (95% CI 0.34–2.57; P=.885). Full aligned-model definitions are provided in Supplementary Table S8.

Supplementary Table S3. Construct-validity diagnostics for prior applicant-level AA activity

Diagnostic	Value
Prior-activity indications	91
Lag since most recent qualifying prior AA, median days	355 days
Lag since most recent qualifying prior AA, median years	0.97 years
Lag <1 year	47 (51.6%)
Lag <2 years	60 (65.9%)
Sponsors contributing both naive and prior-activity resolved indications	10
Within mixed sponsors: naive verified	8 (80.0%)
Within mixed sponsors: prior-activity verified	13 (72.2%)

The within-sponsor comparison is descriptive, not a fixed-effects causal estimate, and is based on only 10 sponsors contributing both exposure states.

Supplementary Table S4. Sponsor concentration and dependence sensitivities

Panel A. Largest resolved-cohort sponsor clusters

Sponsor	Resolved N	Verified	Withdrawn
Merck Sharp & Dohme	16	14	2
Bristol Myers Squibb	13	11	2
Novartis Pharmaceuticals	6	5	1
Genentech	5	2	3
Janssen Biotech	5	5	0
Loxo Oncology	5	5	0
AstraZeneca	4	3	1
EMD Serono	3	3	0
Pharmacyclics	3	1	2
AbbVie	2	2	0

Merck Sharp & Dohme and Bristol Myers Squibb together contributed 29 of 76 (38.2%) prior-activity resolved observations.

Panel B. Selected leave-one-sponsor-out refits

Excluded sponsor	N	OR (95% CI)	P value
Bristol Myers Squibb	85	2.47 (0.88–6.98)	0.087
Genentech	93	3.09 (1.16–8.19)	0.024
Merck Sharp & Dohme	82	2.34 (0.84–6.53)	0.105
Novartis Pharmaceuticals	92	2.58 (0.93–7.10)	0.068

Panel C. Shared regulatory-decision / concentration sensitivities

Analysis	N	OR (95% CI)	P value
Exclude Merck + Bristol Myers Squibb	69	2.14 (0.71–6.40)	0.175
Collapse 3 shared combination regulatory decisions	95	2.50 (0.92–6.74)	0.071

Analysis	N	OR (95% CI)	P value
Extended collapse incl same-day dual Ukoniq action	94	2.34 (0.87–6.34)	0.094
One resolved indication per sponsor-date	93	2.29 (0.84–6.25)	0.106

Supplementary Table S5. Cohort reconciliation

Benchmark	N	Role	Notes
Current FDA Project Confirm therapeutic indication records, 2013-2022	122	Study analytic cohort	Verified + withdrawn + ongoing pages
Current FDA Project Confirm Other records, 2013-2022	6	Excluded	Formulation/dosing records; not distinct therapeutic indication-level AAs
Project Confirm display records reviewed, 2013-2022	128	122 included + 6 excluded	Current FDA pages
Liu et al. published cancer AA cohort, Jan 2013-Jul 2023	129	External benchmark	JAMA 2024
Current Project Confirm qualifying Jan-Jul 2023 records	7	Explains 129 vs 122 difference	Tukysa, Jaypirca, Zynyz, Padcev, Keytruda, Epkinly, Columvi

The current Project Confirm index-window records reconcile to the study cohort as 128 records reviewed = 122 included therapeutic product–indication pairs + 6 excluded Other records. The 129-record Liu et al. January 2013–July 2023 benchmark differs from the study window by seven current Project Confirm qualifying product–indication rows dated January–July 2023.

Supplementary Table S6. Descriptive competing cumulative incidence

Sponsor activity group	Years after AA	Outcome	Cumulative incidence
Pathway-naive	3	Verification	32.3%
Pathway-naive	3	Withdrawal	16.1%
Pathway-naive	5	Verification	32.3%
Pathway-naive	5	Withdrawal	19.4%
Pathway-naive	7	Verification	46.1%
Pathway-naive	7	Withdrawal	33.2%
Prior-activity	3	Verification	28.6%
Prior-activity	3	Withdrawal	5.5%
Prior-activity	5	Verification	54.0%
Prior-activity	5	Withdrawal	12.4%
Prior-activity	7	Verification	66.5%
Prior-activity	7	Withdrawal	19.1%

These estimates are descriptive. The 7-year values are retained for transparency but should not be interpreted: only 2 pathway-naive and 7 prior-activity indications remained at risk at 7 years. Figure 3 is therefore truncated before either group falls below 5 indications at risk. No cause-specific or subdistribution hazard ratio was fitted.

Supplementary Table S7. Prespecified sensitivity and exploratory analyses retained from the frozen protocol

Analysis	N	OR (95% CI)	P value	Status
Binomial GEE, exchangeable within sponsor	98	2.56 (0.98–6.72)	0.056	prespecified sensitivity
Generic-drug clustered robust SE	98	2.62 (0.89–7.69)	0.079	prespecified sensitivity

Analysis	N	OR (95% CI)	P value	Status
Categorical approval-era adjustment	98	2.65 (0.97–7.21)	0.057	prespecified sensitivity
Exploratory model adding confirmatory readiness: sponsor activity effect	98	2.72 (1.03–7.16)	0.043	prespecified exploratory; not causal mediation
Exploratory model adding confirmatory readiness: readiness effect	98	4.75 (0.78–28.83)	0.090	prespecified exploratory; not causal mediation

The confirmatory-readiness model was prespecified as exploratory and is not interpreted as causal mediation. Its nominal sponsor coefficient P value should not be read as a new primary finding.

Supplementary Table S8. Follow-up-aligned models added after the post-freeze methodological stress test

Estimand	N	OR (95% CI where available)	P value	Notes
Resolved within 5 years only: verification vs withdrawal, unadjusted	69	2.22	0.287	Aligned follow-up but conditions on resolution; 16 withdrawals.
Resolved within 5 years only: verification vs withdrawal, adjusted	69	1.16 (0.29–4.70)	0.832	Sponsor-clustered model; 4 fitted parameters including intercept; EPV≈4 by withdrawal count.
Verification within 5 years among all mature indications, adjusted	108	1.59 (0.46–5.48)	0.466	Does not condition on regulatory resolution.
Withdrawal within 5 years among all mature indications, adjusted	108	0.93 (0.34–2.57)	0.885	Does not condition on regulatory resolution.

The conditional 5-year landmark adjusted model contains 16 withdrawal events for four fitted parameters including the intercept (approximately 4 withdrawal events per parameter) and yields a very wide confidence interval. It is therefore treated as an imprecise sensitivity analysis, not as evidence that the prespecified association is absent.

Supplementary Table S9. Corporate-family sensitivity excluding the moderate-confidence lineage

Analysis	N	OR (95% CI)	P value
Corporate-family sensitivity excluding moderate-confidence AA019 lineage	98	1.98 (0.73–5.35)	0.180

This sensitivity retains only the four High-confidence family reclassifications in Supplementary Table S1 and returns AA019 (Janssen/ALZA/Sequus-Doxil lineage) to its applicant-level exposure classification.