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SYSTEMATIC REVIEW & META-ANALYSIS

# Does Germline *BRCA1/2* Status Modify the Effect of Neoadjuvant Pembrolizumab on Pathological Complete Response in Early-Stage Triple-Negative Breast Cancer? A Systematic Review and Meta-analysis of Treatment-Biomarker Interactions

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**ABSTRACT**

**Background:** Germline *BRCA1/2* pathogenic variants are associated with chemotherapy response, but higher response among pembrolizumab-treated carriers does not establish a treatment-predictive interaction.

**Objective:** To determine whether germline *BRCA1/2* status modifies the effect of neoadjuvant pembrolizumab on pathological complete response in early-stage triple-negative breast cancer, estimated as a within-study treatment-by-biomarker interaction on the ratio-of-odds-ratios scale.

**Methods:** Accessible bibliographic, registry, and citation sources were searched from inception through the final accessible-source update for comparative cohorts of neoadjuvant pembrolizumab plus chemotherapy versus chemotherapy alone reporting pathological complete response (pCR) by germline *BRCA1/2* status. One author approved screening, extraction, ROBINS-I, and ICEMAN judgements. Treatment-by-biomarker interactions were expressed as ratios of odds ratios (RORs) and pooled by restricted-maximum-likelihood random effects with Hartung-Knapp inference.

**Results:** Three retrospective cohorts (655 participants) were included; two (415 participants) provided complete interaction cells. Study RORs were 3.65 (95% CI 0.52-25.62) and 2.76 (0.39-19.39). The pooled ROR was 3.17 (0.54-18.51; p=0.076), with tau-squared=0 and I-squared=0%. The third cohort remained qualitative because noncarrier cells were irreconcilable. Risk of bias was serious, interaction credibility was low, and certainty was very low.

**Conclusion:** The direction of effect is compatible with greater relative pembrolizumab-associated pCR improvement among carriers, but the evidence does not establish a predictive interaction. Prospective adjusted interaction analyses are required.



## 1. Introduction

Triple-negative breast cancer (TNBC) is defined clinically by the absence of estrogen receptor and progesterone receptor expression and the absence of human epidermal growth factor receptor 2 overexpression or amplification. This operational definition encompasses biologically diverse tumors rather than a single molecular entity. Compared with hormone-receptor-positive disease, TNBC more often presents with high histological grade, rapid proliferation, an early recurrence peak, and a greater probability of visceral or central nervous system relapse. Molecular profiling has further divided TNBC into basal-like, mesenchymal, immune-enriched, and other transcriptional states, although these taxonomies have not yet displaced routine clinicopathological classification. The clinical challenge is therefore twofold: to deliver curative systemic therapy early and to identify biomarkers that predict which component of a multidrug regimen produces incremental benefit rather than merely marking a favorable or unfavorable disease phenotype[1–3].

The phase III KEYNOTE-522 program changed the treatment landscape for stage II-III TNBC by showing that pembrolizumab added to neoadjuvant chemotherapy, followed by adjuvant pembrolizumab, increased pathological complete response (pCR) and improved event-free and overall survival at the trial-population level[4,5]. Exploratory residual-cancer-burden analyses also supported a clinically meaningful shift in the distribution of residual disease after pembrolizumab-containing therapy, while patient-reported outcomes contextualized treatment burden[6,7]. These average effects justify pembrolizumab for appropriately selected high-risk early TNBC, but they do not imply that every molecular subgroup derives the same relative or absolute contribution from the immune-checkpoint inhibitor. The distinction matters because the regimen combines multiple cytotoxic agents, immunotherapy, surgery, and postoperative

treatment; a biomarker associated with chemosensitivity can appear favorable in the pembrolizumab arm even when it does not modify the incremental pembrolizumab effect.

Other neoadjuvant immune-checkpoint studies reinforce both the promise and the heterogeneity of this therapeutic strategy. GeparNuevo reported durable outcome signals with durvalumab, NeoTRIP did not show a statistically significant pCR increase with atezolizumab on its carboplatin-taxane backbone, and the final IMpassion031 analysis showed that regimen context and endpoint selection remain important[8–10]. NeoPACT, an adaptive nivolumab trial, the randomized PLANeT study, and an immune-signature analysis supplied additional contemporary evidence across distinct designs and treatment backbones[11–14]. Consequently, a retrospective comparison across treatment eras or chemotherapy backbones cannot be interpreted as if pembrolizumab were the only difference between groups.

pCR is a clinically useful early endpoint in TNBC because individual patients who achieve pCR generally have substantially better event-free and overall outcomes than patients with residual invasive disease. Nevertheless, trial-level improvement in pCR is not a perfect surrogate for a proportional survival improvement, and the strength of association varies by biological subtype, treatment, and analytical level, as illustrated by long-term randomized and residual-disease studies[15–17]. In a treatment-biomarker review, pCR therefore provides a feasible primary endpoint for comparing relative short-term treatment effects, but it must not be silently translated into a claim about event-free survival, overall survival, or quality of life. A subgroup interaction for pCR and a subgroup interaction for survival are distinct estimands. This review prespecified pCR at definitive surgery as its primary outcome and regarded longer-term outcomes as separate secondary questions that required directly reported interaction data.

Germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* are biologically compelling candidate effect modifiers. Loss of homologous-recombination repair function promotes genomic instability and can increase sensitivity to DNA-damaging agents. Contemporary neoadjuvant and natural-history studies have reported high response or distinctive outcomes among germline *BRCA* carriers, while matched analyses show that adding platinum or a PARP inhibitor does not create a uniform carrier-specific incremental effect[18–21]. *BRCA* status is unquestionably actionable for genetic counselling, familial risk management, surgical decision-making, and PARP-inhibitor therapy in appropriate settings, as illustrated by the primary and overall-survival reports from OlympiA[22,23]. That broader clinical importance must not be conflated with evidence that *BRCA* status predicts the incremental effect of neoadjuvant pembrolizumab.

Three recently reported retrospective comparative cohorts provide the direct evidence relevant to this narrower question[24–26]. Each contains patients treated with pembrolizumab plus chemotherapy and patients treated with chemotherapy without pembrolizumab, with at least some pCR information stratified by germline *BRCA* status. Their subgroup proportions are clinically interesting, but the validity of a predictive claim depends on comparing treatment effects between biomarker strata, not on testing response in carriers alone or comparing carriers with noncarriers within one treatment arm. Subgroup claims are especially vulnerable to sparse data, multiple testing, post hoc direction selection, and ecological or aggregation bias. A within-study framework that preserves the randomized or comparative treatment contrast is therefore essential[27]. A formal treatment-by-biomarker interaction estimand is therefore required. For binary outcomes, the ratio of odds ratios (ROR) directly compares the pembrolizumab-versus-control odds ratio among carriers with the corresponding odds ratio among noncarriers.

Novelty and aim of the study. The defensible novelty of this review is an estimand refinement rather than a claim that *BRCA*-associated response has never been reviewed. Earlier reports and evidence syntheses largely described prognosis, chemosensitivity, platinum response, or carrier-versus-noncarrier pCR within treated cohorts. Our protocol instead required an external chemotherapy-only comparison and estimated a within-study treatment-by-germline-*BRCA* interaction for the incremental effect of adding pembrolizumab. The primary aim was to determine whether germline *BRCA1/2* pathogenic or likely pathogenic variant status modifies the relative effect of neoadjuvant pembrolizumab plus chemotherapy versus chemotherapy alone on pCR in adults with stage II-III TNBC. Secondary aims were to characterize clinical comparability across cohorts, evaluate risk of bias and interaction credibility, assess certainty of evidence, and define the clinical and research implications without extrapolating a pCR interaction to survival benefit.

## 2. Methods

### *Protocol, registration, and reporting*

The review protocol was finalized and frozen before the formal search and was prospectively registered in PROSPERO (CRD420261472135). Eligibility criteria, the primary outcome, interaction estimand, risk-of-bias approach, synthesis model, sensitivity analyses, and amendment policy were defined before pooled results were inspected. Substantive departures from the frozen protocol were retained in an amendment log rather than being overwritten. Reporting was mapped to PRISMA 2020[28], while risk of bias, interaction credibility, and certainty were assessed with ROBINS-I, ICEMAN, and GRADE, respectively[29–31]. The review is described as a systematic review and meta-analysis of

treatment-biomarker interactions, not as an original participant-level study.

### *Review question and eligibility criteria*

The population comprised adults with histologically confirmed stage II-III, non-metastatic TNBC who received systemic therapy before definitive breast surgery. The intervention was pembrolizumab added to a neoadjuvant chemotherapy backbone. The comparator was chemotherapy without an immune-checkpoint inhibitor from the same study, whether contemporaneous or historical, provided that the report allowed the treatment contrast to be evaluated separately by germline *BRCA* status. The prespecified effect modifier was a germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant. Variants of uncertain significance were excluded from the carrier group whenever the publication permitted separation. Somatic-only *BRCA* alterations, homologous-recombination-deficiency scores without separable germline *BRCA* results, and mixed metastatic populations without extractable early-stage data were ineligible.

The primary outcome was pCR at definitive surgery, preferentially ypT0/Tis ypN0. Alternative published definitions were retained verbatim and were not described as fully harmonized. Eligible reports had to provide either an adjusted treatment-by-*BRCA* interaction estimate or sufficient counts to form the four treatment-by-biomarker outcome cells in both carrier and noncarrier strata. Randomized trials and comparative prospective or retrospective cohorts were eligible. Single-arm pembrolizumab cohorts were excluded from the interaction analysis because response differences between carriers and noncarriers within one treatment arm cannot identify incremental pembrolizumab effect modification. Case reports, reviews, editorials, laboratory-only studies, and conference records without usable comparative data were excluded.

Event-free survival, overall survival, and treatment-limiting toxicity were prespecified as secondary outcomes only if a treatment-by-*BRCA* interaction or sufficient stratified comparative data were reported. We did not use pCR as a mathematical surrogate for these outcomes and did not infer survival effects from carrier pCR proportions. When multiple reports described the same underlying cohort, they were linked at study level so that reports, comparisons, and effect estimates were not double counted. The most complete source was used for each variable, with companion publications used only to clarify design, treatment, follow-up, or subgroup definitions.

### *Information sources and search strategy*

MEDLINE/PubMed, Europe PMC, and ClinicalTrials.gov were searched from inception through the final accessible-source update. Search concepts combined early or neoadjuvant TNBC, pembrolizumab or KEYNOTE-522 terminology, and *BRCA1*/*BRCA2* or germline-*BRCA* terminology. No date, language, outcome, comparator, or study-design filter was applied. Crossref and OpenAlex were used for supplementary ranked discovery, metadata reconciliation, and forward citation searching from candidate comparative reports. Backward reference checking was performed from the included reports and closely related reviews. Exact strings, platforms, audit metadata, raw responses, exported records, and code for reproducible deduplication were archived.

The public-source search was incomplete relative to the protocol. Embase, Cochrane CENTRAL, Scopus, and Web of Science Core Collection could not be executed in the available session because licensed or authenticated access was unavailable. Frozen draft strategies were retained for later platform-specific adaptation, but results from unexecuted sources were not simulated and no record counts were invented. This gap is material because the question is narrow, only two studies entered the quantitative synthesis, and one additional eligible cohort could materially alter precision or direction. Accordingly, the search is described throughout as the executed accessible-source search rather than as proof that all relevant studies have been identified. Any future licensed-source update must be deduplicated, screened, and propagated through extraction, bias assessment, analysis, GRADE, tables, figures, abstract, and text.

### *Record management and study selection*

Bibliographic records were deduplicated sequentially by exact PubMed identifier, exact normalized DOI, and normalized title. Registry records were retained separately because a trial registration and a journal article are reports of a study rather than necessarily duplicate records. Title/abstract screening decisions were recorded with source-linked reasons. Full reports were then evaluated against the prespecified population, treatment comparator, germline-*BRCA* definition, and outcome-data requirements. Exclusion reasons were assigned at full text using mutually interpretable categories, with lack of an eligible chemotherapy-only comparator prioritized when it precluded the target interaction.

IMAS (first author) served as verifier and reviewed every current title/abstract decision, full-text inclusion or exclusion, and study-to-report linkage before analysis. Second author (MOS) check of the critical inclusion, extraction, and bias decisions was not available for this version; the resulting risk of selection and transcription error is acknowledged as a methodological limitation. The verified screening log, reasons, and PRISMA accounting were locked before statistical synthesis.

### *Data extraction and harmonization*

Extraction captured study setting, design, recruitment period, center structure, eligibility, genetic testing approach, *BRCA1*/*BRCA2* scope, treatment era, chemotherapy backbone, pembrolizumab schedule,

comparator construction, pCR definition, arm denominators, pCR events, missing genetic data, covariate adjustment, funding, and conflicts. Each numerical value was accompanied by a page, table, figure, supplement, or registry location. Adjusted estimates were preferred when they represented the target within-study interaction; otherwise, verified four-cell counts were used. Rounded percentages were not converted to event counts, and irreconcilable denominators were not imputed.

Clinical comparability was assessed explicitly rather than assumed. We compared calendar era, stage and risk distribution, germline testing coverage, chemotherapy components, carboplatin exposure, anthracycline use, dose or sequence where reported, pembrolizumab exposure, surgery timing, pCR definition, and whether the chemotherapy-only group was contemporaneous or historical. Comparisons with a materially different backbone were retained only when they still addressed the review question and were interpreted as confounded observational contrasts. The protocol anticipated sensitivity analysis restricted to closely comparable backbones, but the number and reporting quality of studies did not support a separate pooled analysis. Comparator non-equivalence was therefore incorporated into ROBINS-I, GRADE, and the clinical interpretation rather than being concealed by statistical pooling.

For the BRCAPATH cohort, carrier cells were reported directly, whereas noncarrier cells required a transparent derivation from supplementary totals after excluding variants of uncertain significance. The pembrolizumab noncarrier denominator was 234 minus 35 carriers minus 9 variants of uncertain significance, yielding 190; pCR events were 190 minus 91 non-pCR cases, yielding 99. The control noncarrier denominator was 54 minus 7 carriers minus 3 variants of uncertain significance, yielding 44; pCR events were 44 minus 29 non-pCR cases, yielding 15. All four derivations and their source locations were verified by the named human verifier. For the Connors/Lang cohort, carrier cells were available but noncarrier denominators were discordant or non-separable; no reconstructed interaction was created, and the study remained qualitative.

### *Risk of bias and credibility of effect modification*

Risk of bias in non-randomized intervention evidence was assessed with ROBINS-I across bias due to confounding, participant selection, intervention classification, deviations from intended intervention, missing data, outcome measurement, and selection of the reported result[29]. The central confounding problem was whether calendar era, chemotherapy backbone, clinical risk, testing patterns, or treatment selection differed between pembrolizumab and chemotherapy-only groups and between *BRCA* strata. A study could not be considered low risk merely because pCR was objectively ascertained; an unbiased outcome measurement does not repair confounded treatment allocation or selective subgroup reporting.

Credibility of effect modification was assessed item by item using ICEMAN, including whether the direction of modification was prespecified, whether the biomarker was measured at baseline, whether a within-study interaction test was reported, whether multiplicity was controlled, whether the number of candidate modifiers was limited, whether the interaction was consistent across studies, and whether a biological rationale existed[30]. I Made Aridana Sandika assessed the domain-level ROBINS-I and item-level ICEMAN judgements. Overall ratings were not computed by averaging items; decisive limitations were carried forward explicitly.

### *Effect measure and statistical synthesis*

The estimand was the within-study relative treatment interaction on the odds-ratio scale[27]. For each biomarker stratum s, a represented pCR events with pembrolizumab, b represented non-pCR with pembrolizumab, c represented pCR events with chemotherapy alone, and d represented non-pCR with chemotherapy alone. The stratum-specific odds ratio was $OR_s=(a_s\times d_s)/(b_s\times c_s)$. With C denoting carriers and N denoting noncarriers, the interaction estimand was $ROR=OR_C/OR_N$. Thus, ROR>1 indicates a larger relative pembrolizumab-associated pCR effect among carriers, ROR=1 indicates no relative interaction, and ROR<1 indicates a smaller relative effect among carriers. It is not a direct carrier-versus-noncarrier comparison and is not an absolute risk difference.

The model used $\log(ROR)=\log(OR_C)-\log(OR_N)$. Under independence of the disjoint strata, $Var[\log(ROR)]=(1/a_C+1/b_C+1/c_C+1/d_C)+(1/a_N+1/b_N+1/c_N+1/d_N)$. The executable analysis applied a 0.5 continuity correction to all eight study cells if any cell was zero; no included quantitative study contained a zero cell, so no correction affected the reported estimates. Study estimates were calculated from verified integer counts and checked against an independent arithmetic reconstruction.

Log RORs were pooled using a random-effects model with restricted maximum likelihood (REML) estimation of between-study variance and Hartung-Knapp inference, as prespecified. Analyses used R version 4.5.3 and metafor version 4.8-0. Because inference is fragile with very few studies, we also reported a normal-interval REML model and an inverse-variance common-effect model as sensitivity analyses. REML was retained rather than selecting an estimator from the observed heterogeneity result.

We reported $\tau^2$, $I^2$, Cochran Q, and the Q-test p value, but did not treat $I^2$ as a standalone verdict. With k=2, estimation of heterogeneity and the Hartung-Knapp degrees of freedom are exceptionally fragile; zero estimated heterogeneity cannot demonstrate clinical homogeneity. A prediction interval was not presented because it would be dominated by poorly estimated heterogeneity and provide misleading apparent

precision in this two-study setting, despite its value in adequately sized meta-analyses. Funnel plots and asymmetry tests were not performed because k=2 is far below the range in which these methods are interpretable. No subgroup analysis, meta-regression, or influence analysis was performed because each would overfit the evidence.

### *Certainty of evidence and reproducibility*

Certainty was evaluated with GRADE, beginning at low certainty for observational evidence and considering risk of bias, inconsistency, indirectness, imprecision, and publication bias[31]. Interaction credibility informed but did not automatically duplicate ROBINS-I downgrading. Treatment-era and backbone confounding was primarily represented under risk of bias; sparse events and the extremely wide confidence interval were represented under imprecision. We did not separately downgrade inconsistency solely because clinical differences existed when statistical inconsistency could not be estimated reliably. Publication bias was rated uncertain rather than absent. Upgrading for a large effect was not considered defensible because the unadjusted point estimate was vulnerable to residual confounding and its confidence interval crossed the null interaction.

The reproducibility package contains the verified four-cell CSV, study-characteristics data, screening logs, domain-level ROBINS-I judgements, item-level ICEMAN judgements, R code, package and session information, study-level estimates, pooled-model outputs, figures, and a file manifest. Copyrighted full texts and publisher supplements are retained for audit but are not designated for public redistribution. At the time of this manuscript version, the package had not been assigned a persistent public repository identifier; the declarations therefore state the precise controlled-availability route rather than claiming an unperformed deposit.

Missing information was handled conservatively. A field absent from a source was recorded as not reported rather than inferred from customary practice, adjacent studies, rounded percentages, or an abstract. When a report supplied several eligible outcome definitions or timepoints, the definition closest to ypT0/Tis ypN0 at definitive surgery was preferred, while any deviation was retained in the characteristics table. No statistical imputation was used for missing interaction cells. Authors were not contacted during the current production window because the quantitative studies supplied sufficient verified cells and the qualitative study contained inconsistencies that could not be resolved from published materials. A future author clarification would be treated as new source evidence, versioned, independently verified, and followed by a complete rerun rather than a manual manuscript-only correction.

Quality control linked every reported number to a single analysis output. Event counts and denominators were range checked; pCR events could not exceed arm totals; carrier and noncarrier categories were required to be mutually exclusive after removal of variants of uncertain significance. Study-level RORs were independently recalculated from the eight cells, and pooled values in the abstract, text, tables, and forest plot were compared against the machine-generated model file. Revisions requested by the internal clinical-editorial and methods-statistics reviews were incorporated only when supported by existing evidence. Requests requiring a second human reviewer, licensed database access, or a persistent external repository were reported as unresolved process limitations rather than described as completed. This approach separates improvement of reporting from fabrication of a workflow that did not occur.

## 3. Results

### *Search results and study selection*

The executed searches yielded 52 records or reports: 41 bibliographic records, 7 registry records, and 4 records retained from supplementary discovery or citation methods. Deduplication removed 18 bibliographic duplicates, leaving 34 unique records for screening. Thirty records were excluded before full-text assessment. Four reports were assessed in full; one Korean single-arm pembrolizumab cohort was excluded because it lacked an eligible chemotherapy-only comparator and therefore could not identify the target interaction. Three retrospective comparative cohorts containing 655 participants were included in the systematic review[24–26]. Two cohorts containing 415 participants provided complete verified treatment-by-*BRCA* four-cell data and entered the quantitative synthesis. One cohort containing 240 participants contributed qualitative evidence only. The complete identification and selection pathway is detailed in Figure 1. These counts distinguish records, reports, studies, and quantitative comparisons and reconcile with the verified screening log.

### *Study and comparator characteristics*

The included studies were conducted in Israel, France, and the United States. Etan et al. was a single-center retrospective cohort of 127 patients comparing neoadjuvant chemotherapy with or without pembrolizumab among germline *BRCA* carriers and noncarriers[24]. BRCAPATH was a multicenter French retrospective study of 288 patients and provided supplementary information that allowed variants of uncertain significance to be separated from pathogenic variants[25]. The United States real-world cohort reported by Connors et al., with Lang as senior author, included 240 patients treated in routine practice and supplied directly interpretable *BRCA1*-carrier counts but not a reconcilable complete noncarrier interaction table[26].

No study randomized pembrolizumab within germline *BRCA* strata, and none reported a prospectively specified, covariate-adjusted treatment-by-*BRCA* interaction coefficient. Chemotherapy-only comparators were partly historical or derived from earlier treatment periods. Regimens differed in details of carboplatin, paclitaxel, and anthracycline exposure, and clinical selection for pembrolizumab could have changed with calendar time. Germline testing completeness and the handling of variants of uncertain significance also varied. BRCAPATH explicitly defined pCR as ypT0/TisN0; the exact ypT definition was not reported for Etan et al. in the accessible source and was retained as not reported. These differences limit exchangeability of the treatment groups and clinical comparability across studies. These design, treatment, biomarker, and outcome details are summarized in Table 1.

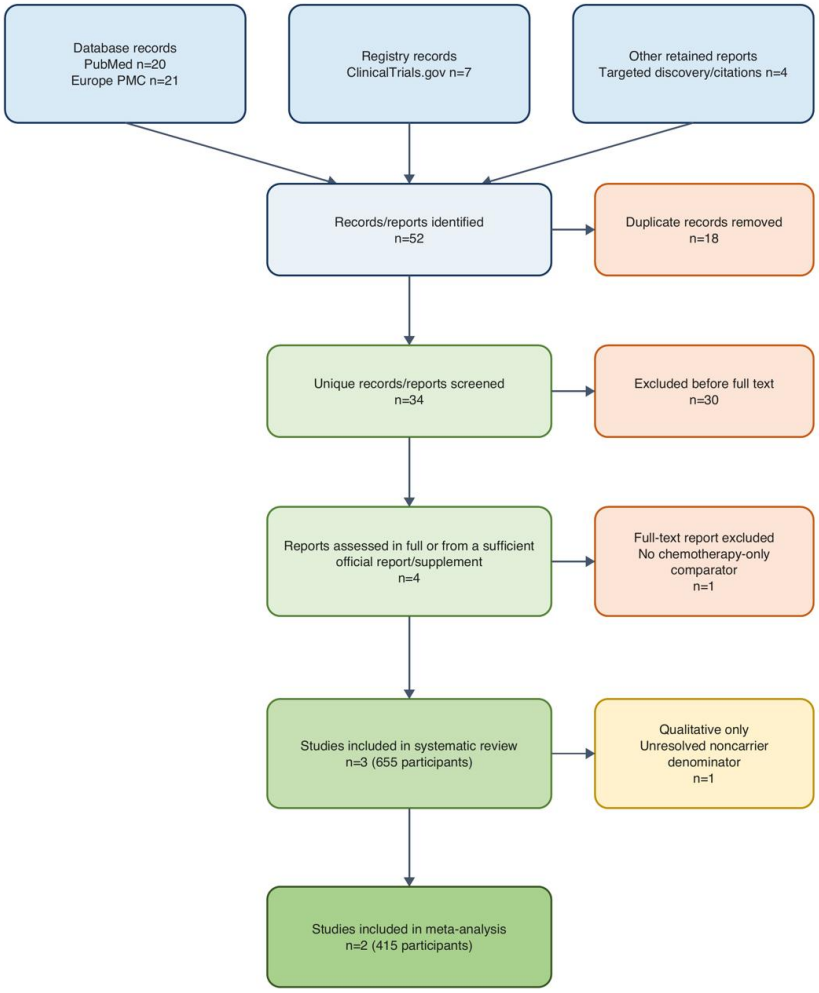


**Figure 1.** PRISMA 2020 flow diagram. Study identification and selection from executed public-source searches and supplementary methods. The licensed database access gap is described in Methods and Limitations.

**Table 1. Characteristics of included studies.**

| Study | Setting/design | N | Intervention | Comparator | *BRCA* definition | pCR definition | Disposition |
|---|---|---|---|---|---|---|---|
| Etan 2026 | Israel; single-center retrospective | 127 | Pembrolizumab + AC/carboplatin/paclitaxel | Same chemotherapy without pembrolizumab | g*BRCA1/2* mutation; exact classification method not reported | pCR as reported; exact ypT definition not reported | Quantitative; serious RoB |
| BRCAPATH 2026 | France; multicenter retrospective | 288 | Pembrolizumab + chemotherapy | Chemotherapy alone | Pathogenic g*BRCA1/2* variants; VUS excluded | ypT0/TisN0 | Quantitative; serious RoB |
| Connors et al. 2025 | United States; single-center retrospective | 240 | KEYNOTE-522 regimen | Standard neoadjuvant chemotherapy | g*BRCA1* reported; *BRCA2* not separable | pCR as reported; denominator inconsistencies | Qualitative only; serious RoB |

*Abbreviations: AC, anthracycline/cyclophosphamide; gBRCA, germline BRCA; pCR, pathological complete response; RoB, risk of bias; VUS, variant of uncertain significance.*

The qualitative Connors/Lang cohort reported carrier pCR counts of 4/5 with the KEYNOTE-522 regimen and 9/12 with standard neoadjuvant chemotherapy. These proportions were not converted into a treatment interaction because the corresponding noncarrier denominators and labels could not be reconciled without assumptions. The study therefore informed the range of observed carrier responses and highlighted real-world reporting limitations, but it did not contribute a reconstructed ROR or statistical weight.

### *Study-level treatment-by-BRCA interactions*

In Etan et al., pCR occurred in 24 of 26 carriers who received pembrolizumab plus chemotherapy and 10 of 18 carriers who received chemotherapy alone. Among noncarriers, pCR occurred in 32 of 53 and 11 of 30, respectively. The pembrolizumab-versus-control OR was 9.60 among carriers and 2.63 among noncarriers, giving an ROR of 3.65 (95% CI 0.52-25.62). The estimate is directionally compatible with a larger relative effect among carriers, but the interval includes no interaction and is consistent with both substantially smaller and much larger modification. All contributing cells and study-level estimates are detailed in Table 2 and displayed graphically in Figure 2.

**Table 2. Study-level treatment-by-germline-*BRCA* interaction estimates.**

| Study/model | Carrier pembro | Carrier control | Noncarrier pembro | Noncarrier control | OR carrier | OR noncarrier | ROR (95% CI) |
|---|---|---|---|---|---|---|---|
| Etan 2026 | 24/26 | 10/18 | 32/53 | 11/30 | 9.60 | 2.63 | 3.65 (0.52–25.62) |
| BRCAPATH 2026 | 31/35 | 4/7 | 99/190 | 15/44 | 5.81 | 2.10 | 2.76 (0.39–19.39) |
| Pooled REML-HK | — | — | — | — | — | — | 3.17 (0.54–18.51) |

*ROR >1 indicates a larger relative pembrolizumab effect among carriers. The pooled p value was 0.076; tau$^2$=0, I$^2$=0%, Q=0.039 (p=0.844). BRCAPATH noncarrier cells exclude nine pembrolizumab-group VUS and three control-group VUS and were derived from its supplement. HK, Hartung–Knapp; OR, odds ratio; REML, restricted maximum likelihood; ROR, ratio of odds ratios.*

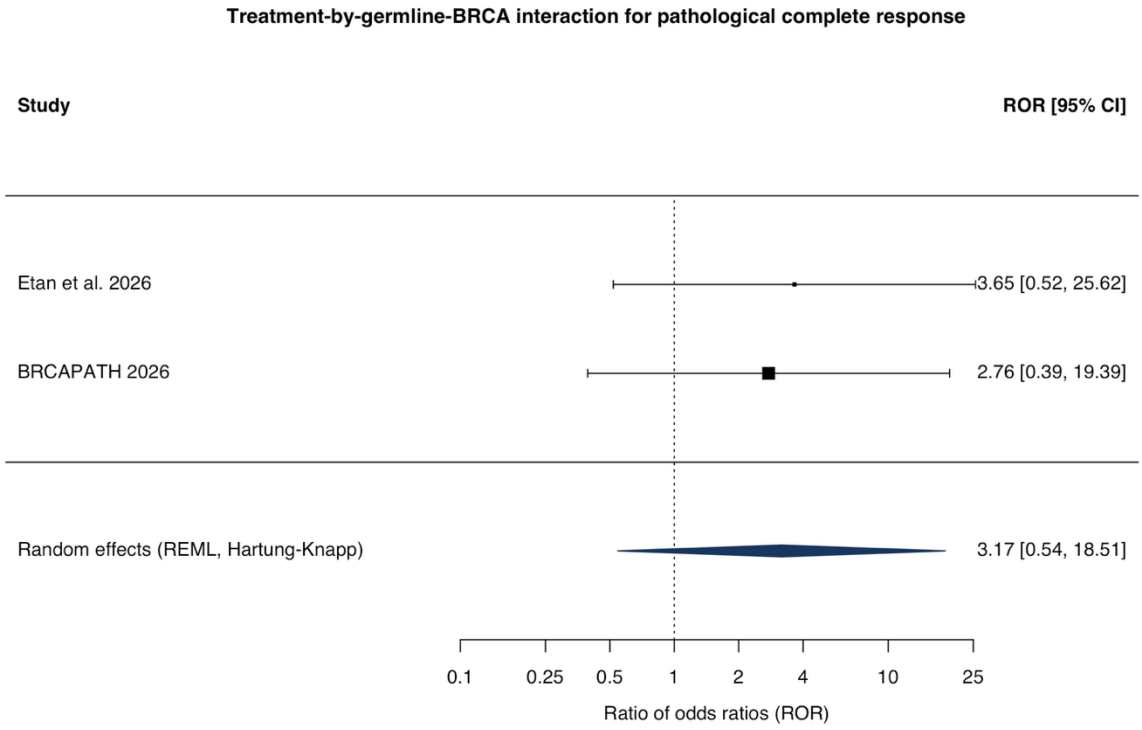


**Figure 2.** Forest plot of treatment-by-germline-BRCA interaction. Ratios of odds ratios (RORs) for pathological complete response. ROR >1 indicates a larger relative pembrolizumab effect among germline BRCA1/2 carriers. The diamond shows the REML random-effects estimate with Hartung–Knapp confidence interval.

In BRCAPATH, pCR occurred in 31 of 35 carriers receiving pembrolizumab plus chemotherapy and 4 of 7 carriers receiving chemotherapy alone. After the prespecified exclusion of variants of uncertain significance, the derived and verified noncarrier cells were 99 of 190 and 15 of 44, respectively. The pembrolizumab-versus-control OR was 5.81 among carriers and 2.10 among noncarriers, giving an ROR of 2.76 (95% CI 0.39-19.39). This interval also crossed the no-interaction value of 1. The four underlying pCR proportions are presented with the corresponding ROR

in Table 2 so that readers can distinguish absolute observed response from relative interaction.

### *Quantitative synthesis and sensitivity analyses*

The prespecified random-effects REML model with Hartung-Knapp inference produced a pooled ROR of 3.17 (95% CI 0.54-18.51; p=0.076). ROR>1 was defined in advance as a larger relative pembrolizumab-associated pCR effect among carriers. The confidence interval crossed 1 and spanned more than an order of magnitude, so the analysis did not demonstrate treatment-effect modification. The pooled estimate and its confidence interval are shown in Table 2 and Figure 2. The point estimate describes the center of the available unadjusted interaction evidence; it is not a probability that carriers benefit, not a direct carrier-versus-noncarrier OR, and not an estimate of absolute pembrolizumab benefit.

Estimated between-study variance was tau-squared=0, I-squared=0%, and Cochran Q=0.039 (p=0.844). With two studies, these estimates have very low diagnostic value; the result was recorded but not interpreted as evidence that the cohorts were homogeneous. Because tau-squared was estimated as zero, the normal-interval REML and common-effect sensitivity analyses yielded the same point estimate and standard-error structure: ROR 3.17 (95% CI 0.80-12.59; p=0.100). The narrower sensitivity interval reflects the inferential method, not additional information. No prediction interval, subgroup analysis, meta-regression, funnel plot, asymmetry test, or leave-one-out analysis was presented.

### *Risk of bias, interaction credibility, and certainty*

All three studies were judged at serious overall risk of bias. Confounding was serious because treatment allocation was non-randomized and could differ by calendar era, clinical risk, chemotherapy backbone, testing patterns, and treatment availability. Participant selection and missing genetic information could alter the composition of carrier and noncarrier strata. Intervention classification and pCR measurement were generally clearer than the allocation process, but objectively measured pCR did not remove confounding. Selection of the reported result remained a concern because subgroup data were not consistently prespecified or fully reported. The qualitative cohort had the additional limitation of irreconcilable noncarrier cells.

ICEMAN credibility was low for Etan et al. and BRCAPATH and very low for the Connors/Lang qualitative evidence. Germline status was measured before outcome ascertainment and a biological rationale exists, but no study reported a prespecified direction of pembrolizumab interaction, a formal adjusted within-study interaction test, or an adequate multiplicity strategy. Carrier strata were sparse, and the apparent directional agreement of two imprecise RORs provided limited reassurance. The qualitative cohort could not supply an interaction estimate.

GRADE certainty for the pooled pCR interaction was very low. Observational evidence began at low certainty and was downgraded for serious risk of bias and very serious imprecision. The wide interval encompassed no interaction, a smaller relative effect among carriers, and a very large positive interaction. Clinical differences were incorporated primarily through risk-of-bias and applicability judgements rather than a mechanical additional downgrade. Publication bias could not be assessed and was categorized as uncertain. No upgrading criterion was considered defensible. The complete certainty judgement is detailed in Table 3.

**Table 3. GRADE summary of findings for treatment-by-g*BRCA* interaction.**

| Outcome | Studies | Effect | Certainty | Key judgements | Interpretation |
|---|---|---|---|---|---|
| Treatment-by-g*BRCA* interaction for pCR | 2 retrospective cohorts (415 participants) | ROR 3.17 (95% CI 0.54-18.51) | Very low | Serious risk of bias; very serious imprecision; low ICEMAN credibility; publication bias uncertain | Evidence is very uncertain and includes no interaction or a large positive interaction |

*GRADE began at low certainty for observational evidence and was downgraded for risk of bias and imprecision. No upgrading criterion was considered defensible.*

## 4. Discussion

### *Principal findings*

This systematic review identified three retrospective comparative cohorts addressing germline *BRCA* and neoadjuvant pembrolizumab in early TNBC. Two cohorts supplied complete data for an explicit treatment-by-biomarker interaction. Both ROR point estimates were above 1, and the pooled point estimate was 3.17, but every confidence interval crossed the no-interaction value. The Hartung-Knapp interval was extremely wide, risk of bias was serious, interaction credibility was low, and certainty was very low. The appropriate conclusion is therefore that the observed direction is compatible with a larger relative pembrolizumab-associated pCR effect among carriers, while the available evidence does not establish germline *BRCA1/2* as a predictive biomarker for pembrolizumab.

The analysis answers a more demanding question than whether carriers have high pCR. In both quantitative studies, carriers receiving pembrolizumab had high observed response proportions, but carriers receiving chemotherapy alone also responded frequently. A

predictive interpretation depends on the difference between those treatment contrasts relative to the same contrast in noncarriers. This is why the ROR, rather than a carrier-only pCR proportion or a carrier-versus-noncarrier comparison in the pembrolizumab arm, was the prespecified estimand. The distinction is central to precision oncology: prognostic enrichment can be clinically important without identifying the component of a multidrug regimen responsible for the outcome.

### *Biological interpretation without predictive overreach*

A positive biological rationale exists for studying immunotherapy in *BRCA*-associated TNBC. Homologous-recombination deficiency can increase genomic instability and potentially generate immunogenic features, while TNBC commonly exhibits immune infiltration and checkpoint-pathway activity. However, biological plausibility does not determine the sign or magnitude of a clinical interaction. Germline *BRCA* status is also associated with basal-like phenotype, younger age, inherited-cancer ascertainment, DNA-damage sensitivity, and treatment choices. Each of these pathways can influence pCR or treatment allocation without indicating that PD-1 blockade contributes a larger incremental effect.

Chemotherapy sensitivity is the most immediate alternative explanation. Contemporary neoadjuvant evidence shows high pCR among some *BRCA* carriers even without immunotherapy, and randomized or matched comparisons have not yielded a uniform carrier-specific incremental effect[18–23]. In the current cohorts, differences in carboplatin exposure, anthracycline sequencing, calendar era, supportive care, and eligibility for pembrolizumab could produce nonexchangeable treatment groups. An unadjusted ROR reduces the error of comparing biomarker strata within one arm, but it cannot by itself remove confounding within the pembrolizumab-versus-control comparison. Prospective randomization or carefully harmonized individual-participant data with an adjusted interaction term would provide stronger evidence.

### *pCR modification is not equivalent to survival modification*

The present endpoint was pCR, not event-free or overall survival. At the individual-patient level, pCR is strongly associated with favorable outcome in TNBC, but a biomarker interaction on pCR does not guarantee an interaction on survival[15–17]. Survival incorporates post-surgical therapy, residual-disease treatment, competing events, follow-up duration, and non-proportional treatment effects. The KEYNOTE-522 population-average survival results support pembrolizumab in eligible early TNBC, but they do not supply the missing germline-*BRCA* interaction[4–7]. None of the included retrospective studies provided sufficiently mature, adjusted, and comparable treatment-by-*BRCA* survival data for pooling.

This boundary changes the language of clinical interpretation. The pooled result may motivate a hypothesis that the pCR contribution of pembrolizumab differs by germline *BRCA* status, but it cannot establish that carriers experience a larger survival gain, fewer recurrences, or better quality of life. Conversely, the absence of a statistically conclusive pCR interaction does not prove equal survival benefit. Future trials should report biomarker interactions separately for pCR, event-free survival, overall survival, and toxicity, and should avoid treating significance in one endpoint as validation in another.

### *Clinical implications*

The findings should not be used to select, prioritize, omit, or de-escalate pembrolizumab according to germline *BRCA* status. For patients who meet established clinical indications for a KEYNOTE-522-type regimen, the totality of randomized trial evidence remains more reliable than this sparse retrospective subgroup synthesis. A secondary randomized-trial analysis and a nationwide real-world cohort support the transportability of pembrolizumab-based treatment while showing that case mix matters[32,33]. Real-world safety and dose-intensity studies further emphasize that toxicity management and chemotherapy delivery are part of the treatment effect observed outside trials[34,35]. The pooled ROR does not provide an individual probability of pCR and cannot be converted into an absolute benefit without a defensible baseline risk, a clinically comparable regimen, and a valid causal model. Shared decision-making should continue to address stage, comorbidity, immune-mediated toxicity, fertility, treatment burden, and patient values rather than presenting *BRCA* status as a validated pembrolizumab selector.

At the same time, germline *BRCA* testing remains clinically important for reasons independent of this interaction question. A pathogenic variant can affect hereditary counselling, cascade testing, risk-reducing strategies, surgical planning, surveillance, and eligibility for PARP-inhibitor therapy[22,23]. Therefore, the conclusion that *BRCA* status is not yet a validated pembrolizumab-predictive biomarker must not be misread as an argument against genetic assessment. The appropriate message is separation of indications: *BRCA* testing is important, and pembrolizumab is important in eligible high-risk early TNBC, but the available evidence does not show that one should currently determine use of the other.

Generalizability is also constrained by the settings and treatment periods represented. Contemporary observational work has identified clinical predictors of pCR and described recurrence timing after chemoimmunotherapy[36,37], documented feasibility in a Japanese treatment setting[38], and begun to report *BRCA*-specific outcomes in multicenter real-world cohorts[39,40]. These studies are clinically informative but do not replace an adjusted treatment-by-*BRCA* interaction. The included cohorts came from Israel,

France, and the United States and may not reflect genetic testing access, ancestry, stage distribution, comorbidity, chemotherapy delivery, or supportive care in other health systems. Germline *BRCA* variant prevalence and founder mutations differ across populations, while variant interpretation and testing eligibility can change over time. The observed cells therefore should not be transported directly to a local clinic without considering whether patients would have met the same treatment and testing criteria. A clinically useful predictive biomarker requires not only a reproducible statistical interaction but also analytical validity, consistent variant classification, treatment-context relevance, and evidence that using the biomarker improves decisions or outcomes. None of those implementation conditions is established by the current pooled estimate.

Broader TNBC trials further demonstrate why biomarker meaning depends on treatment setting. Adjuvant-only atezolizumab did not improve invasive disease-free survival[41], whereas a phase II trial combining oncolytic virotherapy with neoadjuvant chemotherapy evaluated a distinct route to immune priming[42]. I-SPY2 combined durvalumab, olaparib, and paclitaxel in high-risk HER2-negative disease[43], while IMpassion131 and ASCENT biomarker analyses concerned metastatic TNBC and cannot be transported directly to the curative neoadjuvant setting[44,45]. NeoSACT provided another phase II chemoimmunotherapy signal using sintilimab and anlotinib[46]. Collectively, these primary studies support biological activity but also show that drug, timing, backbone, endpoint, and disease setting govern interpretation.

Recent translational studies likewise show that treatment response is distributed across multiple biological layers rather than explained by *BRCA* status alone. Intratumoral microbiota, senescent CD8-positive T-cell states, and the architecture of tertiary lymphoid structures have each been associated with response to neoadjuvant therapy or immunotherapy[47–49]. Plasma proteomic profiling and post-treatment magnetic resonance imaging have also generated response-prediction signals[50,51]. These observations identify research directions, but none validates germline *BRCA* as a stand-alone pembrolizumab selection rule.

### *Methodological implications for biomarker meta-analysis*

The review illustrates why subgroup meta-analysis should preserve within-study interactions. Pooling carrier-only effects and noncarrier-only effects separately and then informally comparing statistical significance would be invalid; a difference between a significant and a non-significant estimate is not itself a significant interaction. Similarly, meta-regression of study-level carrier prevalence would invite ecological bias. A within-study ROR uses the correct contrast for binary outcomes and can be combined on the log scale, although it remains only as credible as the underlying treatment comparisons and reporting[27].

Sparse interactions also challenge conventional random-effects practice. With two studies, tau-squared is poorly estimated, I-squared can be misleading, and Hartung-Knapp inference has one degree of freedom. The very wide primary interval appropriately communicates uncertainty but should not be treated as a calibrated prediction distribution. The normal-interval sensitivity analysis answers how much the interval depends on the inferential convention; it does not supersede the prespecified model. The correct response to imprecision is not to select the narrowest method or to reinterpret p=0.076 as a near-positive result, but to emphasize the effect estimate, interval, design limitations, and need for additional information.

### *Strengths*

The principal strength is alignment of the clinical question with an explicit interaction estimand. The protocol was prospectively registered and frozen before formal searching; eligibility required an external chemotherapy-only comparator; pCR, *BRCA* classification, and direction of effect were defined in advance. The extraction preserved source locations, integer counts, missingness, and report-to-study mapping. BRCAPATH variants of uncertain significance were excluded through a transparent, reproducible derivation rather than being silently grouped with carriers or noncarriers. The irreconcilable Connors/Lang noncarrier data were not imputed, protecting the meta-analysis from an unverifiable third estimate.

Additional strengths include domain-level ROBINS-I assessment, item-level ICEMAN assessment, explicit GRADE reasoning, and reproducible statistical code. The four underlying pCR proportions accompany each interaction estimate, reducing the risk that readers mistake an ROR for an absolute effect. Primary and sensitivity models are reported together, and analyses that were not credible with k=2 were identified as not performed rather than omitted without explanation. Finally, the human-machine workflow is reported as it occurred: machine assistance prepared screening, extraction, and code, while a named human verified all decisions and analytic values used in the synthesis.

### *Limitations*

The most important limitation is incomplete database coverage. Embase, CENTRAL, Scopus, and Web of Science were not searched because authenticated access was unavailable. Public-source searching, registry searching, citation methods, and metadata discovery were reproducible, but they are not equivalent to the complete multidatabase strategy specified in the protocol. In a two-study meta-analysis, a missed cohort could change the pooled estimate, heterogeneity, risk-of-bias profile, and certainty. The current numerical synthesis must therefore be interpreted as the result of the executed accessible-

source search and should be updated if the licensed sources become available.

The evidence base itself is highly vulnerable to bias. All comparisons were retrospective and non-randomized; treatment groups may differ in calendar era, chemotherapy backbone, stage, clinical fitness, genetic testing, and access to pembrolizumab. No study reported a prospectively planned adjusted interaction test. Carrier strata were small, one study required derivation of noncarrier cells, and another could not provide a complete interaction table. These limitations affect causal interpretation even if the arithmetic is correct. Statistical heterogeneity cannot be characterized reliably with k=2, and the pooled interval is compatible with markedly different clinical conclusions.

Only one named human verifier reviewed screening, extraction, and bias judgements. Although every analytic value and decision was source linked and verified, the workflow lacks the error-control benefit of a second independent human reviewer and adjudication. Selective subgroup reporting and publication bias could not be evaluated statistically. Outcome definitions were not completely harmonized, *BRCA1* and *BRCA2* could not be analyzed separately, and variants of uncertain significance were not handled uniformly across all reports. No credible interaction synthesis was available for event-free survival, overall survival, or toxicity. The analysis package did not yet have a persistent public repository identifier, limiting immediate external reproducibility despite complete local provenance.

### *Research priorities*

The most efficient next step is not a larger carrier-only response series but an analysis that preserves a valid treatment comparator. Trial sponsors and collaborative groups should report germline *BRCA* subgroup counts for both randomized arms of neoadjuvant immunotherapy trials, together with an adjusted treatment-by-biomarker coefficient and its variance. Analyses should prespecify the expected direction, distinguish *BRCA1* from *BRCA2* when sample size permits, exclude or separately classify variants of uncertain significance, and document testing coverage. Chemotherapy backbone, carboplatin exposure, stage, nodal status, age, and relevant postoperative therapy should be harmonized or adjusted.

An individual-participant-data collaboration could improve denominator reconciliation, treatment-era adjustment, and endpoint harmonization while reducing aggregation bias. It should estimate interactions on both relative and absolute scales, because a constant relative effect can still yield different absolute benefit across baseline risks. pCR analyses should be paired with event-free survival, overall survival, immune-related toxicity, and patient-reported outcomes. Replication across trials and external real-world cohorts should be planned before clinical implementation. Until such evidence exists, germline *BRCA* should be treated as a biologically plausible research modifier, not a validated decision rule for pembrolizumab.

Evidence updates should be designed prospectively because this topic is likely to change quickly as real-world KEYNOTE-522 cohorts mature and trial biomarker analyses are released. The update trigger should be a new eligible comparative dataset, corrected subgroup denominator, or directly reported adjusted interaction, not merely a new single-arm carrier series. Each update should rerun the frozen search concepts across all accessible databases, retain prior exports, document deduplication against the existing corpus, and distinguish a new report from a new study. If the evidence base expands sufficiently, prespecified analyses could compare contemporaneous versus historical controls, closely matched versus materially different chemotherapy backbones, *BRCA1* versus *BRCA2*, and adjusted versus reconstructed interactions. These analyses should be withheld until their information size avoids the overfitting that would occur in the present dataset.

Future reporting should also make the clinical scale explicit. Relative interactions answer whether the treatment contrast differs proportionally between biomarker strata, whereas patients and clinicians often need absolute differences under a specific baseline risk. Once credible randomized or adjusted estimates exist, investigators should present subgroup-specific risks, risk differences, numbers needed to treat, and uncertainty alongside the interaction coefficient. Such displays must use baseline risks from a clinically relevant population rather than back-calculating absolute benefit from a pooled ROR across nonexchangeable retrospective cohorts. This would connect methodologically valid interaction testing with decisions while preserving the distinction between biological interest, statistical evidence, and clinical utility.

## 5. Conclusion

Very-low-certainty retrospective evidence is directionally compatible with a larger relative effect of adding neoadjuvant pembrolizumab on pCR among germline *BRCA1/2* carriers, but it does not demonstrate treatment-effect modification. The confidence interval crosses no interaction, the evidence is confounded and sparse, and pCR findings cannot be extrapolated to survival. Germline *BRCA* status should not currently be used to select or withhold pembrolizumab, while genetic testing remains important for its established hereditary and therapeutic indications. Prospective or harmonized individual-participant analyses with adjusted within-study interaction estimates are required.

## Declarations

### *Funding*
None.

### *Conflicts of interest*
The authors declare no conflicts of interest.

### *Author contributions*
IMAS: Conceptualization and Methodology. MOS and NGBAW: Data curation. All authors must approve the final post-update manuscript before external submission.

### *Data and code availability*
The verified screening logs, de-identified extraction tables, domain-level risk-of-bias judgements, item-level interaction-credibility judgements, analysis code, package versions, and generated results are retained in the auditable project package. They may be supplied with the article or through a controlled repository route, excluding copyrighted full texts and publisher supplements. No persistent public repository identifier had been assigned at the time of this manuscript version.

### *Ethics approval*
Not applicable. This systematic review used published or publicly available evidence and involved no new collection of participant data.

### *Registration*
PROSPERO CRD420261472135.

### *Generative AI disclosure*
The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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