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CLINICAL RISK FACTORS ASSOCIATED WITH TRASTUZUMAB DERUXTECAN LUNG TOXICITY IN ADVANCED SOLID TUMORS

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Abstract:

This analysis examines how published clinical risk associations and toxicity severity inform the international interpretation of pulmonary safety during trastuzumab deruxtecan treatment. Descriptive secondary analysis combines four adjusted hazard ratio contrasts with aggregate outcomes from 1,150 participants across nine clinical trials, with observations through December 2020. Adjudicated interstitial lung disease or pneumonitis affected 15.4 percent of participants, while fatal toxicity affected 2.2 percent. Published Cox estimates indicate higher relative hazards among participants younger than 65 years, those receiving doses above 6.4 mg/kg, and those with baseline lung comorbidities, with hazard ratios of 1.56, 2.92, and 1.75, respectively. Their confidence intervals exclude one, although precision varies. The comparison between 6.4 and 5.4 mg/kg remains inconclusive. Toxicity proportions differ across tumor categories without standardized follow up. The contribution is an integrated interpretation that distinguishes relative association, absolute burden, severity, and uncertainty rather than establishing causal mechanisms. These distinctions support transparent safety communication and contextual assessment across oncology settings.

Key Words: Trastuzumab Deruxtecan; Interstitial Lung Disease; Antibody Drug Conjugates; Clinical Risk Assessment; Descriptive Secondary Analysis.

1. Introduction:

Pulmonary toxicity can compromise the clinical value of trastuzumab deruxtecan even when treatment achieves selective delivery of a cytotoxic payload to tumor cells. The central problem is therefore not whether tumor targeting improves therapeutic specificity, but how pulmonary adverse outcomes should be interpreted alongside treatment exposure and patient characteristics. Antibody drug conjugates combine antibody binding, cellular uptake, linker processing, and payload activity within one therapeutic construct. These processes influence both antitumor activity and toxicity outside the intended target tissue. Beck et al., 2017, explain that the safety of these therapies depends on the properties of the complete conjugate. This pharmacological perspective makes pulmonary toxicity an integral consideration in evaluating treatment rather than an isolated adverse event.

Trastuzumab deruxtecan illustrates the tension between therapeutic targeting and pulmonary safety. Tarantino et al., 2021, identify interstitial lung disease as a clinically consequential complication of ERBB2 directed antibody drug conjugates and discuss its recognition and management. However, the frequency of pulmonary events alone provides an incomplete account of their clinical significance. An overall proportion combines events of different severity, while a relative hazard describes an association over follow up rather than an absolute probability. Interpretation therefore requires attention to the outcome definition, denominator, observation period, and uncertainty surrounding each estimate. The substantive question addressed here concerns how these distinct forms of evidence can be interpreted together without treating them as interchangeable measures of risk.

Administered dose provides one connection between treatment characteristics and pulmonary outcomes. Greater systemic exposure may increase the opportunity for cytotoxic injury, but administered dose does not directly measure the exposure experienced by individual tissues. Yin et al., 2021, examined exposure response relationships in patients receiving trastuzumab deruxtecan and identified associations between exposure and safety outcomes. Their analysis establishes the relevance of pharmacological exposure while also clarifying why comparisons between clinical dose categories require careful interpretation. A higher point estimate in one category does not establish a continuous dose response relationship, and a confidence interval that includes the null value does not establish equivalent safety. This analysis retains those distinctions when comparing the available administered dose categories.

Patient characteristics provide a complementary perspective on susceptibility. Age group may correspond to differences in treatment tolerance, but chronological age does not directly measure physiological reserve. Wildiers et al., 2014, emphasize heterogeneity in functional status, comorbidity, and vulnerability among older patients with cancer. Baseline lung comorbidities identify a more organ specific clinical characteristic, although a combined indicator cannot distinguish the contribution of individual respiratory diagnoses. Mechanistic evidence also cautions against attributing pulmonary injury solely to

the intended tumor target. Kumagai et al., 2020, identified pulmonary injury and alveolar macrophage uptake in monkeys receiving trastuzumab deruxtecan. These findings provide biological context for evaluating pulmonary susceptibility, while remaining distinct from evidence that a particular mechanism explains the observed clinical associations.

The closest literature addresses related but different analytical questions. Exposure response analysis examines pharmacological relationships, geriatric assessment evaluates clinical vulnerability, and pulmonary toxicity research examines adverse outcome recognition and possible biological pathways. The present analysis addresses the interpretive task of bringing selected clinical associations together with absolute toxicity counts and severity distributions. Its contribution is a structured descriptive synthesis of existing evidence. It distinguishes the magnitude of a reported association from its precision and separates the frequency of toxicity from its consequences among affected patients. This contribution does not depend on presenting published estimates as newly discovered relationships.

The empirical material consists of published clinical summaries represented in a consolidated workbook. The underlying population comprises 1,150 participants from nine phase I and phase II trastuzumab deruxtecan monotherapy trials, with clinical observations extending to 21 December 2020. The retained analytical records contain four adjusted association contrasts covering age group, administered dose, and baseline lung comorbidities. Aggregate toxicity counts describe six exclusive tumor categories, including a residual category for missing tumor classification. The outcome is adjudicated drug related interstitial lung disease or pneumonitis. Published hazard ratios concern time to the first qualifying event, while severity counts classify affected participants by their highest recorded grade. The descriptive approach preserves these measurement distinctions and avoids treating repeated summaries from the same cohort as independent studies.

This study aims to describe pulmonary toxicity during trastuzumab deruxtecan treatment and interpret its published associations with age group, administered dose, and baseline lung comorbidities. The overarching research question asks how these clinical characteristics are associated with adjudicated pulmonary toxicity and how the reported associations relate to the observed burden and severity of events. The specific objectives are to interpret the age comparison, assess the two dose comparisons against their shared reference category, and examine the association involving baseline lung comorbidities. A complementary objective is to describe the distribution of pulmonary toxicity across tumor categories and severity grades.

The findings support differentiated interpretation rather than a uniform classification of risk. The highest dose category has the largest reported association but also substantial uncertainty, while the intermediate dose comparison remains less conclusive. Younger age and baseline lung comorbidities have positive reported associations, although their lower confidence limits lie close to the null value. The severity distribution further shows that a predominance of lower grade events can coexist with consequential fatal toxicity. Together, these observations support reviewing treatment category, pulmonary history, event severity, and estimate precision as separate elements of clinical evidence. Their international relevance lies in this transferable approach to interpretation rather than in an assumed equivalence of risks across healthcare settings.

2. Theory Conceptual Framework and Research Questions Development:

This analysis uses pharmacological reasoning to examine lung toxicity during trastuzumab deruxtecan treatment in advanced solid tumors. Antibody drug conjugates connect tumor targeting with systemic delivery of a cytotoxic payload. Their therapeutic selectivity depends on antibody binding, cellular uptake, linker stability, and payload release. These processes also determine exposure outside the tumor. Beck et al., 2017, explain that toxicity reflects the properties of the complete conjugate rather than antibody specificity alone. This reasoning places treatment exposure and patient susceptibility within a common framework for interpreting pulmonary adverse outcomes.

The focal outcome is adjudicated drug related interstitial lung disease or pneumonitis. It represents pulmonary injury attributed to treatment after clinical assessment. Mechanistic evidence supports distinguishing tumor targeting from pulmonary toxicity. Kumagai et al., 2020, identified alveolar injury and uptake of trastuzumab deruxtecan by pulmonary macrophages in monkeys, while pulmonary HER2 expression did not correspond directly to the location of injury. These findings support a possible pathway involving uptake independent of the intended tumor target. They provide biological context for examining clinical risk characteristics without establishing that the same pathway explains every human event.

Age group represents the first observed dimension of the clinical risk profile. Age may correspond to differences in organ reserve, recovery capacity, and treatment tolerance, but chronological age does not measure these characteristics directly. Wildiers et al., 2014, emphasize that older patients with cancer differ in functional status, comorbidity, and physiological vulnerability. Consequently, an age category can organize clinical comparisons without identifying a uniform biological state. This analysis compares patients younger than 65 years with those aged 65 years or older and interprets the published association without imposing a predetermined direction.

Research question 1: What adjusted association is reported between age group and adjudicated drug related interstitial lung disease or pneumonitis during trastuzumab deruxtecan treatment?

Administered dose represents the treatment dimension of the framework. Pharmacological reasoning suggests that greater exposure may increase the opportunity for cytotoxic injury in susceptible tissues. Nevertheless, administered dose and systemic exposure are distinct concepts. Patients receiving the same dose may experience different concentrations, while comparisons across dose categories may also reflect differences in clinical populations. Yin et al., 2021, identified relationships between exposure and safety outcomes during trastuzumab deruxtecan treatment, supporting the relevance of exposure to the therapeutic balance. This analysis examines the available categories of 5.4 mg/kg, 6.4 mg/kg, and above 6.4 mg/kg, administered every three weeks. These categories support descriptive comparisons of published associations rather than an assumed linear dose relationship.

Research question 2: What adjusted associations are reported between administered dose categories and adjudicated drug related interstitial lung disease or pneumonitis during trastuzumab deruxtecan treatment?

Baseline lung comorbidities represent the pulmonary susceptibility dimension. Existing respiratory disease may reduce the capacity to tolerate additional injury and may complicate the distinction between treatment toxicity and deterioration of an underlying condition. Skeoch et al., 2018, describe drug induced interstitial lung disease as a heterogeneous clinical condition whose interpretation requires attention to underlying disease and competing explanations. This supports examining pulmonary history while preserving the distinction between biological susceptibility and diagnostic attribution. The available measure classifies baseline lung comorbidities as present or absent. It therefore supports interpretation of the combined category rather than separate conclusions about individual respiratory disorders.

Research question 3: What adjusted association is reported between the presence of baseline lung comorbidities and adjudicated drug related interstitial lung disease or pneumonitis during trastuzumab deruxtecan treatment?

The conceptual framework connects three observed clinical characteristics with one adjudicated pulmonary outcome. Clinical risk profile serves as an organizing term for age group, administered dose, and baseline lung comorbidities rather than a numerical composite. This analysis addresses the research questions through descriptive interpretation of published adjusted hazard ratios and their confidence intervals. Aggregate counts describe the observed proportion of affected patients and the distribution of toxicity grades across tumor categories. Hazard ratios characterize associations over follow up, whereas patient proportions summarize the observed burden of toxicity. Keeping these measures distinct aligns the conceptual argument with the available evidence.

3. Data:

This analysis consolidates published clinical summaries to describe lung toxicity during trastuzumab deruxtecan treatment in advanced solid tumors. Source documentation, sample construction, mathematical definitions, and consistency checks connect the available evidence to the descriptive research questions.

3.1 Data Sources, Population, and Sample Construction:

The empirical source is the pooled clinical analysis reported by Powell et al., 2022, in ESMO Open. The publication combines nine phase I and phase II trastuzumab deruxtecan monotherapy trials. Its persistent identifiers are DOI 10.1016/j.esmoop.2022.100554 and PubMed Central accession PMC9434416. The article is available under the Creative Commons Attribution 4.0 licence. The workbook records an extraction date of 28 October 2026. Clinical observations extend to 21 December 2020, which is distinct from the publication and extraction dates.

The target population comprises patients receiving trastuzumab deruxtecan for advanced solid tumors. The accessible sampling frame consists of published summaries covering 1,150 trial participants who received at least one monotherapy dose of 5.4 mg/kg or higher. Participants were enrolled in Japan and other countries. The extracted records do not identify individual patients, treatment centres, or countries outside Japan.

The dataset contains cumulative clinical summaries at a common reporting cutoff. It has no regular observation frequency. Follow up varies across participants. The analytical records comprise published adjusted hazard ratio contrasts and aggregate tumor categories. Consequently, the number of spreadsheet records differs from the number of underlying participants.

Selection followed the three clinical dimensions represented in the framework: age group, administered dose, and baseline lung comorbidities. Four association contrasts were extracted from Figure 2B. Toxicity counts were extracted from Table 3, and category denominators were checked against Table 2. The overlapping subgroup of patients with HER2 positive breast cancer receiving 5.4 mg/kg was excluded from the tumor classification table because these participants were already included in the breast cancer category.

Table 1: Construction of the descriptive dataset

Stage	Units Represented	Retained Records	Selection or Construction Rule
Underlying clinical population	1,150 participants across nine trials	Published aggregate source	Receipt of at least one qualifying monotherapy dose
Age comparison	Two age categories	1 contrast	Younger than 65 years compared

Stage	Units Represented	Retained Records	Selection or Construction Rule
			with 65 years or older
Dose comparisons	Three dose categories	2 contrasts	Each higher dose category compared with 5.4 mg/kg
Pulmonary comorbidity comparison	Two comorbidity categories	1 contrast	Presence compared with absence
Reported toxicity summaries	Five named tumor categories and the overall cohort	6 records	Retain exclusive named categories and a separate overall summary
Residual tumor category	Two participants with missing tumor classification	1 derived record	Subtract named category counts from overall counts
Completed descriptive dataset	One underlying clinical cohort	4 association contrasts and 7 toxicity records	Six exclusive tumor categories and one overall summary

3.2 Data Integration, Cleaning, and Quality Assurance:

Integration combined summaries from different locations within the same publication. Association estimates and tumor toxicity counts remain separate because they represent different analytical units. Stable contrast and tumor category identifiers support traceability. No patient identifier linkage or temporal matching was performed.

Association records preserve comparison categories, reference categories, category sizes, adjusted hazard ratios, and confidence limits. Toxicity records preserve patient denominators and counts for grades 1 through 5. Both record types retain source identifiers and publication locations. Repeated cohort denominators across association records identify shared participants rather than additional samples.

Checks confirmed four unique association contrast identifiers and seven unique toxicity record identifiers. All selected association records contain category sizes, positive hazard ratios, and ordered confidence limits enclosing the corresponding estimate. Every toxicity record satisfies the conditions that grade counts sum to affected patients and affected patients do not exceed the category denominator. The exclusive tumor categories reconcile to 1,150 participants and 177 affected patients.

The five named tumor categories contain 1,148 participants. Equation 1 reconstructs the residual category for each count field.

$$x_{unknown} = x_{overall} - \sum_{i=1}^{5} x_i$$

Here, $x_{unknown}$ is the residual count for participants with missing tumor classification, $x_{overall}$ is the corresponding overall count, and $x_i$is the count for named tumor category i. The calculation is applied separately to patient denominators, affected patient counts, and individual grade counts.

Equation 1 identifies two participants with missing tumor classification and zero adjudicated events within that residual category. These zeros follow from the reported totals. They do not replace unavailable clinical measurements.

No selected association estimate or retained toxicity count required imputation or interpolation. The highest dose category contains 27 participants and remains in the dataset. Its small size represents a feature of the evidence rather than a data error. No trimming, winsorization, or adjustment of published estimates was applied.

3.3 Variable Measurement, Construction, and Validation:

The clinical risk profile comprises three observed categorical characteristics. It is an organizing construct rather than a latent variable or composite index. Age distinguishes participants younger than 65 years from those aged 65 years or older. Administered dose distinguishes 5.4 mg/kg, 6.4 mg/kg, and above 6.4 mg/kg, each given every three weeks. Baseline lung comorbidities distinguish the presence and absence of respiratory conditions grouped by the source.

The outcome is adjudicated drug related interstitial lung disease or pneumonitis. Published hazard ratios concern time to the first qualifying event. Aggregate toxicity counts classify affected participants according to their highest event grade. These measures describe different aspects of pulmonary toxicity and retain separate interpretations.

Table 2: Variable dictionary

Variable or Indicator	Analytical Role	Definition and Construction	Source and Identifier	Unit and Frequency	Transformation and Direction	Missing Value Rule	Coverage and Limitation
Age group	Clinical characteristic	a < 65versus a ≥ 65, where ais baseline age in years	Table 2 and Figure 2B	Baseline category	Older group is the reference	Preserve reported categories	One published contrast
Administered dose	Treatment characteristic	d = 5.4,d = 6.4ord > 6.4,	Table 2 and Figure 2B	Dose category	5.4 mg/kg is the reference	Preserve reported	Two contrasts sharing a

Variable or Indicator	Analytical Role	Definition and Construction	Source and Identifier	Unit and Frequency	Transformation and Direction	Missing Value Rule	Coverage and Limitation
		mg/kg every three weeks				categories	reference category
Baseline lung comorbidities	Clinical characteristic	Presence or absence of grouped respiratory conditions	Table 2 and Figure 2B	Baseline category	Absence is the reference	Preserve reported categories	Individual respiratory diagnoses are grouped
Adjusted hazard ratio	Published association measure	HR_j for contrast jrelative to its reference category	Figure 2B	Ratio over follow up	Values above one indicate higher relative hazard	No missing selected estimates	Extracted from the source model
Confidence limits	Published uncertainty measure	L_j and U_j, the lower and upper 95 percent limits	Figure 2B	Ratio bounds	Retain original scale	No missing selected limits	Published bounds are rounded
Category size	Descriptive denominator	Reported participants in each comparison and reference category	Table 2 and Figure 2B	Participants	No transformation	Preserve reported counts	Does not provide category specific event counts
Tumor category denominator	Descriptive denominator	N_i, the participants in tumor category i	Tables 2 and 3	Participants at reporting cutoff	No transformation	Derive residual category using Equation 1	Overall row overlaps category rows
Affected patients	Outcome count	E_i, the participants with at least one qualifying event	Table 3	Participants over follow up	Higher values indicate greater absolute burden	Preserve reported zeros	Counts patients rather than events
Toxicity grade counts	Severity description	G_{ig}, the participants assigned to highest grade gin category i	Table 3	Participants over follow up	Higher grades indicate greater severity	Preserve reported zeros	Each affected patient contributes to one grade
Observed toxicity proportion	Calculated outcome summary	$p_i = E_i/N_i$	Workbook calculation	Proportion over follow up	Higher values indicate a larger affected share	Require a positive denominator	Not a fixed duration risk
Participants without an adjudicated event	Calculated descriptive count	$C_i = N_i - E_i$	Workbook calculation	Participants	Higher values indicate more participants without a recorded qualifying event	Derive from complete counts	Does not establish absence of future toxicity
Log hazard ratio	Supporting calculation	$\ell_j = \ln H R_j$	Workbook calculation	Log ratio	Zero corresponds to a hazard ratio of one	Require a positive hazard ratio	Not a newly estimated coefficient
Approximate standard error	Supporting uncertainty calculation	Equation 6	Workbook calculation	Log ratio scale	Higher values indicate lower precision	Require positive confidence limits	Reconstructed from rounded bounds
Interval exclusion indicator	Descriptive evidence flag	Equation 7	Workbook calculation	Binary condition	One indicates an interval excluding the null value	Require both confidence limits	Not an independent statistical test

Equation 2 reconciles grade counts with the number of affected participants.

$$E_i = \sum_{g=1}^{5} G_{ig}$$

Here, E_i is the number of affected participants in tumor category i, and G_{ig} is the number assigned to highest toxicity grade g. Grade 5 represents fatal toxicity. Equation 3 calculates the complementary patient count.

$$C_i = N_i - E_i$$

Here, C_i is the number of participants without an adjudicated qualifying event, $N_i$is the category denominator, and $E_i$is the affected patient count. Equation 4 calculates the observed proportion and its percentage representation.

$$pi = \frac{E_i}{N_i} \text{Where } N_i > 0$$

$$P_i = 100pi.$$

Here, pi is the observed toxicity proportion and $P_i$is the corresponding percentage. Both use the same numerator and denominator. Equation 5 transforms the published association estimate.

$$\ell_j = \ln H R_j$$

Here, ℓ_j is the log hazard ratio for contrast j, and $HR_j$is its published adjusted hazard ratio. Equation 6 reconstructs the approximate standard error.

$$SE_j = \frac{\ln U_j - \ln L_j}{2z_{0.975}}$$

Here, SE_j is the approximate standard error of the log hazard ratio, U_j and L_j are the published upper- and lower-95 percent confidence limits, and $z_{0.975} = 1.95996398454005$is the standard normal quantile. Approximation arises because the published confidence limits are rounded. Equation 7 defines the interval exclusion indicator.

$$D_j = \begin{cases} 1, & L_j > 1 \text{ or } U_j < 1, \\ 0, & L_j \le 1 \le U_j. \end{cases}$$

Here, D_j equals one when the published interval excludes the null hazard ratio of one and zero when it includes that value. The workbook displays these conditions as Yes and No.

The selected clinical categories have completed reported counts. Participants younger than 65 years number 754, representing 65.6 percent of the cohort. Participants aged 65 years or older number 396. Dose categories contain 315, 808, and 27 participants, respectively. Baseline lung comorbidities are present in 81 participants and absent in 1,069.

Overall, 177 participants experienced adjudicated lung toxicity, representing 15.4 percent of the cohort. Highest recorded grades comprise 48 participants at grade 1, 89 at grade 2, 14 at grade 3, one at grade 4, and 25 at grade 5. Measurement validation concerns transcription accuracy, category consistency, denominator integrity, and arithmetic reconciliation.

3.4 Analytical Framework, Identification, and Reproducibility:

This analysis applies descriptive secondary analysis to published clinical evidence. The research questions concern the reported associations of age, administered dose, and baseline lung comorbidities with adjudicated pulmonary toxicity. Aggregate counts describe the distribution of affected participants across tumor categories and toxicity grades.

The source estimated exploratory multivariable Cox models stratified by breast versus other cancer types. This analysis retains the published adjusted estimates without refitting those models. The four contrasts share an underlying cohort, while the two dose contrasts also share a reference category. They therefore represent related comparisons rather than independent studies.

Interpretation separates relative association, absolute burden, and uncertainty. Hazard ratios describe relative hazards over follow up. Observed proportions describe the share of participants with adjudicated toxicity. Confidence intervals describe uncertainty around the published associations. The log transformations, reconstructed standard errors, and interval flags support transparent presentation without generating additional clinical observations.

The descriptive proportions are not standardized to a common treatment duration. Differences across tumor categories therefore describe the observed clinical experience without attributing those differences exclusively to tumor type. The risk contrasts retain their interpretation as adjusted associations rather than causal effects.

Reproducibility rests on source identifiers, publication locations, stable record identifiers, preserved inputs, and visible spreadsheet formulas. Risk contrasts remain separate from toxicity counts. The residual tumor category is marked as derived, and the overall cohort remains separate from the exclusive category totals. These conventions align measurement and aggregation while preventing repeated counting of participants.

4. Methods:

4.1 Research Design and Analytical Scope:

This analysis uses a descriptive secondary design to examine pulmonary toxicity during trastuzumab deruxtecan treatment in advanced solid tumors. The research questions concern the published associations of age group, administered dose, and baseline lung comorbidities with adjudicated drug related interstitial lung disease or pneumonitis. Aggregate patient counts provide a complementary description of toxicity frequency and severity.

Two analytical units are distinguished. The first is a published adjusted association contrast, represented by a hazard ratio, confidence limits, and comparison and reference category sizes. The second is an aggregate tumor category, represented by its patient denominator and toxicity counts. Table 1 documents record selection, while Table 2 defines the measures used in the analysis.

The association component contains four contrasts drawn from one underlying cohort. These contrasts are interpreted as related results rather than independent studies. Both dose comparisons share the same reference category. Consequently, the analysis does not combine the contrasts into a pooled effect or treat repeated cohort denominators as additional participants.

The descriptive component examines cumulative outcomes through 21 December 2020. Because follow up varies across participants, observed proportions describe the recorded clinical experience rather than risk over a standardized duration. The design supports interpretation of reported conditional associations and aggregate outcome distributions. It does not identify causal effects.

4.2 Measurement and Descriptive Calculations:

Measurement follows the clinical categories preserved in the workbook. Age compares participants younger than 65 years with those aged 65 years or older. Administered dose compares 6.4 mg/kg and above 6.4 mg/kg with a reference dose of 5.4 mg/kg, each administered every three weeks. Baseline lung comorbidities compare presence with absence. These characteristics remain separate observed measures rather than components of a composite score.

The pulmonary outcome retains the source adjudication definition. Association estimates concern time to the first qualifying event, whereas severity summaries classify each affected participant by the highest recorded toxicity grade. This distinction prevents recurrent events or multiple grades from being interpreted as additional affected patients.

The residual tumor category is calculated using Equation 1. Grade counts are reconciled with affected patient totals using Equation 2. Complementary counts, observed proportions, and percentages follow Equations 3 and 4. The overall cohort row remains separate from the exclusive tumor categories during aggregation.

Severe toxicity is summarized by combining grades 3, 4, and 5. Equation 8 defines the calculation.

$$S_i = \sum_{g=3}^{5} G_{ig}$$

Here, S_i is the number of participants with grade 3 or higher toxicity in tumor category i, and $G_{ig}$is the number assigned to highest toxicity grade g. The corresponding severe toxicity percentage is calculated by applying Equation 4 with $S_i$as the numerator. Severity shares among affected participants use a different denominator. Equation 9 defines this calculation.

$$Q_{lower} = 100\frac{G_1 + G_2}{E}$$

$$Q_{fatal} = 100\frac{G_5}{E}$$

Here, Q_{lower} is the percentage of affected participants whose highest toxicity grade is 1 or 2, Q_{fatal} is the percentage whose highest grade is 5, $G_g$is the overall number assigned to grade \(g\), and \(E\) is the overall number of affected participants. These conditional severity shares are distinguished from percentages calculated using all treated participants.

Category composition is described through counts and percentages. Means and standard deviations are not calculated for grouped age categories, categorical treatment assignments, or published association estimates. Numerical results are calculated from the underlying counts before rounding for presentation.

4.3 Interpretation of Published Association Estimates:

The association analysis retains the published adjusted hazard ratios and confidence intervals without refitting the underlying survival model. The source used exploratory multivariable Cox regression stratified by breast versus other cancer types. Adjustment belongs to that original analysis; the consolidated workbook supplies the selected results rather than individual event histories or a new estimation sample.

Each contrast is evaluated through its reference category, direction, magnitude, and uncertainty. A hazard ratio above one indicates a higher reported relative hazard in the comparison category. A value below one indicates a lower reported relative hazard. These interpretations concern hazards over follow up and do not represent absolute probability differences. Equation 10 expresses the relative hazard contrast as a percentage.

$$\Delta_j = 100(HR_j - 1)$$

Here, Δ_j is the percentage difference in relative hazard for contrast j, and HR_j is its published adjusted hazard ratio. Positive values indicate higher relative hazards, while negative values indicate lower relative hazards. The same transformation is applied to the confidence limits when expressing their range in percentage terms.

Log hazard ratios follow Equation 5. Approximate standard errors are reconstructed using Equation 6 from the published confidence limits. Because those limits are rounded, reconstructed standard errors remain supporting approximations rather than exact outputs from the original model.

Equation 7 identifies whether each published confidence interval excludes the null hazard ratio of one. This indicator is interpreted alongside interval width and substantive magnitude. An interval crossing one is not treated as evidence of equivalence or absence of association. An interval excluding one is not treated as proof of causality or independent replication.

The analytical sequence follows the research questions: age group, administered dose, and baseline lung comorbidities. Dose comparisons are considered separately because the available categories do not establish a continuous exposure scale. The shared reference category also prevents the two contrasts from being interpreted as independent estimates of a dose response curve.

4.4 Processing, Quality Assurance, and Reproducibility:

Processing begins with the selected published inputs and retains their original numerical meaning. Association records preserve category definitions, category sizes, hazard ratios, and confidence limits.

Toxicity records preserve patient denominators and grade counts. Stable identifiers and publication locations connect each record to its source.

Risk contrasts and toxicity categories remain in separate worksheets. No patient level merge is attempted. The overlapping breast cancer treatment subgroup is excluded from the tumor classification summaries, while the overall cohort is retained as a separate reference row. Participants with missing tumor classification remain in an explicitly labelled residual category.

Quality assurance checks record uniqueness, numerical completeness, confidence interval ordering, and count consistency. Association records must contain positive hazard ratios and confidence limits, with the lower bound not exceeding the point estimate and the point estimate not exceeding the upper bound. Toxicity records must contain nonnegative integer counts, affected patient totals must not exceed denominators, and grade counts must reconcile with affected patient totals.

Aggregate reconciliation then compares the exclusive tumor categories with the overall cohort. The residual category is checked through subtraction rather than imputation. Reported zero counts remain unchanged. Derived zeros are retained only where they follow from complete overall and category totals.

No imputation, interpolation, trimming, or winsorization is applied. The small highest dose category remains in the analysis because its limited size affects precision rather than establishing a data error. All calculations use the complete selected records, and no additional participant exclusions arise from the descriptive procedures.

Calculations are implemented through visible spreadsheet formulas, with record structure and arithmetic independently checked using Python. Formula checks cover proportions, complementary counts, logarithmic transformations, reconstructed standard errors, and interval indicators. The completed workbook preserves source identifiers, comparison categories, reference categories, and the distinction between reported and derived values.

The resulting method answers the research questions through traceable descriptive calculations and calibrated interpretation of published associations. Its analytical strength lies in preserving denominators, uncertainty, and dependence between records while keeping the clinical conclusions within the information supplied by the dataset.

5. Findings:

This analysis examines the distribution of adjudicated lung toxicity and the reported associations of age, administered dose, and baseline lung comorbidities with that outcome. The findings combine aggregate patient counts with four published adjusted hazard ratio contrasts reproduced in the supplied workbook. Interpretation separates observed toxicity burden, relative association, and statistical uncertainty.

5.1 Sample Composition and Clinical Coverage:

The underlying cohort comprises 1,150 participants across nine phase I and phase II trastuzumab deruxtecan monotherapy trials, with clinical observations extending to 21 December 2020. The analytical dataset contains four association contrasts and six exclusive tumor categories, alongside a separate overall summary. These records describe one shared cohort rather than independent patient samples.

Participants younger than 65 years account for 754 patients, or 65.6 percent of the cohort. The remaining 396 patients, representing 34.4 percent, are aged 65 years or older. Dose allocation is concentrated at 6.4 mg/kg every three weeks, received by 808 participants, or 70.3 percent. The 5.4 mg/kg category contains 315 participants, or 27.4 percent, while doses above 6.4 mg/kg account for 27 participants, or 2.3 percent. Baseline lung comorbidities are present in 81 participants, representing 7.0 percent.

This composition matters for interpretation. The highest dose category and the pulmonary comorbidity group contain fewer participants than their reference categories. Their association estimates must therefore be assessed alongside confidence intervals rather than ranked solely by magnitude. Age categories also represent chronological distinctions rather than direct measurements of physiological reserve. Wildiers et al., 2014, distinguish chronological age from the functional and clinical characteristics that shape treatment tolerance.

5.2 Distribution and Severity of Pulmonary Toxicity:

Adjudicated drug related interstitial lung disease or pneumonitis affected 177 participants, corresponding to 15.4 percent of the cohort. The remaining 973 participants had no adjudicated qualifying event within the observed follow up. Among affected participants, 137 had a highest recorded toxicity grade of 1 or 2, representing 77.4 percent of affected patients. Forty participants experienced grade 3 or higher toxicity, corresponding to 3.5 percent of the overall cohort.

Fatal toxicity occurred in 25 participants, representing 2.2 percent of the cohort and 14.1 percent of affected patients. Thus, the predominance of lower grade events coexists with a clinically consequential fatal component. The overall proportion alone does not capture this severity distribution.

Table 3: Adjudicated pulmonary toxicity by tumor category

Tumor Category	Participants	Affected Patients	Observed Toxicity Percentage	Patients With Grade 3 or Higher Toxicity	Grade 3 or Higher Percentage	Fatal Events
Breast cancer	510	105	20.6	22	4.3	15

Tumor Category	Participants	Affected Patients	Observed Toxicity Percentage	Patients With Grade 3 or Higher Toxicity	Grade 3 or Higher Percentage	Fatal Events
Gastric cancer	294	25	8.5	5	1.7	1
Lung cancer	203	31	15.3	8	3.9	6
Colorectal cancer	107	9	8.4	4	3.7	3
Other cancers	34	7	20.6	1	2.9	0
Tumor classification missing	2	0	0.0	0	0.0	0
Overall cohort	1,150	177	15.4	40	3.5	25

Breast cancer contributes the largest absolute burden, with 105 affected participants and 15 fatal events. Its observed toxicity proportion exceeds that of gastric cancer by 12.1 percentage points. However, the breast cancer and other cancer categories both have an observed proportion of 20.6 percent despite containing 510 and 34 participants, respectively. Identical percentages therefore represent substantially different volumes of clinical evidence.

The lung cancer category has an observed toxicity proportion of 15.3 percent and a grade 3 or higher proportion of 3.9 percent. Colorectal cancer has a lower overall proportion of 8.4 percent, but four of its nine affected participants experienced grade 3 or higher toxicity. These differences show why event frequency and severity require separate assessment.

The tumor category comparisons are descriptive. They are not standardized for treatment duration, administered dose, or other clinical characteristics. Hackshaw et al., 2020, documented variation in reported pulmonary toxicity across HER2 targeting treatment settings, supporting attention to clinical context when interpreting crude proportions.

5.3 Reported Associations With Clinical Risk Characteristics:

The main estimates table presents the four adjusted contrasts retained in the workbook. These estimates originate from the source's exploratory multivariable Cox analysis, stratified by breast versus other cancer types. They describe associations with time to the first adjudicated qualifying pulmonary event.

Table 4: Published adjusted associations with pulmonary toxicity

Clinical Characteristic	Comparison Category	Reference Category	Comparison Participants	Reference Participants	Adjusted Hazard Ratio	Lower 95 Percent Confidence Limit	Upper 95 Percent Confidence Limit
Age group	Younger than 65 years	65 years or older	754	396	1.56	1.02	2.38
Administered dose	6.4 mg/kg every three weeks	5.4 mg/kg every three weeks	808	315	1.30	0.85	1.99
Administered dose	Above 6.4 mg/kg every three weeks	5.4 mg/kg every three weeks	27	315	2.92	1.32	6.42
Baseline lung comorbidities	Present	Absent	81	1,069	1.75	1.03	2.98

For research question 1, participants younger than 65 years have a reported adjusted hazard ratio of 1.56 relative to participants aged 65 years or older. The point estimate corresponds to a 56 percent higher relative hazard. The confidence interval extends from 1.02 to 2.38, ranging from a small elevation to a substantially larger association. Its lower bound lies close to one. The result identifies the direction of the reported association without establishing that younger age itself causes greater susceptibility.

For research question 2, the two dose comparisons differ in magnitude and precision. The adjusted hazard ratio for 6.4 mg/kg relative to 5.4 mg/kg is 1.30, with a confidence interval from 0.85 to 1.99. Although the point estimate indicates a 30 percent higher relative hazard, the interval includes both a lower hazard and an appreciable increase. This comparison does not establish equivalence between the doses or demonstrate the absence of an association.

The category above 6.4 mg/kg has an adjusted hazard ratio of 2.92 relative to 5.4 mg/kg. The point estimate corresponds to a 192 percent higher relative hazard. Its confidence interval extends from 1.32 to 6.42. The interval lies above one but remains wide, consistent with uncertainty surrounding the magnitude of the association in a category containing 27 participants.

The dose findings therefore indicate a larger reported association at the highest administered category, while the intermediate comparison remains less conclusive. They do not establish a continuous

dose response curve or a precise toxicity threshold. Yin et al., 2021, identified relationships between systemic exposure and safety outcomes during trastuzumab deruxtecan treatment. That evidence provides pharmacological context, while preserving the distinction between administered dose categories and measured systemic exposure.

For research question 3, baseline lung comorbidities are associated with an adjusted hazard ratio of 1.75 relative to their absence. The point estimate corresponds to a 75 percent higher relative hazard. The confidence interval extends from 1.03 to 2.98, indicating uncertainty from a small elevation to almost three times the reference hazard. Because the measure groups several respiratory conditions, this result applies to the combined comorbidity category rather than to each diagnosis separately.

Kumagai et al., 2020, demonstrated pulmonary injury and alveolar macrophage uptake in a preclinical investigation of trastuzumab deruxtecan. Those findings support the biological relevance of pulmonary toxicity but do not identify the mechanism responsible for the clinical comorbidity association reported here.

5.4 Integrated Interpretation of the Research Questions:

The three research questions yield differentiated answers. Younger age and the presence of baseline lung comorbidities have published confidence intervals entirely above the null hazard ratio, although both lower limits are close to one. Doses above 6.4 mg/kg show the largest point estimate and the widest confidence interval among the selected contrasts. The comparison between 6.4 mg/kg and 5.4 mg/kg remains compatible with several plausible association magnitudes.

The aggregate toxicity results add an absolute clinical perspective. Pulmonary toxicity affected approximately one in six participants, while grade 3 or higher events affected 3.5 percent of the cohort. Fatal events represented a smaller share of all participants but a substantial share of those with adjudicated toxicity. Relative hazard estimates and absolute event proportions therefore provide complementary information.

The evidence does not support treating tumor targeting as sufficient assurance of pulmonary safety. Beck et al., 2017, explain that antibody drug conjugate toxicity depends on the properties of the complete therapeutic construct, including payload delivery and processing. The present descriptive synthesis is consistent with evaluating treatment characteristics alongside patient susceptibility, while retaining the distinction between mechanistic reasoning and observed clinical association.

Taken together, the findings identify reported associations involving age, the highest administered dose category, and baseline lung comorbidities. They also show that the intermediate dose comparison is less conclusive and that the largest association is estimated with substantial uncertainty. These conclusions describe the published evidence represented in the workbook rather than independent model validation.

6. Discussion:

Pulmonary toxicity requires interpretation beyond the overall frequency of adverse events. Table 4 shows that the largest published relative hazard occurs in the highest dose category, while the intermediate dose comparison remains compatible with both lower and higher hazards. Younger age and baseline lung comorbidities also have reported associations above the null value, although their lower confidence limits lie close to one. Equations 5 and 7 distinguish association magnitude from interval exclusion, preventing a binary interpretation from obscuring differences in precision. The contribution of this analysis is the integrated interpretation of clinical susceptibility, dose categories, and absolute toxicity burden within one descriptive framework. Tarantino et al., 2021, position pulmonary toxicity as a distinct concern in the development and clinical use of ERBB2 directed antibody drug conjugates. The present synthesis sharpens that perspective by showing why a single toxicity percentage cannot represent the clinical information contained in the available evidence.

The dose and pulmonary comorbidity associations are compatible with an interaction between treatment exposure and tissue susceptibility, but they do not establish the biological pathway responsible. Table 4 identifies clinical characteristics associated with the outcome rather than measured cellular processes. Mahalingaiah et al., 2019, describe several possible routes through which antibody drug conjugates enter normal tissues independently of the intended tumor target. This pharmacological reasoning provides context for considering pulmonary vulnerability alongside administered treatment. However, the dose categories cannot be interpreted as direct measurements of intracellular payload exposure, and the grouped comorbidity indicator cannot isolate susceptibility arising from individual respiratory conditions. The theoretical implication is therefore a distinction between clinical risk markers and biological explanations. This distinction allows the framework to accommodate the observed associations without presenting a plausible mechanism as an empirically demonstrated transmission pathway.

The severity distribution in Table 3 changes the interpretation of the overall toxicity burden. Lower grade events constitute most affected patients, yet fatal events account for approximately one seventh of those with adjudicated pulmonary toxicity. Equations 2 and 4 make the distinction explicit: severity counts partition affected patients, whereas the observed toxicity proportion uses all treated participants as its denominator. These measures answer different clinical questions. A predominance of lower grade events does not eliminate the importance of a smaller fatal component, and a modest overall proportion

can coexist with substantial consequences among affected patients. The analytical contribution is this denominator specific interpretation of frequency and severity. It directs attention toward both the probability of observing toxicity and the distribution of outcomes after toxicity occurs, without treating descriptive severity shares as a decomposition of causal mechanisms.

Precision also changes the clinical meaning of the apparent risk ordering. The highest dose category in Table 4 contains only 27 participants and produces the widest confidence interval among the selected contrasts. Equation 6 expresses that uncertainty on the logarithmic scale. Consequently, the largest point estimate does not provide the most precise estimate of association. The intermediate dose interval crosses one, while the age and comorbidity intervals only narrowly exclude it. These patterns require calibrated interpretation rather than categorical labels of safety or danger. Table 3 adds a related constraint: equal observed percentages in the breast cancer and other cancer categories arise from markedly different denominators. This analysis therefore separates numerical similarity from evidential comparability. For clinical interpretation, effect magnitude, uncertainty, category size, and event severity should remain visible together.

The international relevance lies in a transferable interpretation of evidence across treatment settings rather than a demonstrated difference between national health systems. Modi et al., 2020, evaluated trastuzumab deruxtecan in a multicentre breast cancer population, while Shitara et al., 2020, evaluated treatment in gastric cancer populations enrolled in Japan and South Korea. These reports arise from different disease and treatment contexts and contribute to the clinical evidence represented in the pooled source; they are not independent replications of the present synthesis. Their contextual differences reinforce the need to interpret the tumor proportions in Table 3 without treating them as standardized comparisons. For clinicians and multidisciplinary teams, Tables 3 and 4 support reviewing administered dose and pulmonary history alongside the consequences of toxicity, while avoiding reassurance based on chronological age or an interval crossing one. The broader contribution is an evidence framework that keeps absolute burden, relative association, and uncertainty distinct when clinical findings move across tumor types and healthcare settings.

7. Conclusion and Implications:

The global value of targeted cancer treatment depends on recognizing pulmonary harm without overstating what clinical evidence can establish. This analysis brings treatment related associations and patient susceptibility into a framework that separates event frequency, severity, and uncertainty. Its contribution is an integrated interpretation of published evidence rather than discovery of a causal pathway. The findings show why the largest relative association should not automatically determine clinical priorities when precision differs across comparisons. They also demonstrate that predominantly lower severity events can coexist with consequential fatal outcomes. The theoretical implication is that therapeutic selectivity and clinical safety require distinct assessments: targeting malignant tissue does not by itself establish pulmonary protection. For clinical teams, the evidence supports reviewing treatment characteristics and respiratory history alongside the potential consequences of toxicity, while avoiding reassurance based on broad demographic categories. Healthcare managers can use this distinction to structure multidisciplinary review and communicate uncertainty consistently. Policy relevance centres on transparent safety reporting that preserves denominators, severity categories, and observation periods. Operationally, separating these measures can improve the interpretation of adverse event summaries across treatment settings. The transferable contribution is a disciplined basis for discussing pulmonary safety across tumor populations without assuming equivalent risks or identical clinical contexts.

The aggregate evidence creates specific opportunities for further investigation. Individual participant data could distinguish treatment exposure from baseline susceptibility and support consistent adjustment across comparisons. Prospective follow up could estimate toxicity over common observation periods and clarify differences between event occurrence and progression to severe outcomes. Larger samples within less represented treatment categories would improve precision. Comparative cohorts across healthcare systems could assess transferability while accounting for diagnostic practices and monitoring intensity. Mechanistic investigations could then connect clinical associations with measured biological processes. These extensions would strengthen causal interpretation and establish whether the descriptive patterns persist across populations and care settings.

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