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Unfinished business: Terminated cancer trials and the relevance of treatment intent, sponsors and intervention types

Daniel Buergy[1] | Julian Riedel[1] | Gustavo R. Sarria[2] | Michael Ehmann[1] | Davide Scafa[2] | Maurizio Grilli[3] | Frederik Wenz[4] | Ralf D. Hofheinz[5]

[1]Department of Radiation Oncology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[2]Department of Radiation Oncology, University Hospital Bonn, University of Bonn, Bonn, Germany

[3]Library for the Medical Faculty of Mannheim, Heidelberg University, Mannheim, Germany

[4]Board of Directors, Freiburg Medical Center, Freiburg, Germany

[5]Day Treatment Center (TTZ), Interdisciplinary Tumor Center Mannheim (ITM) and 3rd Medical Clinic, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Correspondence
Daniel Buergy, Department of Radiation Oncology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
Email: daniel.buergy@medma.uni-heidelberg.de

Abstract

The aim of the study was to report on the association of trial sponsors with intervention type, treatment intent, recruitment success and reasons to terminate cancer trials. The ClinicalTrials database was searched for interventional Phase 3 cancer trials (01/2006-05/2017). Noncancer studies and ongoing studies were excluded, permanently suspended studies were counted as terminated. Trials were stratified according to sponsors (industry/nonindustry), intervention type, setting (curative/palliative) and intent of intervention (curative/symptom-control/life-extending). We identified 345 terminated trials and 1137 completed studies as a control group. The frequency of premature termination did not differ significantly between sponsors. Time to termination was shorter but recruitment per month prior to termination was higher in industry-sponsored studies (7.0 vs 2.2 patients/month; $P < .001$). Drug interventions were more common in industry-sponsored, all other interventions in nonindustry-sponsored settings ($P < .001$). Life-extending palliative interventions occurred more frequently, symptom-control interventions in a curative setting less frequently in industry-sponsored trials (both $P < .001$). Intervention, setting and intent were not associated with termination in industry-sponsored trials. In nonindustry-sponsored trials, the frequency of drug interventions and life-extending (noncurative) interventions were increased in terminated trials (both $P < .05$); symptom-control interventions in curative settings occurred more frequently in completed studies. Industry-sponsored trials were more often terminated due to toxicity/inefficacy while lack of accrual

Abbreviations used in the supplementary appendix are explained in each supplementary figure separately.

occurred more frequently in nonindustry-sponsored trials ($P < .01$). Interventions, treatment setting/intent and reasons for termination differed between sponsor types. In nonindustry-sponsored trials, drug interventions and life-extending (noncurative) interventions were associated with premature termination and symptom-control interventions (curative setting) were associated with trial completion.

KEYWORDS

cancer, ClinicalTrials, terminated trials, trial recruitment

1 | INTRODUCTION

Failure to complete clinical trial accrual goals has been recognized as "the ultimate inefficacy" in a landmark analysis by the Institute of Medicine about the status of clinical trials in the National Cancer Institute program.[1] Data by Cheng et al[2] showed that 37.9% of clinical cancer trials approved by the NCI Cancer Therapy Evaluation Program failed to meet the minimum recruitment goals. Another report on the subject was published by Stensland et al,[3] who identified poor accrual as the major reason for trial termination. In contrast to previous analyses, the authors included industry-sponsored trials in their data set. More recently, Khunger et al published a similar analysis, which focused on immunotherapy trials compared to other oncology drug trials. The authors did not find a significantly different withdrawal or termination rate of immunotherapy trials compared to all other systemic cancer therapy studies; in line with the previous data, the authors confirmed lack of accrual as the major reason for trial termination.[4]

Another aspect of the clinical trials landscape is the increasing percentage of industry-sponsored trials. Industry sponsorship has increased from 4% in 1975 to 57% in 2004.[5] The implications of this trend are discussed controversially. Some authors suggested that industry sponsorship was associated with more favorable reporting of outcomes, for example, Riaz et al found that reporting of favorable outcomes was seven times more likely in industry-sponsored cardiovascular trials[6] and some authors suggested that systematic bias favors industry-sponsored trial reporting.[7] Another study on gastrointestinal trials did not find an increase in favorable trial reporting in industry-sponsored studies; on the contrary, the authors noted that the industry-sponsored studies were of superior methodological quality compared to the nonindustry-sponsored studies.[8]

In the setting of oncology trials, the implication of industry funding has not been analyzed in detail. We set out to evaluate if industry-sponsored trials differ from other sponsors with regard to type of intervention, treatment intent, treatment setting, success rate of trials and reasons why trials failed to complete recruitment. Early clinical trials are often safety studies or studies to show early efficacy signals; therefore, we focused on late-stage trials that are typically conducted in the setting where an approval (or a clinical use) is the desired outcome. Our main question was to identify the association of trial sponsors with the type, intent and setting of an intervention; furthermore, we aimed to identify if aforementioned factors would be associated with an increased chance of success or an increased risk of failure to complete a clinical trial.

What's new?

Industry sponsorship of clinical trials to investigate novel cancer treatment strategies in patients has grown significantly in recent decades. Little is known, however, about the termination and completion rates of industry-sponsored trials. Here, terminated and completed late-stage cancer trials were analyzed and stratified by sponsor type. Termination frequency of trials was found to be similar between industry sponsors and other sponsors. In addition, industry-sponsored trials had a shorter time to termination but recruited participants more quickly than trials sponsored by other entities. Commonly observed reasons for termination in industry-sponsored trials included issues concerning lack of efficacy or toxicity.

2 | METHODS

The ClinicalTrials.gov database was queried on 7 May 2017 for the condition "neoplasm," which includes terms such as "malignancy," "tumor," "cancer" and "oncology" among others. We restricted the search to phase III interventional cancer trials. The timeframe included trials submitted after January 2006 with the latest update prior to May 2017. In addition to trials marked as terminated, we included studies that were permanently suspended, assuming that a reinitiation of these trials would be unlikely after a ≥1.5-year suspension period. As a control group with successful recruitment, we queried ClinicalTrials.gov for completed trials using aforementioned criteria for terminated trials. False-positive database hits were identified by two reviewers (DB and JR) and excluded if they were not related to treatment of cancer and not conducted in a cancer population (eg, trials that included "cancer" as an *exclusion* criterion or trials about certain nonmalignant conditions such as uterine fibroids).

Reasons for termination were identified using the ClinicalTrials.gov record; if records were inconclusive, primary investigators and/or sponsors were contacted via email and asked to provide further details. Furthermore, a literature search for trial publications was performed using PubMed with primary investigators, study titles and the ClinicalTrials.gov identifier ("NCT Number") as search terms. In case of company studies, press releases of the sponsors were analyzed via company websites for reasons of study termination. All trials were stratified by sponsoring (industry vs all other entities). The type of the tested intervention in each trial was classified; we used a classification system as previously published[9]; however, we modified the categories to account for late-stage trials with complicated designs including multiple different types of interventions and to account for diagnostic studies. This resulted in the following categories that were applied by three reviewers (JR, GS, DB) to all terminated and completed trial records:

1. Systemic drug intervention (including supplements)
2. Local treatment (eg, surgery, radiation therapy, stent application, catheter intervention, high intensity focused ultrasound)
3. Diagnostic study (including studies that analyzed an intervention guided by a new diagnostic, eg, a novel tracer for sentinel node biopsy used in an established surgery approach)
4. Multiple treatments or combinations of interventions in one study (eg, chemoradiation compared to induction chemotherapy plus surgery)
5. Other intervention (eg, psychosocial interventions, physical exercise intervention, web-based counseling, nurse navigator, among others in cancer populations)

Therapeutic studies (as opposed to preventive or diagnostic studies) were then stratified by the intent of the therapeutic intervention as curative, noncurative but life-extending or palliative (defined as symptom-control). In addition, the general treatment setting was categorized as potentially curative vs noncurative; this was done to account for palliative/symptom-control interventions in generally curative settings (eg, treatment of lymph edema following curative breast surgery). Such an approach leads to the following categories of intervention with regard to curation:

1. Potentially curative interventions in curative settings
2. Symptom-control interventions in curative settings (eg, treatment of lymph edema in curative breast cancer)
3. Symptom-control interventions in palliative settings
4. Potentially life-extending interventions that are not curative in a noncurable/palliative setting

In case the intent of the intervention or the treatment setting was unclear and/or could not be classified in aforementioned categories, studies were censored for this analysis. The reason to terminate a clinical trial was classified by two reviewers (JR and DB) using the following categories:

1. Business reasons or funding ceased
2. Efficacy and/or toxicity issues
3. Insufficient accrual (includes insufficient accrual due to: competing studies, clinicians not supporting the trial, scientific advances in other disciplines, new study has been started in similar indication)
4. Unknown
5. Other reasons

Statistical analyses were performed using "R," a language and environment for statistical computing. Differences between continuous variables were computed using the Student's *t*-test after controlling for equality of variances using Levene's test. Kaplan-Meier graphs were used to show timelines until termination of trials; differences were computed using the log-rank test. In case of multiple binary categories, data were analyzed as contingency tables using (omnibus) chi-square tests; if expected cell counts were below 5, Fisher's exact test (the Fisher-Freeman-Halton test) was used instead. In case of a significant omnibus test using an unadjusted alpha of 0.05 (chi-square or Fisher's), within-group tests were performed. Finally, an adjustment for multiplicity was done for the resulting *P* values of all univariate tests using the Holm-Bonferroni procedure; in case of an unadjusted significant omnibus test that triggered within-group tests, only the latter were adjusted. In addition to the univariate analyses, multivariate models with termination and with recruitment per month prior to termination were calculated; detailed information on the models is provided in the Appendix, Supplementary Tables 1 and 7A,B.

3 | RESULTS

In total, 4903 phase III trials were identified, out of which 371 were marked as terminated (7.6%). Another 11 studies (2.2%) fulfilled the criterion of being permanently suspended (≥ 1.5 years). False-positive database hits (n = 37) were excluded, resulting in 345 studies of which 9 (2.6%) were permanently suspended and 336 (97.4%) were terminated. Out of 1383 completed trials, we also excluded noncancer trials, resulting in 1137 trials that successfully completed recruitment. The overall data set is shown in the CONSORT diagram (see Figure 1) and consists of 1482 trials out of which 792 were conducted by industry sponsors (53.4%); there was no significant difference between the frequency of industry-sponsored trials that were terminated compared to nonindustry-sponsored trials that were terminated (24.1% vs 22.3%).

3.1 | Differences between industry-sponsored trials and nonindustry-sponsored trials

Industry-sponsored trials were terminated after a median time of 33 months, and nonindustry-sponsored trials were ongoing for a significantly longer period of 51 months before termination (Figure 2A; $P < .001$). A total of 50 325 patients were recruited in 280 out of

345 terminated trials (81.1%) that included the number of recruited patients at the time of termination. Despite the shorter recruitment period, industry-sponsored trials recruited numerically more patients before termination (mean: 230.3 vs 120.6 patients/trial; $P = .119$); consecutively, the recruitment per month prior to termination was higher in industry-sponsored terminated trials (7.0 vs 2.2 recruited patients per month; $P < .001$; Figure 2B); to further explore this observation, a multivariate model was generated to identify possible predictors for the recruitment rate among intervention types and intent of intervention. This model confirmed industry sponsoring as an independent predictor for an increased recruitment rate in terminated trials; additionally, local interventions and/or interventions with the intent of symptom control in a palliative setting were independently associated with a decreased recruitment rate (see Supplementary Table 1 for details). Initially preplanned accrual numbers did not differ significantly between industry and nonindustry sponsors (mean: 494.2 vs 508 patients).

The frequencies of tested interventions differed significantly between sponsor type ($P < .001$). In within-group analyses, systemic drug application was the most common intervention in both groups; however, with a significantly higher frequency in industry-sponsored compared to nonindustry-sponsored trials (90.5% vs 55.8%; $P < .001$). All other interventions occurred significantly (all $P < .01$) more frequently in nonindustry-sponsored trials (see Figure 3A and Supplementary Table 2 for details). The frequency of curative and palliative treatments also differed significantly between industry-sponsored and nonindustry-sponsored trials ($P < .001$). Life-extending (noncurative) interventions were more common in industry-sponsored trials (66.7% vs 31.2%; $P < .001$). In trials that were not industry-sponsored, curative interventions and palliative/symptom-control interventions in curative setting were significantly more common (38.5% vs 13.6%; $P < .001$ and 13.1% vs 1.3%; $P < .001$). Palliative/symptom-control interventions in palliative overall settings did not differ in frequency between sponsors after Holm-Bonferroni adjustments were applied (see Figure 3B and Supplementary Table 3 for details).

3.2 | Comparisons of terminated trials with completed trials

After stratification according to sponsors, the distribution of interventions did not differ significantly between terminated vs completed

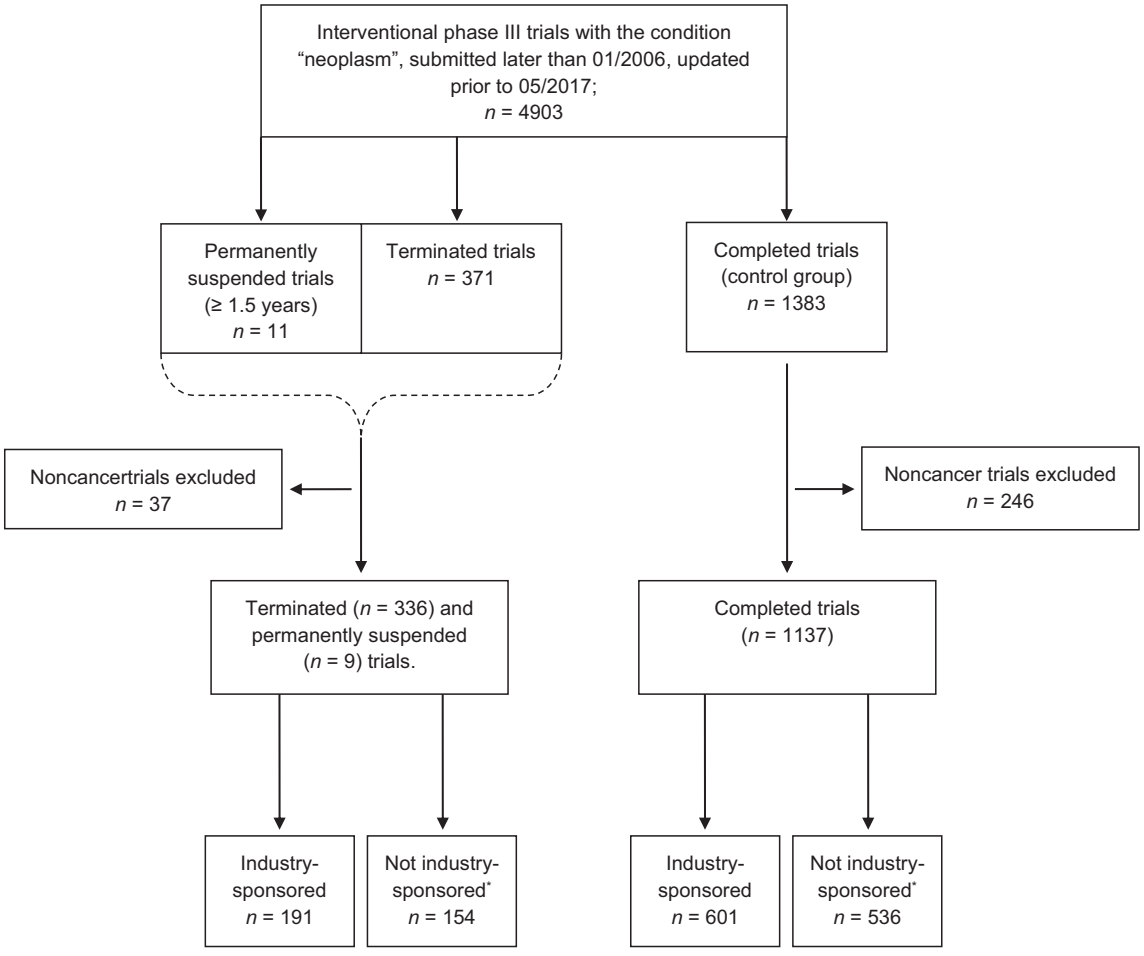

FIGURE 1 CONSORT diagram of the interventional late-stage cancer trials included in this analysis

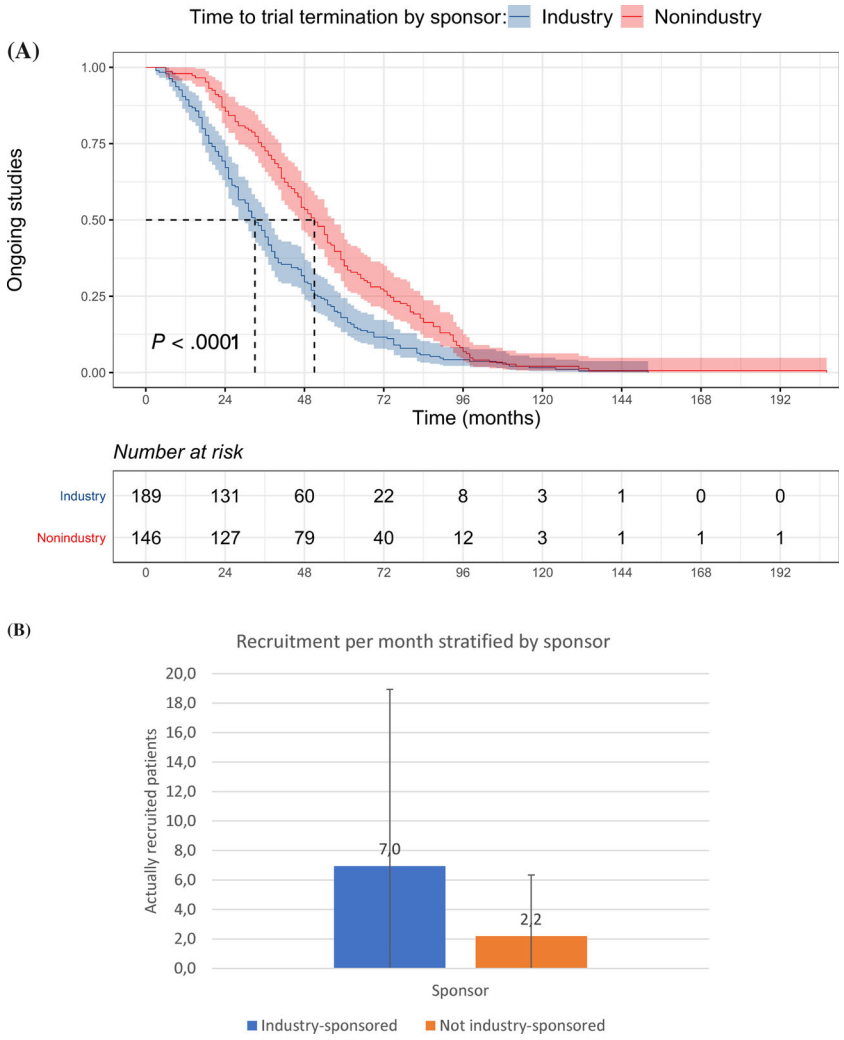

FIGURE 2 A, The time to termination of trials stratified by sponsors is shown in this figure. Time to termination of industry-sponsored and nonindustry-sponsored trials is shown in blue and red curves, respectively. Industry sponsors decided earlier to terminate a trial compared to other sponsors ($P < .0001$); 10 trials are missing because exact termination dates were not available. The colored area indicates the 95% confidence intervals. B, Although industry-sponsored trials were terminated 35% faster compared to trials sponsored by other sponsors, they recruited numerically 1.91 times more patients ($P = .12$; 230.3 [SE: 32.4]; vs 120.6 (SE: 26.0) patients). As shown in the graph, this difference was caused by a 3.18 times higher number of patients recruited per month in industry-sponsored trials ($P < .001$; 7.0 [SE: 0.97] vs 2.2 [SE: 0.37]). Error bars in the graph indicate SDs [Color figure can be viewed at wileyonlinelibrary.com]

trials in the industry-sponsored stratum; in both terminated and completed industry-sponsored trials, systemic drug interventions were the most common intervention (93.7% and 89.5%) with all other interventions being observed in small frequencies (all ≤3.8%). The distribution of curative, life-extending and symptom-control interventions in curative or noncurative settings was also not significantly different in industry-sponsored terminated vs completed trials; life-extending interventions occurred most frequently in both groups (64.8% vs 67.3%; the distribution is shown in Supplementary Table 4).

The stratum of nonindustry-sponsored trials showed a significant difference in the distribution of interventions observed in the terminated compared to the completed trials ($P = .003$). Systemic drug interventions in the nonindustry-sponsored group occurred with an increased frequency in terminated trials compared to completed studies (66.2% vs 52.8%; $P = .049$); in contrast, other interventions (eg, psychosocial interventions or exercise interventions) did not differ significantly between groups after Holm-Bonferroni adjustment ($P = .0597$) but occurred numerically more frequently in the group of completed studies (15.5% vs 6.5%). Further variables did not differ significantly between completed and terminated nonindustry-sponsored studies in within-group chi-square tests (see Figure 4A and Supplementary Table 5). When analyzed with regard to treatment intent and treatment setting, we observed a significant difference in the distribution of terminated trials vs completed trials in nonindustry-sponsored trials ($P < .001$). Within-group tests showed that nonindustry-sponsored life-extending interventions occurred more frequently in the group of terminated trials (44.9% vs 26.6%; $P < .001$); nonindustry-sponsored symptom-control interventions in a curative setting were more frequently observed in completed compared to terminated trials (21% vs 5.1%; $P = .001$); there was no significant difference in the distribution of symptom-control interventions in palliative settings and curative interventions (Figure 4B, Supplementary Table 6).

In addition to the univariate models, we generated a multivariate model using aforementioned types of interventions, intent of intervention and sponsors; further independent variables were hematologic vs solid tumors and location of trials (US only vs other). Termination of trials was used as a binary dependent variable. Two-way interaction terms between independent variables were analyzed using a stepwise regression and were kept in case of significant interaction. Results of the multivariate model were mostly in line with the

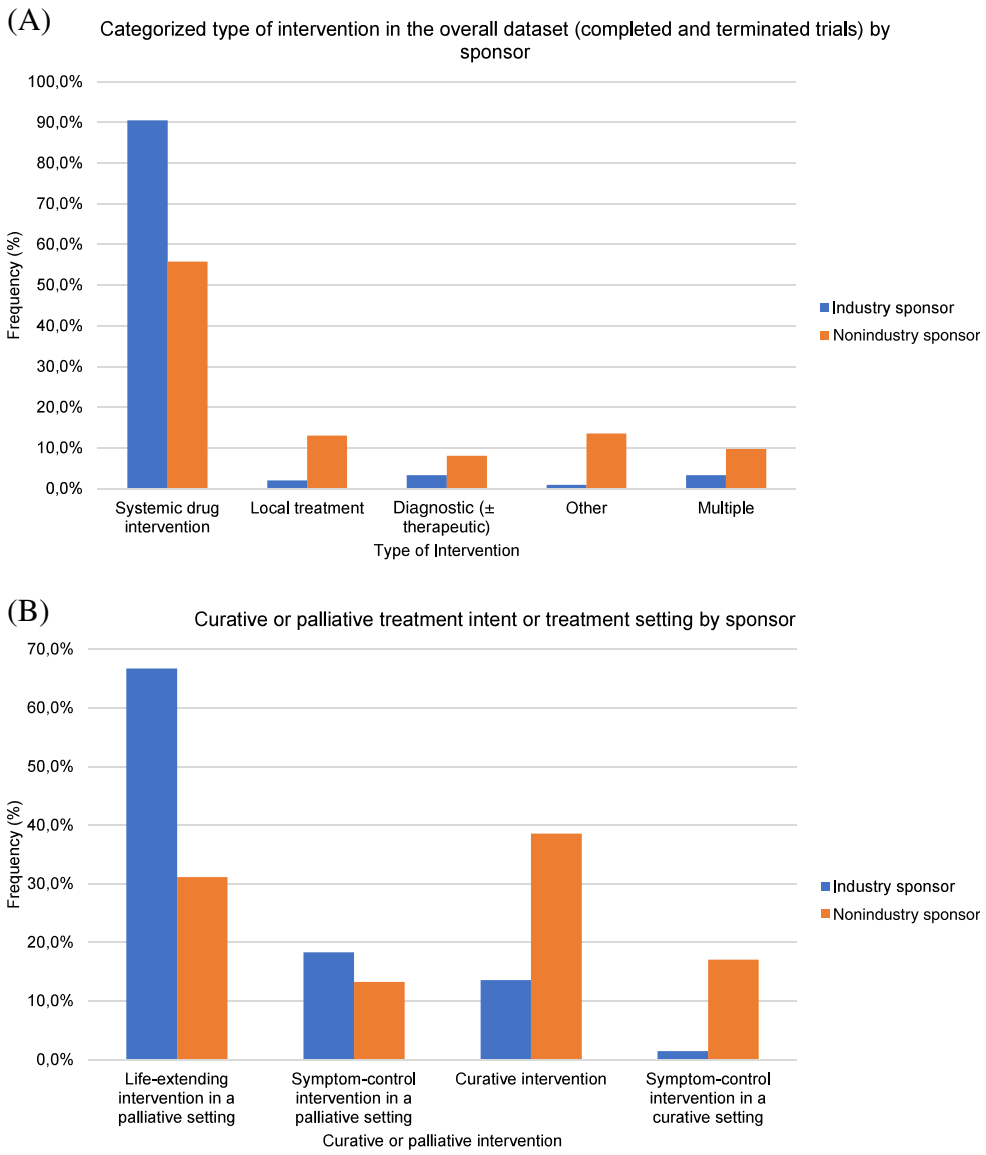

FIGURE 3 A, Frequencies of different interventions stratified by sponsors. Differences are significant for all interventions. Columns show percentages of the industry-sponsored group and of the nonindustry-sponsored group. Other interventions include psychosocial studies, physical exercise studies or hypnotherapy studies, among others. Diagnostic studies included some therapeutic interventions if they were guided by a diagnostic (eg, a new novel tracer to identify sentinel lymph nodes). B, Frequencies of curative studies stratified by sponsors. All curative studies are done in a curative overall setting. Symptom-control interventions can be done in a curative setting or in a palliative setting. Life-extending interventions are all done in a palliative setting. Frequencies of curative and palliative studies differed significantly between sponsors ($P < .001$) for all classifications aside from symptomatic interventions in a palliative setting ($P = .027$). For this analysis, studies in which treatment intent or setting could not be determined were excluded, preventive studies and diagnostic studies were also excluded. Contingency tables for A and B are detailed in the Appendix, Supplementary Tables 2 and 3 [Color figure can be viewed at wileyonlinelibrary.com]

univariate results observed in the nonindustry group: Systemic drug intervention trials were associated with an increased risk of termination; furthermore, trials conducted for symptom control in a curative setting were associated with an increased chance of trial completion. Trials conducted in the US** had an increased risk of termination; a significant interaction was observed between hematologic trials and drug interventions as well as multiple interventions and life-extending interventions; in both cases, the combination of factors was associated with a decreased risk of termination when compared to the risk suggested by the combined odds ratio of each factor (details are shown in Supplementary Table 7A). In addition to this model which allowed for interactions, we created an alternative model without considering interaction effects; in short, this model showed similar results compared to the interaction model (details are shown in Supplementary Table 7B).

Neither of the models provided a modest or good overall performance to predict termination of trials (pseudo $R^2 < 0.1$ in both cases).

3.3 | Reasons for termination of trials

Reasons for termination were available on ClinicalTrials.gov in 287 out of 345 (83.2%) of terminated or permanently suspended trials. Investigators or sponsors provided information about reasons for termination at request in 19 cases (5.5%); furthermore, 4 cases could be clarified by a review of the PubMed database and/or company press releases.

The distribution of reasons for termination between industry-sponsored and nonindustry-sponsored trials differed significantly ($P < .001$). Insufficient accrual occurred significantly more frequently in nonindustry-sponsored trials (34% vs 70.8%; $P < .001$). Lack of efficacy and/or toxicity issues were significantly more often reported as a reason for termination in industry-sponsored studies (32.5% vs 9.1%; $P < .001$). Although numerically higher in industry-sponsored trials (14.7% vs 5.8%), business reasons were not significantly increased compared to nonindustry-sponsored trials ($P = .119$; see Figure 5 and Supplementary Table 8).

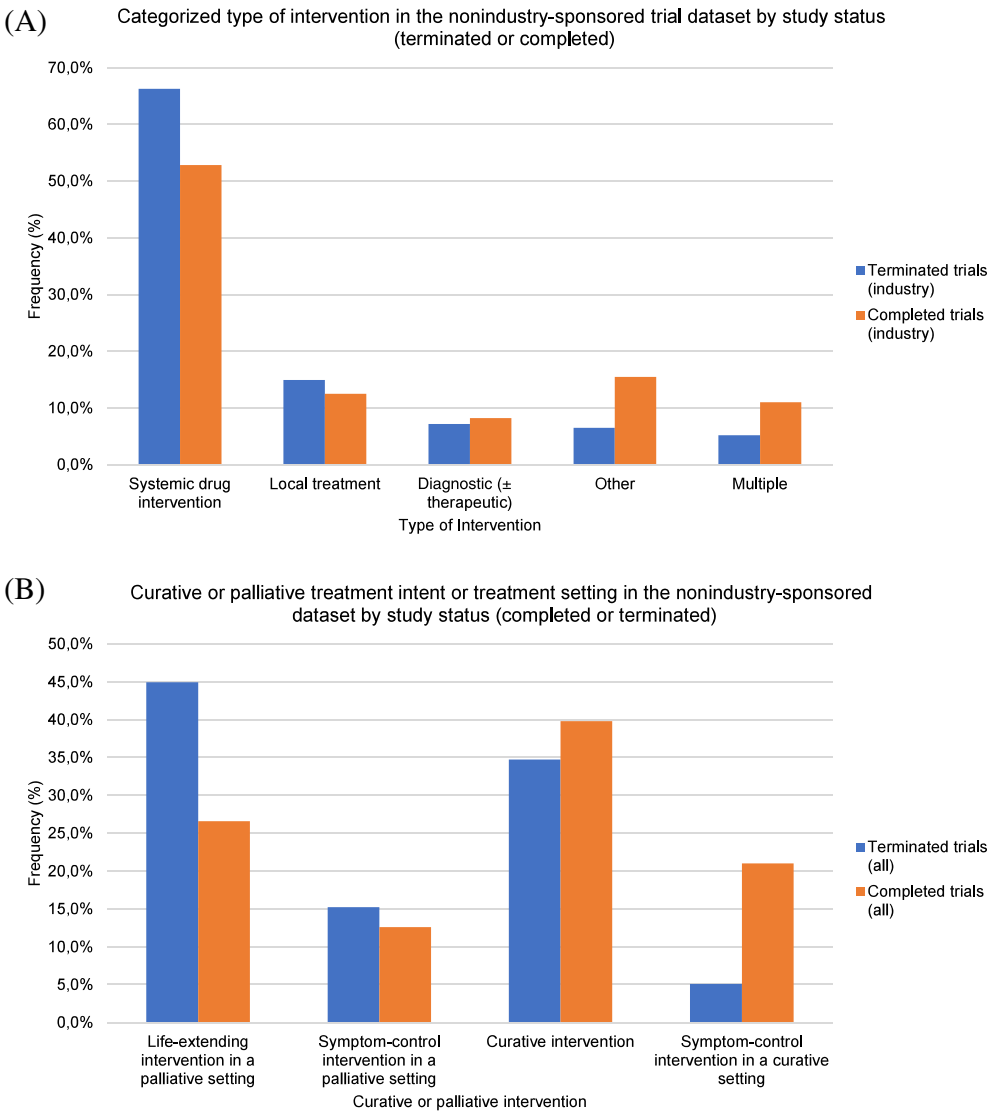

FIGURE 4 A, Terminated studies compared to completed studies in nonindustry-sponsored trials. Systemic drug (including supplement) interventions were more frequent in terminated trials (P = .049). The group of other interventions that included web-based interventions, psychosocial and exercise interventions was numerically more frequent in completed studies; however, the difference was not significant after adjustment for multiplicity (P = .06). Further variables did not differ between completed and terminated studies. B, Treatment intent and setting (curative/palliative) differed between completed and terminated nonindustry-sponsored trials. Life-extending interventions in a generally palliative setting occurred more frequently in terminated studies (P < .001); interventions done for symptom-control in a curative setting were more frequent in completed studies (P < .001); no differences were observed for curative interventions and for symptom-control interventions in a palliative overall setting. Contingency tables for A and B are shown in the Appendix, Supplementary Tables 5 and 6 [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In their analysis about terminated cancer trials registered between 2005 and 2011, which included only about 20% late-stage trials, Stensland et al identified industry-sponsoring as a risk factor for premature discontinuation of trials.[3] Khunger et al, who reported on a data set of studies registered between 2011 and 2015, also included early-stage trials with only a minority of late-stage studies (10%); interestingly, the authors could not confirm industry-sponsorship as a risk factor for early termination but rather found that trials sponsored by individual institutions were more likely to be discontinued than industry-sponsored trials.[4]

Our analysis is conceptually different from aforementioned studies because we analyzed a more homogeneous dataset by excluding all early-stage trials; furthermore, we excluded ongoing trials and compared only terminated and permanently suspended trials with completed trials, as a control group. This approach allowed us to perform a detailed study-by-study evaluation of each trial with regard to treatment intent and treatment setting, that is, palliative or curative in addition to intervention type which was also analyzed by aforementioned studies but slightly modified in our analysis to account for complex late-stage trial protocols with multiple different intervention types.

Over 90% of industry-sponsored interventions included systemic drug (or supplement) administrations; when preventive and diagnostic studies were excluded from the treatment-intent analysis, this percentage was even higher with 93.5% of the remaining industry-sponsored (treatment) studies being drug trials and another 3.4% rated as multiple-intervention trials, some of which also included new drugs in one or more arms. The majority of these trials were conducted as life-extending studies in a generally palliative setting (mostly compromised of chemotherapy or immunotherapy studies in a metastatic or unresectable setting). Industry-sponsored trials for symptom-control were conducted mostly in palliative overall settings; only 10 out of 134 trials for symptom-control interventions were done in a curative setting. Curative interventions were observed in a minority of cases (13.6%) in the industry-sponsored setting and included adjuvant and neoadjuvant treatment settings. The comparison between

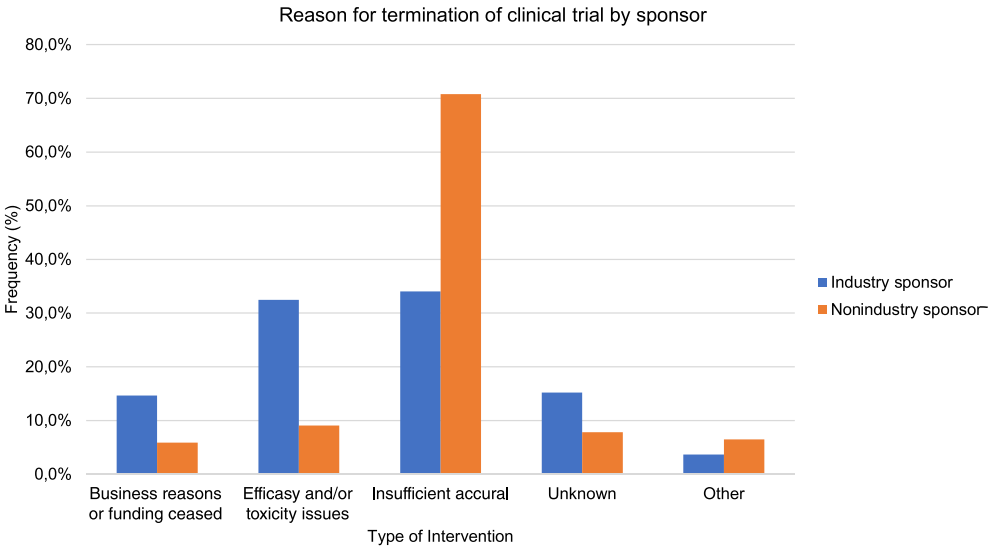

FIGURE 5 Reasons for termination differed between sponsors. Insufficient accrual occurred more frequently in nonindustry-sponsored trials ($P < .001$). Efficacy and toxicity were significantly more often cited as a reason for termination in industry-sponsored trials ($P < .001$). Other reasons did not differ between groups after adjustment for multiplicity (Holm-Bonferroni). Further details are summarized in Supplementary Table 8 [Color figure can be viewed at wileyonlinelibrary.com]

(industry-sponsored) terminated and completed trials was limited by the small number of trials with interventions other than systemic drugs which were each below five in the terminated group. There was no increased risk of trial termination associated with palliative or curative interventions and/or settings in industry-sponsored trials.

The differences between industry-sponsored studies and those sponsored by other entities were pronounced. In the nonindustry-sponsored group, trial designs were more diverse in terms of interventions. Although systemic drug administration was consistently the most common intervention; we observed relevant numbers of all types of other interventions as well (13.5-8%). In the nonindustry-sponsored group, systemic drug trials were at an increased risk of termination; the same association was observed in the multivariate model for the combined dataset irrespective of sponsorship. We did not observe a general correlation of symptom-control interventions with completion or termination of trials, to the contrary, symptom-control interventions performed in a curative setting were associated with an increased chance of success in the multivariate model; again, in the univariate analyses, this association was only observed in nonindustry-sponsored trials. Trials conducted exclusively in the United States were at an increased risk of termination in the multivariate models; however, this observation may be due to a selection bias: It is likely that almost all Phase 3 US oncology trials are registered with ClinicalTrials.gov while trials conducted at other locations are primarily registered locally and those additionally registered with ClinicalTrials.gov might be structurally different from a random sample of (only) locally registered trials.

It must be emphasized that the overall model performance of the predictive models was relatively poor; that is, although the models show that some factors are predictors of trial termination, an accurate prediction of trial termination is not possible with the analyzed combination of factors.

Neither the aforementioned positive[3] nor the negative[4] association of industry-sponsoring with trial termination was confirmed in our data set. We observed a similar distribution of completed and terminated trials irrespective of sponsorship (absolute difference: 1.8%). Trial recruitment rates, on the other hand, were considerably faster (>3 times) in industry-sponsored trials; this association was also observed in a multivariate model. Additionally, local interventions, as well as symptom-control interventions in a palliative setting were associated with decreased recruitment rates in the multivariate model. We cannot provide an explanation for the distinct differences in recruitment rates between sponsors; an association with differential trial designs or incentives by industry sponsors is possible but cannot be proven with this analysis.

Reasons for termination of trials could not be identified in 11.9% of trials; even after a literature review was performed, press releases from companies were screened and primary investigators were contacted. Surprisingly, industry-sponsored trials were considerably more often terminated due to inefficacy or toxicity and nonindustry-sponsored trials due to insufficient accrual; it is possible that these differences reflect an increased risk profile in industry-sponsored trials and, as indicated by the slower recruitment rate, insufficient incentives to recruit patients in nonindustry-sponsored trials. On the other hand, we cannot exclude that reporting quality generally differs between sponsors; furthermore, the reason to terminate a clinical trial might be multifactorial in most cases. As an example, a very toxic intervention with limited efficacy might lead to a slow accrual, thereby delaying completion of a trial leading to exhaustion of available funds; in such a scenario, efficacy/toxicity, insufficient accrual or business reasons/funding would all be appropriate answers.

Aside from possible reporting differences in the database, our study has other limitations; specifically, classifying interventions as either curative, life-extending or symptom-control may be an oversimplification. As an example, a study (NCT00332709) that analyzes if adding zoledronic acid to adjuvant letrozole in a curative overall treatment setting could be classified as a curative intervention because disease-free survival is listed as a secondary endpoint, indicating that investigators hoped the

intervention would improve on the curation rate. On the other hand, the primary endpoints and other secondary endpoints are focused on bone-related outcomes. Therefore, this trial was classified as a study with symptom-control intent in a curative setting. Additionally, it must be acknowledged that sponsors do not necessarily provide funds for a trial and, as noted by Neel et al,[10] industry collaborators might also provide support for a nonindustry-sponsored trial.

Although this data set is far from comprehensive and several independent factors associated with successful trial completion may not be available from the ClinicalTrials.gov registry, our data indicate that certain trials may be at an increased risk of termination or slow patient recruitment. Insufficient accrual is still the major cause of premature trial termination for both industry-sponsored and nonindustry-sponsored late-stage cancer trials; therefore, methods to improve recruitment may also improve completion rates of trials. Investigators may choose to incentivize recruitment with financial incentives; however, the efficacy of such an approach may be limited and it may also be considered as ethically problematic[11,12]; other approaches that may improve recruitment rates are associated with methodological challenges, for example, open trial designs and opt-out strategies.[12] Finally, it has been shown that improvement of patient communication (eg, via educational videos) leads to increased trial participation rates[13] and also to an increased knowledge about the trial subject; such an approach seems ethically and methodologically unproblematic and may be beneficial when slow recruitment is anticipated.

5 | CONCLUSION

Systemic drug interventions were more, all other interventions were less frequently observed in industry-sponsored trials compared to other sponsors and vice versa. Life-extending interventions in a palliative setting also occurred more frequently in the industry-sponsored group while curative interventions were more frequently sponsored by other entities. The relation of terminated and completed trials was similar between sponsors in our data set. If terminated, studies sponsored by industry had recruited more patients in a shorter timeframe prior to termination and were more likely terminated due to lack of efficacy or toxicity issues.

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CONFLICT OF INTEREST

DB reports personal fees from Siemens AG, personal fees from NB Capital Research GmbH, personal fees from NB Capital ApS, personal fees from b.e. Imaging GmbH outside the submitted work; JR, ME, DS and FW have nothing to disclose; GRS reports grants and personal fees from Carl Zeiss Meditec AG outside the submitted work; RDH reports fees for advisory boards or lectures from Amgen, Astra Zeneca, Bayer, BMS, Boehringer, Ipsen, Lilly, medac, Merck, MSD, Roche, Saladax, Sanofi and clinical trial funding from Amgen, medac, Merck, Roche, Saladax, Sanofi outside the submitted work.

DATA AVAILABILITY STATEMENT

All data used and generated in this work will be made available on reasonable request.

ORCID

Daniel Buergy https://orcid.org/0000-0001-5913-3332

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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