original report

RECIST 1.1 for Response Evaluation Apply Not Only to Chemotherapy-Treated Patients But Also to Targeted Cancer Agents: A Pooled Database Analysis

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abstract

PURPOSE The mode of action of targeted cancer agents (TCAs) differs from classic chemotherapy, which leads to concerns about the role of RECIST in evaluating tumor response in trials with TCAs. We investigated the performance of RECIST using a pooled database from 50 clinical trials with at least one TCA.

METHODS We examined the impact of the number of target lesions (TLs) on within-patient variability of tumor response. The prognostic effect of TL response (at 12 weeks or on study on the basis of a maximum five TLs) on survival was studied through landmark and time-dependent Cox models adjusted for baseline tumor load, occurrence of new lesions, or unequivocal progression of nontarget disease.

RESULTS Data were obtained from 23,259 patients with cancer (36% lung, 28% colorectal, 11% breast, and 25% other); 15,620 received TCAs, predominantly transduction or angiogenesis inhibitors, as a single agent (37%), combined with other TCAs (7%), or as chemotherapy (56%); 28% received chemotherapy only; and 5% received best supportive care or placebo. A total of 17,222 patients contributed to the analyses. Within-patient variability decreased with increasing number of TLs, similarly for TCAs (with/without chemotherapy) and chemotherapy only. Mixed responses occurred proportionally in all treatment classes. Landmark analyses showed an ordinal relationship between percentage change from baseline to 12 weeks and overall survival, and demonstrated a clear distinction between tumor shrinkage and progressive disease according to RECIST. Time-dependent analysis showed no marked improvement in the ability to predict survival on the basis of TL tumor growth compared with nontarget progression or new lesion occurrence, regardless of treatment. Similar results were seen for major tumor types and different classes of TCAs.

CONCLUSION This work reinforces that RECIST version 1.1 perform well for response assessment of TCAs.

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INTRODUCTION

The assessment of change in tumor burden, which is a mainstay of the evaluation of cancer therapeutics, defines objective response and disease progression. Both are increasingly important end points in cancer clinical trials, especially for progression and disease-free survival, which are used frequently for drug registration. Because RECIST was published in 2000 they have been widely adopted to assess response in clinical trials.[1,2] The RECIST Working Group further standardized and clarified these response criteria for version 1.1 after validation on a large warehouse containing more than 6,500 patients treated with chemotherapy.

Over the past decades, numerous targeted cancer and immunotherapeutic drugs have been and are being developed, with many already used in routine clinical care. Targeted cancer agents (TCAs) block the growth and spread of cancer by interfering with specific molecules that are involved in the growth, progression, and spread of cancer. Therefore, their mode of action differs from that of chemotherapy for which RECIST was initially developed and validated. Although chemotherapy causes the tumor to shrink, TCAs may not lead to obvious tumor shrinkage or might induce heterogeneous effects on different sites of metastases, which has raised questions about whether variations in response criteria may be required to evaluate the activity of these TCAs. Moreover, it has been questioned whether, for example, signal transduction inhibitors versus angiogenesis inhibitors with different modes of action affect the tumor response differently.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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To address these questions, the RECIST Working Group compiled a large warehouse that comprises studies performed by pharmaceutical companies and academia, including TCA studies.

Immunotherapeutics were not included in the warehouse because not enough data were available at the time and tumors seem to respond differently compared with chemotherapeutic and targeted drugs. A consensus guideline, iRECIST, was recently developed to ensure consistent design and data collection to allow validation in a separate database.[3] Here, we provide a summary of the various analyses that were performed on the TCA warehouse and address the value of RECIST 1.1 in TCAs.

METHODS

The Data

In 2011, the RECIST Working Group launched the first calls for a data warehouse, and the final database was successfully compiled at the European Organisation for Research and Treatment of Cancer (EORTC) Headquarters on the basis of 50 phase II and phase III trials with clinical data from patients treated with TCAs or TCAs in combination with chemotherapy compounds (Appendix Table A1, online only). Data on 23,259 patients were shared by partners from industry (66%) and academia (34%), including general patient information (eg, the start of treatment, survival information, tumor type) and detailed longitudinal tumor measurements (measurement/evaluation date, site of the lesion, method of measurement, size of measured lesions, information on nontarget lesions, and occurrence of new lesions), as available in the study case report forms.

Although the majority of studies were based on RECIST 1.0, some also used modified WHO criteria or RECIST 1.1 (Appendix Table A1), which resulted in heterogeneity in the type of measurable lesions reported. To homogenize this, the definition of a measurable lesion according to RECIST 1.1 was adopted throughout (ie, at least 10 mm in longest diameter [if non-nodal] at baseline, as assessed by computed tomography, spiral computed tomography, or magnetic resonance imaging consistently throughout all assessment times).

Whenever a measurement was missing at an intermediate assessment, the last available one before that assessment for that lesion was imputed to still enable calculation of overall response at that time point. This occurred for at least one lesion in 1,962 patients of the full data set (out of 23,259 [8.4%]). Wherever the measurement method of a target lesion changed from the one used at baseline, the reported measurement was replaced by the last available one before the assessment recorded using the baseline method. This affected at least one lesion in 702 patients of the analysis data set (out of 17,222 [4.1%]). Nodal lesions were considered potential target lesions if they had a short axis (if available) of at least 15 mm. Pathologic lymph nodes between 10 and 15 mm at baseline were considered part of nontarget disease and were considered to represent unequivocal progression if they doubled in size. This changed the nontarget response assessment to progressive disease (PD) for 93 patients (out of 17,222); however, the RECIST 1.1 assessment changed from non-PD to PD for only 16 patients, and the remaining 77 patients already had PD on the basis of either target or new lesions. Furthermore, target lesions selected in the brain and osseous structures (only a few cases reported), or for which the site of metastasis could not be properly classified in one of the categories listed in Appendix Table A3 (online only) were not considered.

Target lesions were then selected from the measurable lesions according to size (ie, the largest first with a maximum of two per site). Nonselected but measurable lesions were demoted to the status of nontarget disease and, for the purpose of this analysis, considered to have unequivocally progressed if they doubled in size. RECIST 1.1 require that nontarget disease results in a 73% increase in volume in the total disease burden to call unequivocal progression of nontarget disease. For the current analysis, a more conservative rule was adopted to avoid the possibility that nontarget PD would be called on the basis of one of these demoted lesions alone. This changed the nontarget response assessment to PD for 541 patients and the RECIST 1.1 assessment from non-PD to PD for 20 patients (out of 17,222). When lesions were surgically removed (as far as this was possible to deduce from the data), the measurements were censored at the last assessment before surgery.

Statistical Methodology

Variability of within-patient lesions: impact of number of target lesions. Because of their focused mechanism of action, mixed type of responses may be seen in patients treated with TCAs. We explored this by studying the variability in the activity of a TCA on different lesions within a patient. We investigated the impact of the number of target lesions selected on the variability in response assessment.[4] For this purpose, all possible groupings of the available target lesions for each patient were considered. For instance, for a patient with two lesions, there are three possible combinations (lesion 1, lesion 2, and lesion 1 and 2); for a patient with 10 lesions, there are 1,023 possible combinations.

For 96% of patients, at least one follow-up assessment was available within 12 weeks after study initiation. Therefore, the percentage change from baseline of the sum of lesion diameters (longest diameter for non-nodal lesions, short axis subtracted by 10 mm [with 0 as lower bound] for nodal lesions [ie, a pragmatic approach to adjust for nodal lesions that returned to normal as they regress to < 10 mm in size]) was determined (see Appendix, online only, for more details). A positive percentage change corresponds to a decrease in the sum from baseline; a negative percentage

TABLE 1. Patients by Disease Category and Treatment Class

Disease Category	Treatment Class, No. (%)				Total, No. (%)
	TCA	TCA Plus Chemotherapy	Chemotherapy	Placebo/BSC	
No. of patients	6,915	8,705	6,555	1,084	23,259
Tumor type					
Lung (NSCLC and SCLC)	1,114 (19.3)	3,783 (43.5)	3,171 (48.4)	297 (27.4)	8,365 (36.0)
Colon cancer	1,376 (19.9)	2,917 (33.5)	1,784 (27.2)	519 (47.9)	6,599 (28.4)
Breast cancer	1,286 (18.6)	929 (10.7)	218 (3.3)	0 (0.0)	2,433 (10.5)
GIST	1,187 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	1,187 (5.1)
Melanoma	608 (8.8)	0 (0.0)	318 (4.9)	0 (0.0)	926 (4.0)
Renal cell cancer	772 (11.2)	0 (0.0)	0 (0.0)	145 (13.4)	917 (3.9)
Gastric cancer	0 (0.0)	446 (5.1)	436 (6.7)	0 (0.0)	882 (3.8)
Head and neck cancer	0 (0.0)	345 (4.0)	344 (5.2)	0 (0.0)	689 (3.0)
Pancreatic cancer	6 (0.1)	285 (3.3)	284 (4..3)	0 (0.0)	575 (2.5)
Soft tissue sarcoma	388 (6.7)	0 (0.0)	0 (0.0)	123 (11.3)	511 (2.2)
Prostate cancer	96 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	96 (0.4)
Gynecologic cancer*	50 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	50 (0.2)
Hepatocellular carcinoma	29 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	29 (0.1)

Abbreviations: BSC, best supportive care; GIST, GI stromal tumor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; TCA, targeted cancer agent (single agent or combination of two).

*Cervical, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

change reflects an increase in the sum from baseline. For all possible combinations of target lesions, the percentage change from baseline was determined and categorized according to RECIST as either complete response (CR; 100%), partial response (PR; 100% to 30%), stable disease (SD; 30% to −20%), or PD (≤ −20%).

Association with survival. In the absence of a gold standard for the immediate ascertainment of tumor response/progression, we used overall survival to validate the RECIST response/PD definitions. To avoid lead-time bias because the response is observed while on study treatment, a landmark approach was adopted.[5] The percentage change from baseline to 12 weeks (as introduced in the previous section, but based on a RECIST 1.1 selection of lesions) was associated with survival, landmarked at the same time point, using a Cox proportional hazards regression model adjusted for baseline tumor load, occurrence of new lesions, or unequivocal progression of nontarget disease before the landmark.

The main disadvantage of a landmark analysis is the loss of information because only patients who survive beyond the landmark can be taken into account. Alternatively, Cox models can be used with time-varying covariables to capture the effect of the covariable over time. By following the approach of Litière et al,[6] we explored whether the components of progression, which varied over time, can improve prediction of survival in our warehouse and whether this differs by treatment class. Overall survival was analyzed using a Cox proportional hazards regression model that used a multivariable approach to adjust for baseline tumor load, and at each assessment time, best target response as best percentage improvement from baseline, tumor growth of target lesions as worst percentage change from nadir or as worst increase from nadir (millimeters per week), presence of new lesions, and occurrence of progression in nontarget lesions (see Appendix for more details). These analyses were stratified by trial.

Role of the Funding Source

The pooled database is hosted by EORTC. The funding sources had no role in the design of this research project; collection, analysis, or interpretation of the data; or writing of the article. S.L., G.I., and J.B. had full access to the raw data. S.L. had the final responsibility for the decision to submit for publication.

RESULTS

Description of the Database

For the majority of patients, the primary tumor was either lung (36%), colon (28%), or breast (11%; Table 1). A subset of 15,620 patients (67%) received treatment with TCAs either as a single agent (n = 5,776 [37%]), in combination with other TCAs (n = 1,139 [7%]), or with chemotherapy (n = 8,705 [56%]). A summary of available TCAs, classified according to their mechanism of action, is available in the Appendix Table A2.

We identified 20,643 patients with at least one target lesion at baseline for additional analysis (Fig 1). Of the 2,616

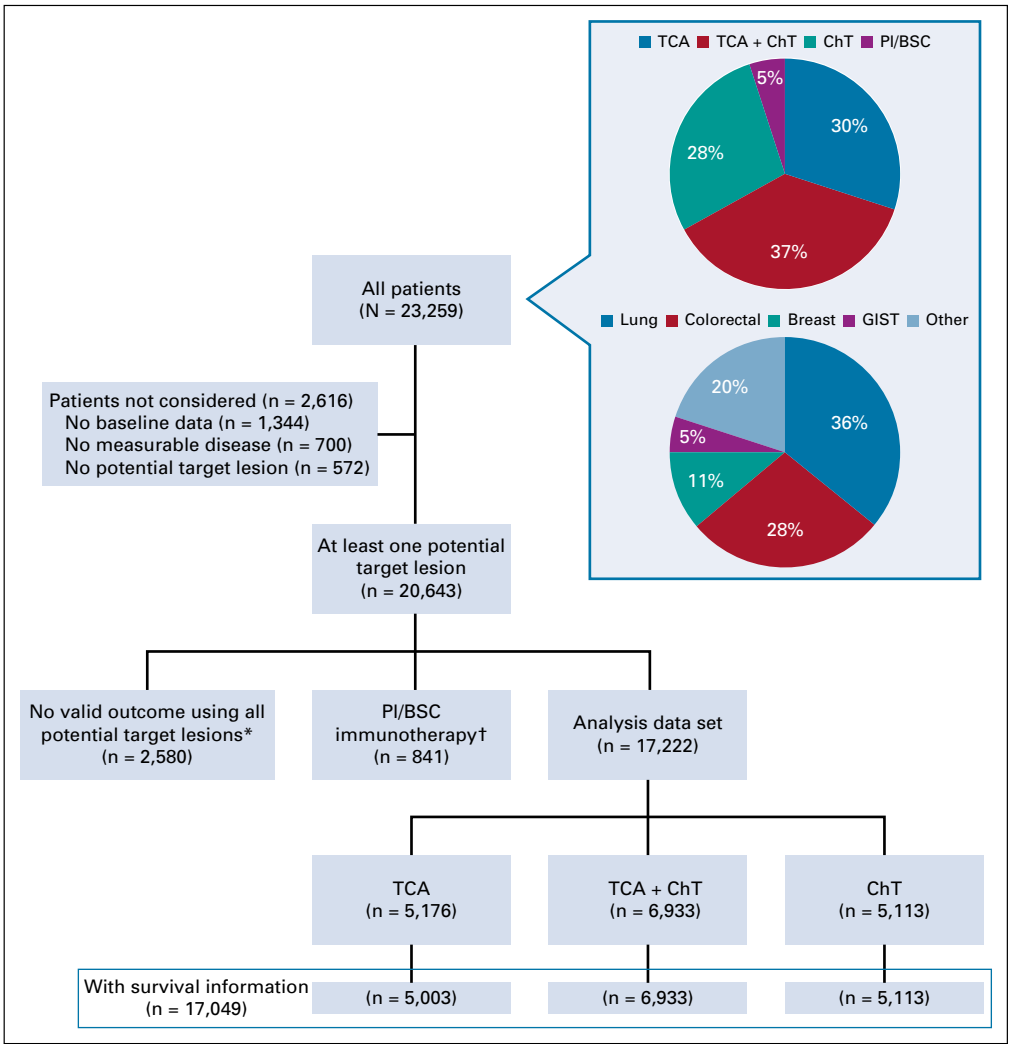

FIG 1. Summary of the number of patients available for analysis. (*) No valid outcome using all target lesions: no follow-up data postbaseline, n = 2,367; complete response, partial response, or stable disease less than 28 days (4 weeks) from baseline (mostly because at least one target lesion was not measured after baseline), n = 177; progressive disease within 21 days from baseline, n = 36. (†) Treatments not selected for analysis: placebo/best supportive care (PI/BSC), n = 647; immunotherapy arms (interleukin-21 and interferon alfa), n = 194. ChT, chemotherapy; GIST, GI stromal tumor; TCA, targeted cancer agent.

patients who were not considered, 1,344 were excluded because no baseline assessment was performed (response assessments were collected only in that trial for a subset of patients; Appendix Table A1), 2,367 patients had no follow-up data available after the baseline assessment, 177 patients had their last complete tumor assessment (CR, PR, or SD) less than 4 weeks from baseline; and 36 patients had PD reported within 3 weeks from baseline. Data on 194 patients treated with immunotherapy (interleukin-21 or interferon alfa) were excluded from this analysis because immunotherapy is part of the separate ongoing initiative of iRECIST.[3] Finally, data on 647 patients treated with a placebo or best supportive care were not included, which resulted in a primary analysis data set that contained information on 17,222 patients (Fig 1). A detailed description of this data set is available in the Appendix Tables A4 to A9. For two studies with targeted agents, no survival information was available (Appendix Table A9); therefore, 17,049 patients contributed to analyses related to overall survival (Fig 1). Table 2 lists the available information for specific subgroups of interest (selected for sufficient patient information from more than one trial arm), which were considered in the analyses presented here and in the Appendix.

Variability of Within-Patient Lesions: Impact of Number of Target Lesions

For all possible combinations of target lesions in a patient, RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome PR, two SD, and one PD), the number of response categories for one selected lesion is three. Figure 2 shows, by treatment class and increasing number of selected target lesions, that the number of different response categories in which a patient could be classified decreases as the number of target lesions to be selected increases. There does not seem to be much difference between the graphs focused on patients treated with TCAs and those treated with chemotherapy or a combination of TCAs and chemotherapy. Regardless of class of treatment, as of five

TABLE 2. Patients in Subgroups of Interest Considered for the Analyses

Treatment Category	Tumor Type					Total
	Lung	Colon	Breast	GIST	Other	
TCA	739 (5/6)	1,151 (4)	734 (1)*	1,043 (2/3)		5,176
Single STI						2,604 (11/12)
Single AI						1,442 (12/13)
TCA plus chemotherapy	2,746 (8)	2,645 (6)	675 (3)			6,933
With single STI						4,682 (15)
With single AI						1,931 (6)
Chemotherapy	2,271 (9)	1,639 (4)	159 (2)			5,113
Total	5,756 (13/14)	5,435 (10)	1,568 (4)	1,043 (2/3)		17,222

NOTE. The numbers in parentheses indicate the number of studies that contributed to this subgroup analysis. If X/Y, then X represents the number of studies with survival information.

Abbreviations: AI, angiogenesis inhibitor; GIST, GI stromal tumor; STI, signal transduction inhibitor; TCA, targeted cancer agent.

*One study, two treatment arms.

selected target lesions, no patients were categorized in more than two response categories. In addition, for those patients with at least five target lesions, more than 80% had a stable response assessment regardless of the selected lesions or treatment. This observation was confirmed by more detailed analyses that looked into within-patient variability (Appendix Tables A10 to A28). Therefore, there does not seem to be more within-patient variability when treated with TCAs compared with chemotherapy, at least not in the clinical trials considered in this database. The variability reduces as the number of lesions used for the response assessment increases, and stabilizes at five or more target lesions, but it does so similarly across treatment categories. The currently used rule for a maximum of five target lesions specified by RECIST 1.1 continues to cover most of the observed variability whether patients are treated with TCAs, chemotherapy, or a combination of both (Appendix).

Association With Survival

The results of the landmark analysis, adjusted for baseline tumor load, occurrence of new lesions, or unequivocal

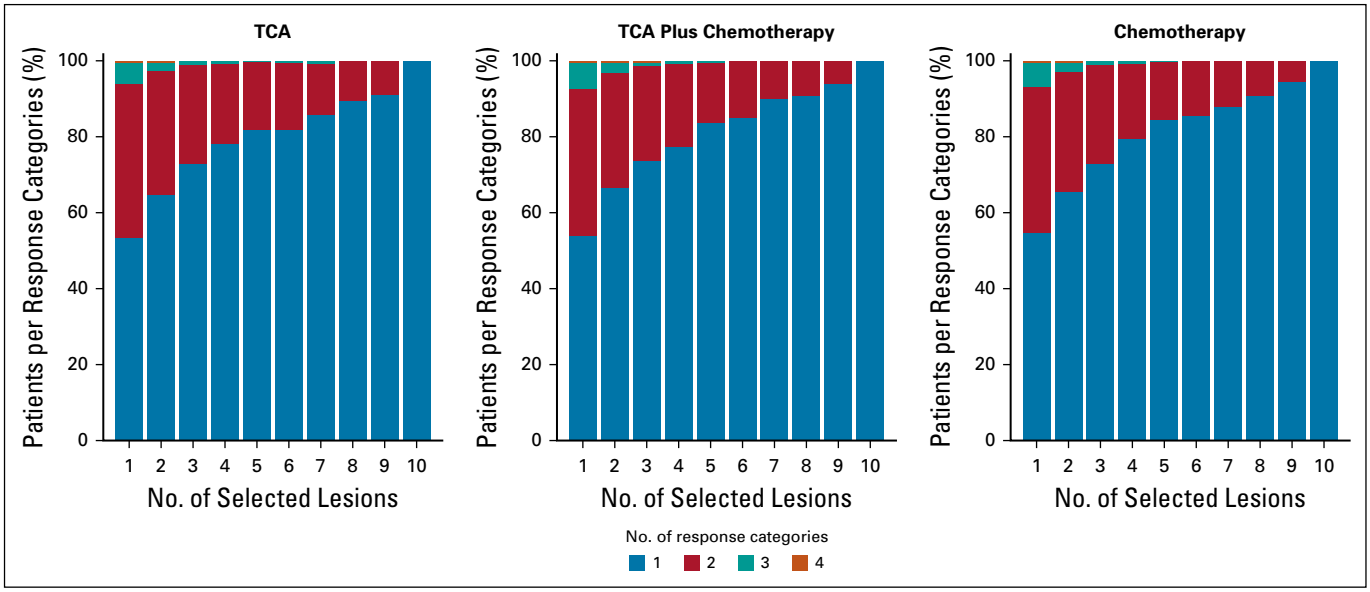

FIG 2. Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three. TCA, targeted cancer agent.

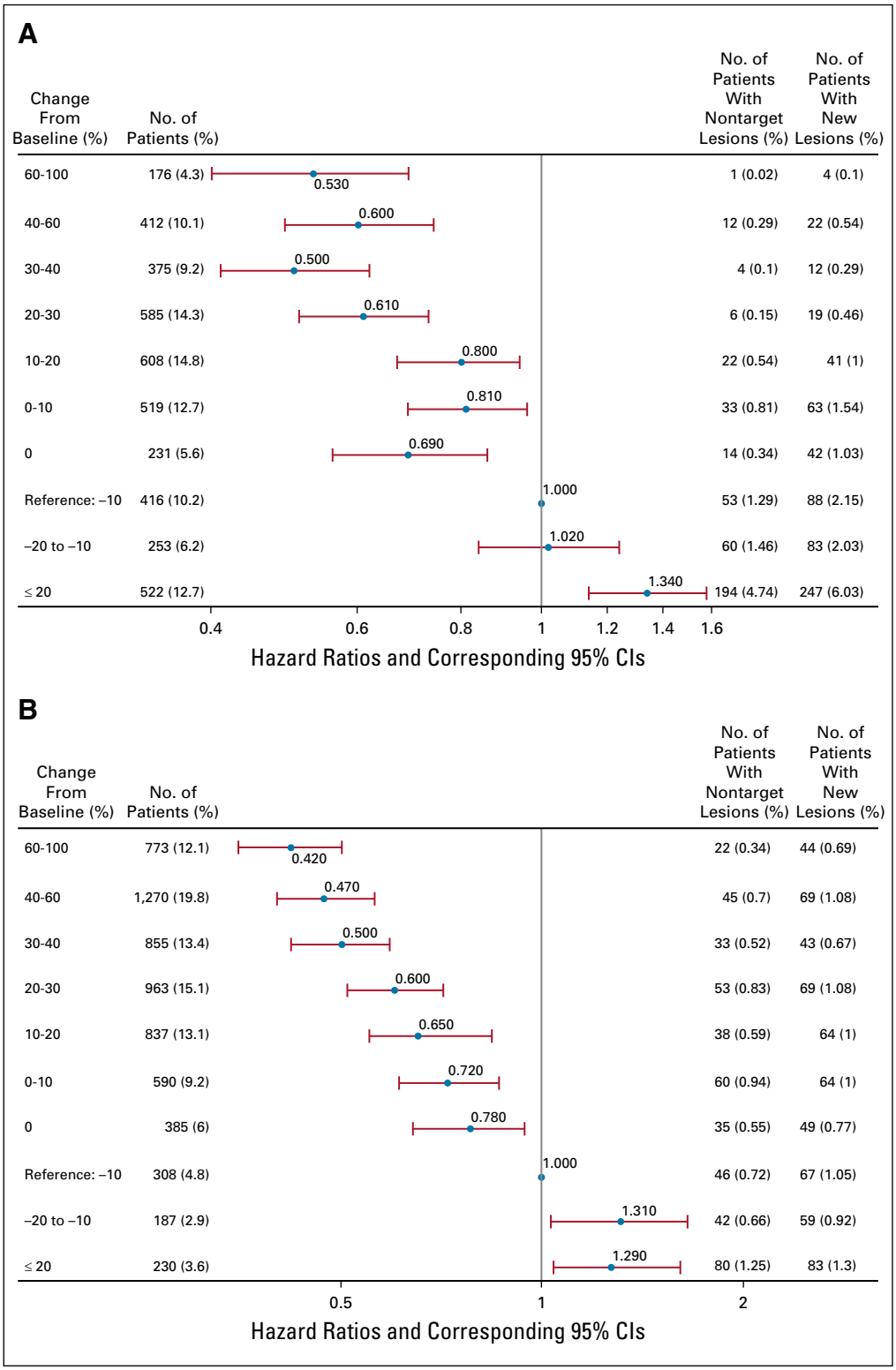

FIG 3. Forest plots by treatment class of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. (A) Targeted cancer agents (TCAs; n = 4,097), (B) TCAs and chemotherapy (n = 6,398), and (C) chemotherapy (n = 4,587). Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

progression of nontarget disease (at 12 weeks), are summarized by treatment class in Figure 3, which shows a gradual relationship between percentage change observed in the sum of target lesions measured from baseline to 12 weeks and overall survival, with a larger percentage improvement associated with a better outcome. The category of no change from baseline (0%) is a difficult category that most likely occurs because of a tendency to record the same measure when lesions have not changed much. Furthermore, the estimated hazard ratios (HRs) and their

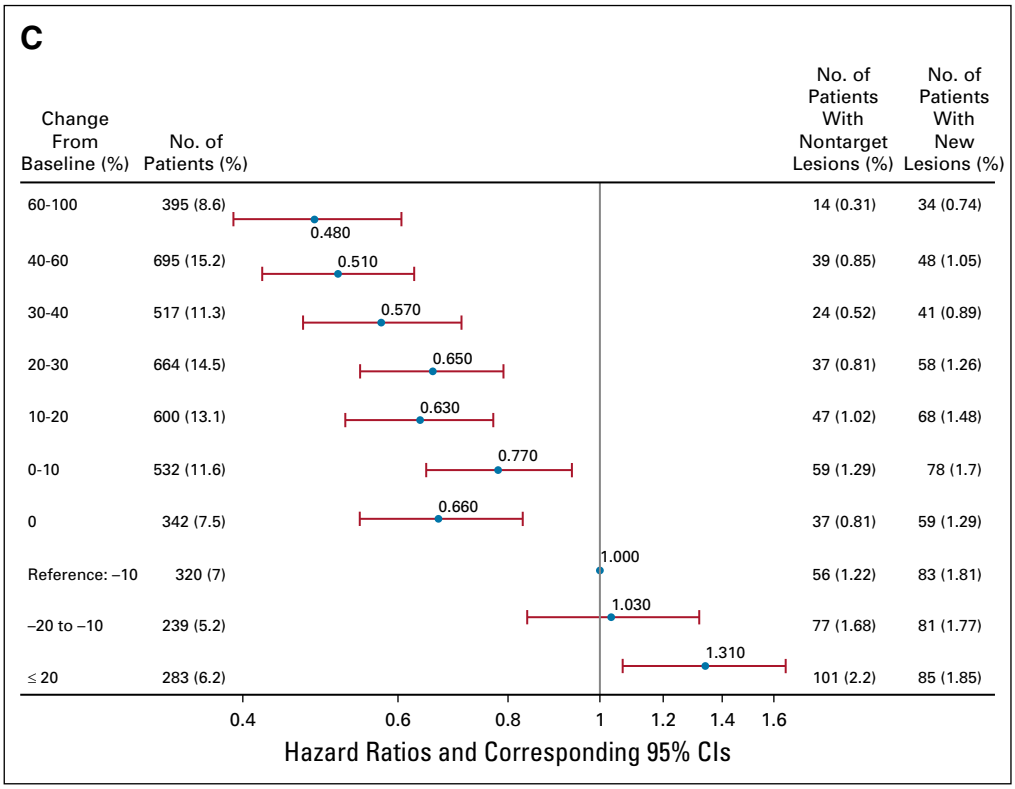

FIG 3. (Continued).

corresponding 95% CIs show a distinction between the impact of tumor shrinkage and PD according to RECIST 1.1 on overall survival. Similar results were observed when looking at the different subgroups (Appendix).

A Time-Dependent Analysis Approach

The HRs estimated from the time-dependent Cox proportional hazards regression model are listed in Table 3 for the model that contained tumor growth rate in millimeters per week (other results are reported in Appendix Tables A29 to A40). The results of the chemotherapy subgroup confirm the results seen from the previous analysis of the RECIST 1.1 database[6] (Appendix). Despite being highly significant as a result of the mere size of the subgroups, the modeling of target lesion tumor growth rate did not show a marked improvement in survival prediction compared with the other components, whereby again, strong effects of the occurrence of new lesions and progression of nontarget disease are seen.

Nevertheless, although tumor growth shows an important impact on survival of 2 mm/wk for chemotherapy, it does so even more on the survival of patients treated with TCAs. This result seems to be driven mainly by patients treated with single-agent signal transduction inhibitors, more specifically, in a study that contributed information of 838 patients with GI stromal tumors treated with imatinib.[7] This is most likely related to this group of patients having a longer follow-up in terms of measurements. In the other subgroups, the predictive effect of the tumor growth rate was found to be more comparable with that observed in the chemotherapy subgroup. Finally, as in previous analyses, a gradual improvement of survival is seen as the best percentage change from baseline increases, regardless of treatment class.

DISCUSSION

There has been some concern that RECIST 1.1 may not be applicable to TCAs because the mechanism of action of these types of agents may result in different response patterns. Therefore, it has been suggested that TCAs require different criteria for response assessment. The database considered in this article is a unique source of data to study this. To our knowledge, it is the largest individual patient database to date with detailed tumor measurements from case report forms of patients treated with TCAs, which focuses mainly on signal transduction inhibitors and angiogenesis inhibitors either as single agents or in combination with chemotherapy or other TCAs. Extensive analyses of this database contained in the Appendix do not seem to support the assumption that more mixed responses are seen in patients treated with TCAs (either pooled or in subclasses). Therefore, RECIST 1.1 is good for evaluating tumor response to TCAs independent of subclass of TCA or tumor type. In all subgroups, progression per RECIST over the first 12 evaluation weeks as well as on

TABLE 3. Time-Dependent Multivariable Cox Proportional Hazards Regression Analysis of Overall Survival Using Components of Response and Progression According to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

	TCA (n = 5,003)		TCA Plus Chemotherapy (n = 6,933)		Chemotherapy (n = 5,113)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.02 (1.02 to 1.03)	< .001 (1)	1.03 (1.02 to 1.03)	< .001 (1)	1.03 (1.03 to 1.04)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	2.14 (1.97 to 2.33)		1.77 (1.65 to 1.90)		1.79 (1.64 to 1.96)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.65 (1.51 to 1.80)		1.44 (1.33 to 1.57)		1.41 (1.29 to 1.55)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.71 (0.63 to 0.80)		0.68 (0.60 to 0.76)		0.61 (0.54 to 0.69)	
15-30	0.55 (0.49 to 0.63)		0.59 (0.53 to 0.66)		0.51 (0.45 to 0.58)	
30-50	0.44 (0.38 to 0.50)		0.43 (0.39 to 0.48)		0.41 (0.36 to 0.46)	
50-70	0.35 (0.30 to 0.42)		0.33 (0.29 to 0.38)		0.35 (0.30 to 0.41)	
70-100	0.33 (0.27 to 0.42)		0.28 (0.24 to 0.33)		0.26 (0.21 to 0.33)	
CR	0.29 (0.22 to 0.39)		0.29 (0.25 to 0.35)		0.25 (0.19 to 0.33)	
Slope: estimated rate of weekly increase, mm/wk						
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	1.09 (0.98 to 1.21)		0.98 (0.90 to 1.06)		0.86 (0.78 to 0.95)	
2-5	1.67 (1.48 to 1.88)		1.42 (1.28 to 1.58)		1.16 (1.03 to 1.31)	
5	2.94 (2.51 to 3.44)		1.88 (1.59 to 2.23)		1.46 (1.22 to 1.76)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; TCA, targeted cancer agent.

study was a strong prognostic factor of worse survival. The analyses do not suggest any refinement for the definition of progression for TCAs specifically or for RECIST 1.1 in general.

Tumor shrinkage during the first 12 evaluation weeks as well as on study was found to be a strong prognostic factor for better outcome, regardless of treatment class or tumor type. A gradual pattern of improvement of HRs was seen with increasing percentage change from baseline for patients treated with chemotherapy with (Fig 3B) or without (Fig 3C) TCAs, but the pattern was less clear for patients treated with TCAs only (Fig 3A). Depth of response, therefore, does not necessarily lead to better overall survival in this patient population, in contrast to previous reports in non–small-cell lung cancer and metastatic colorectal cancer.[8,9]

Although the database is unique in size, it is also heterogeneous (different lines of treatment, different tumor types, and different phases of clinical research) and limited to information that pertains directly to the assessment of each patient's tumor load. In this setting, subsequent therapy could be an important confounder of the relationship between response to treatment and long-term outcomes, such as overall survival. However, in the absence of such information, it is difficult to account for its effect.

To study the association with long-term outcomes, such as overall survival, we have used both landmark analyses and Cox models with time-varying covariables. The first has the advantage of accounting for lead time bias but results in a loss of information because only patients who survive beyond the landmark can be taken into account. The latter can capture the effect of covariables over time, but it is difficult to visualize and interpret the resulting effect estimates because these are more complex than those from a simple Cox model. Nevertheless, both analyses support the general message of this report. In conclusion, on the basis of these analyses of a large data warehouse, the RECIST Working Group recommends that RECIST 1.1 can also be used for tumor response measurements during treatment with targeted cancer drugs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

RECIST 1.1 for Response Evaluation Apply Not Only to Chemotherapy-Treated Patients But Also to Targeted Cancer Agents: A Pooled Database Analysis

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No other potential conflicts of interest were reported.

APPENDIX

In 2011, the RECIST Working Group launched the first calls for a data warehouse, and the final database was successfully compiled at the European Organisation for Research and Treatment of Cancer Headquarters on the basis of 50 phase II and phase III trials with clinical data from patients treated with targeted cancer agents (TCAs) alone or in combination with chemotherapy compounds (Table A1).

General Considerations About the Data Coding

Table A2 lists the TCAs according to their mechanism of action (as per National Cancer Institute guidelines: http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet). Table A3 lists the categories which were considered for the classification of the site of tumour lesions.

Detailed Description of Analysis Data Set

Tables A4 to A9 and Figure A1 list detailed descriptions of the analysis data set.

Variability Assessments

Measurements of the potential target lesions are the focus this section. Nontarget disease or new lesions are not taken into account. We investigated the impact of the number of target lesions to be selected on the variability in response assessment from baseline up to 12 weeks. For 633 of 17,222 patients, the first assessment was beyond the time window. These patients are not included in the analyses.

The percentage change from baseline is a continuous variable calculated as: {[(sum of largest diameters at baseline) − (sum of largest diameters at week 12)] / (sum of largest diameters at baseline)} × 100. A percentage change greater than 0 indicates a decrease of the size of the lesion (≥ 30% would correspond to a partial response). A percentage change less than 0 indicates an increase of the size of the lesion (≤ −20% would correspond to progressive disease). For simplicity of reporting, the treatment categories single TCA and two TCAs were grouped into one category, TCAs. This analysis did not take into account that some lesions belong to the same patient.

By treatment category. There is some more variability in percentage change determined in lesions treated with TCAs, which are listed in Table A11 and Figure A2.

Variance of the percentage change. A summary of the analysis of the variance per patient of percentage change from baseline in single lesions by treatment category is listed in Table A12. Patients with only one potential target lesion did not contribute to this analysis because it was not possible to calculate variance. Furthermore, we determined the average variability of the percentage change per patient over all possible combinations of target lesions (Figure A3). The average response variance plot can be used to identify the number of target lesions for which the variability is minimal and starts to stabilize. The standardized average response variance plot presents the variability standardized relative to the baseline (in this case based on 1 target lesion), so that each line represents for each increase in number of target lesions how much variability relative to the "baseline" we are able to reduce, i.e. standardized mean of variance = standardized mean of variance = mean of variance (selected lesions from two to nine) / mean variance (one selected lesion). This could be very informative if the variability differs a lot between the different treatment categories at the start. Table A13 lists the number of patients who contributed to this analysis.

Until four selected lesions, the average response variance seems to be higher in the TCA category than in the other. From five selected lesions, the difference between those treatment categories decreases.

Number of response categories by treatment according to the number of selected lesions. For each numerical combination of target lesions, we also determined how the selection of target lesions could affect the assessment of the response of a patient. For each numerical combination, we thus classified patients as either complete response (100%), partial response (100% to 30%), stable disease (30% to −20%), or progressive disease (≤ −20%), and we studied in how many different response categories a patient could be classified on the basis of the different selections of target lesions (Figure A4). For those patients with at least five target lesions, more than 80% had a stable response assessment, regardless of the selected lesions or the treatment.

By type of targeted cancer agent. More variability in percentage change was observed in lesions treated with signal transduction inhibitors with or without chemotherapy. In addition, the median per-patient variance of percentage change is largest in signal transduction inhibitors combined with chemotherapy and lowest in angiogenesis inhibitors combined with chemotherapy. Nevertheless, for those patients with at least five target lesions, 80% or more had a stable response assessment regardless of the selected lesions or the treatment, except for single-agent angiogenesis inhibitors (Tables A14 to A16 and Figures A4 to A6).

Tumor types by treatment category. For patients with lung cancer, there is more variability in percentage change determined in lesions from patients treated with TCAs than in those treated with single or combination chemotherapy (Tables A17 to A19). Although the mean per-patient variance of percentage change is largest for patients treated with TCAs, the median per-patient variance of percentage change is smallest, and less than 40% of patients showed mixed responses across the different lesions. In addition, for those patients with at least five target lesions, more than 80% of those with lung cancer treated with TCAs had a stable response assessment regardless of the selected lesions, the highest among the three treatment categories (Figures A7 to A10).

For patients with colorectal cancer, there is more variability in percentage change determined in lesions from patients treated with TCAs than in those treated with single or combination chemotherapy (Tables A20 to A22). The median and mean per-patient variance of percentage change is also largest in this subgroup. For patients with at least five target lesions, approximately 80% of those with colorectal cancer treated with TCAs had a stable response assessment regardless of the selected lesions, the lowest among the three treatment categories (Figures A11 to A14).

For patients with breast cancer, there is more variability in percentage change determined in lesions from patients treated with combinations of TCAs and chemotherapy than in patients treated with TCAs (although results from one study only) or chemotherapy alone in a small number of patients (Tables A23 to A25). Approximately 40% of patients treated with targeted therapies showed mixed responses across the different lesions versus slightly more than 50% of patients treated with combination therapies. The number of patients with at least five target lesions is small, so one has to be careful not to overinterpret the results (Figures A15 to A18).

Tables A26 to A28 list the summary statistics and patient contributions to the variability assessment for patients with GI stromal tumor cancer. Figures A19 to A22 summarize the additional variance assessments.

Association With Survival: Landmark Approach

The results of the landmark analyses, adjusted for baseline tumor load, occurrence of new lesions, or unequivocal progression of nontarget disease (at 12 weeks), are summarized in Figures A23-A39

Time-Dependent Survival Analysis

On the basis of the analysis by Litière et al,[6] this section is dedicated to exploring whether the components of progression, which vary over time, can improve prediction of overall survival in our warehouse and whether this prediction differs by treatment category. For this analysis, target lesions were selected according to RECIST 1.1 (ie, per patient, a maximum of five lesions with a maximum of two per organ). Lymph nodes could only be selected as target lesions if the short axis was larger than 15 mm. They were considered to have returned to normal as soon as the short axis regressed to less than 10 mm. For target

lesions located in the lymph nodes, a short axis less than 10 mm was considered normal. To assess this uniformly throughout the database, we opted for a pragmatic approach whereby all target lymph node short-axis measurements were subtracted by 10 mm (with 0 as lower bound). We determined at each measurement time the best target response as the best percentage improvement from baseline, tumor growth of target lesions as worst percentage change from nadir, tumor growth of target lesions as worst rate of increase from nadir (millimeters per week), presence of new lesions, and occurrence of nontarget progressive disease. Note that calculation of tumor growth as percentage change from nadir is not possible when the nadir is complete response (this results in a division by 0). Patients for whom this is the case are not taken into account in this analysis.

Overall survival was analyzed by treatment category using Cox proportional hazards regression modeling by adjusting for baseline sum and including these parameters as time-dependent covariables (Tables A29 to A40). The goodness of fit of these models was assessed by time-dependent versions of receiver operating characteristic curves and their areas under the curve (AUCs) with incident/dynamic definitions of sensitivity and specificity (Heagerty et al: Biometrics 61:92-105, 2005). The AUC provides a measure of the model's discriminatory power whereby an AUC of 1 reflects a perfect test and an AUC of 0.5 reflects a predictive ability comparable to tossing a coin (Figures A40 to A43).

Time-Dependent Model With Tumor Growth as Percentage

Calculation of tumor growth as percentage change from nadir is not possible when the nadir is complete response (this results in a division by 0). Patients for whom this is the case are not taken into account in this analysis.

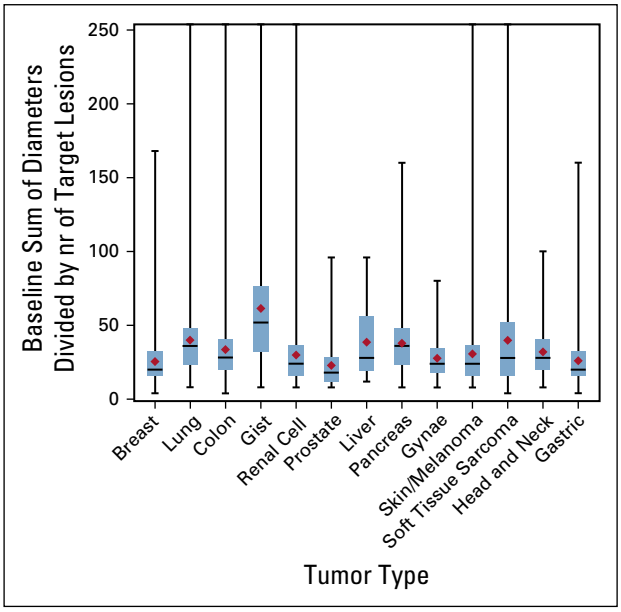

FIG A1. Analysis dataset: extent of disease at baseline.

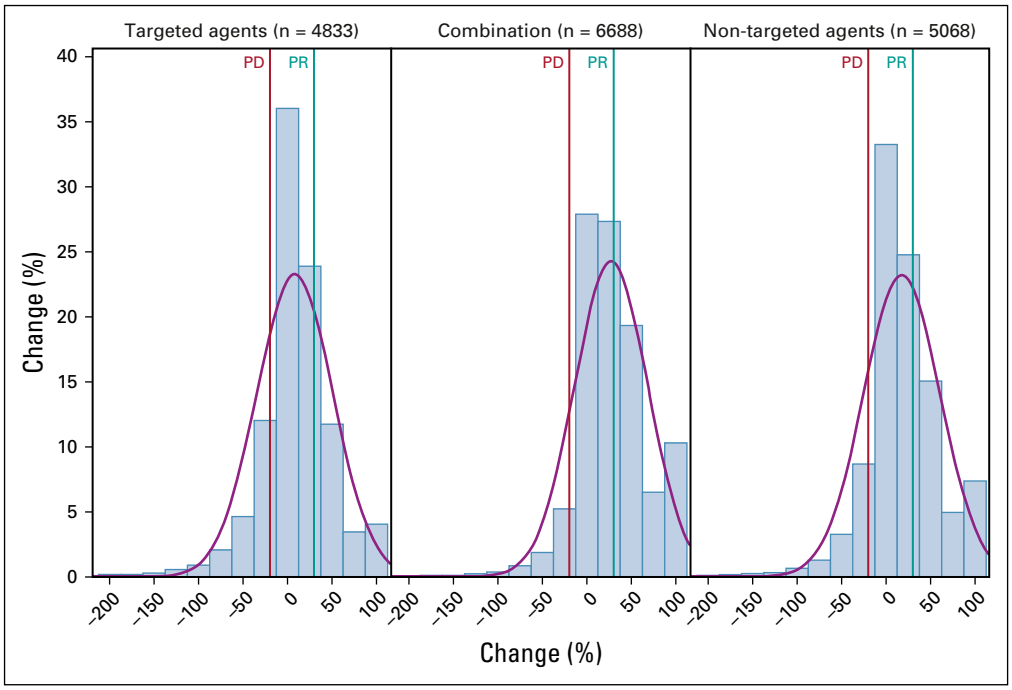

FIG A2. Variability assessments: Percentage change from baseline to week 12 by treatment category.

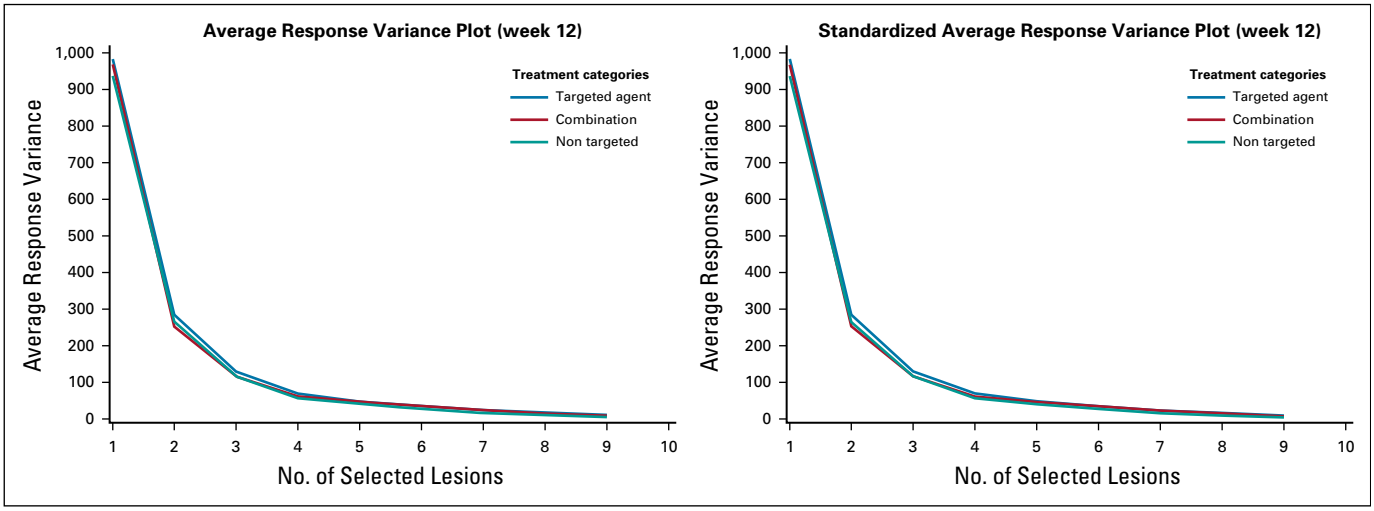

FIG A3. Variability assessments: Variance plots of Percentage change from baseline to week 12 by treatment category.

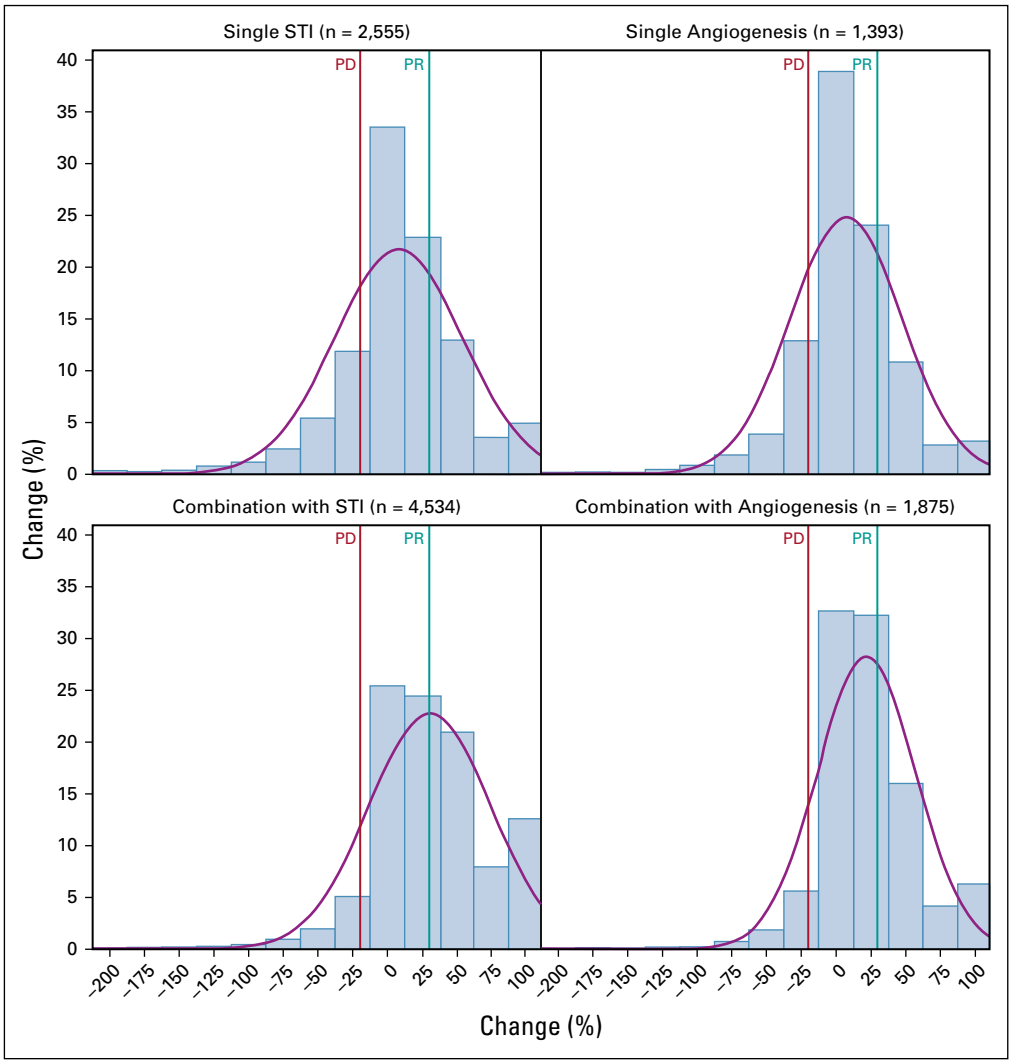

FIG A4. Variability assessments: Percentage change from baseline to week 12 by type of TCA.

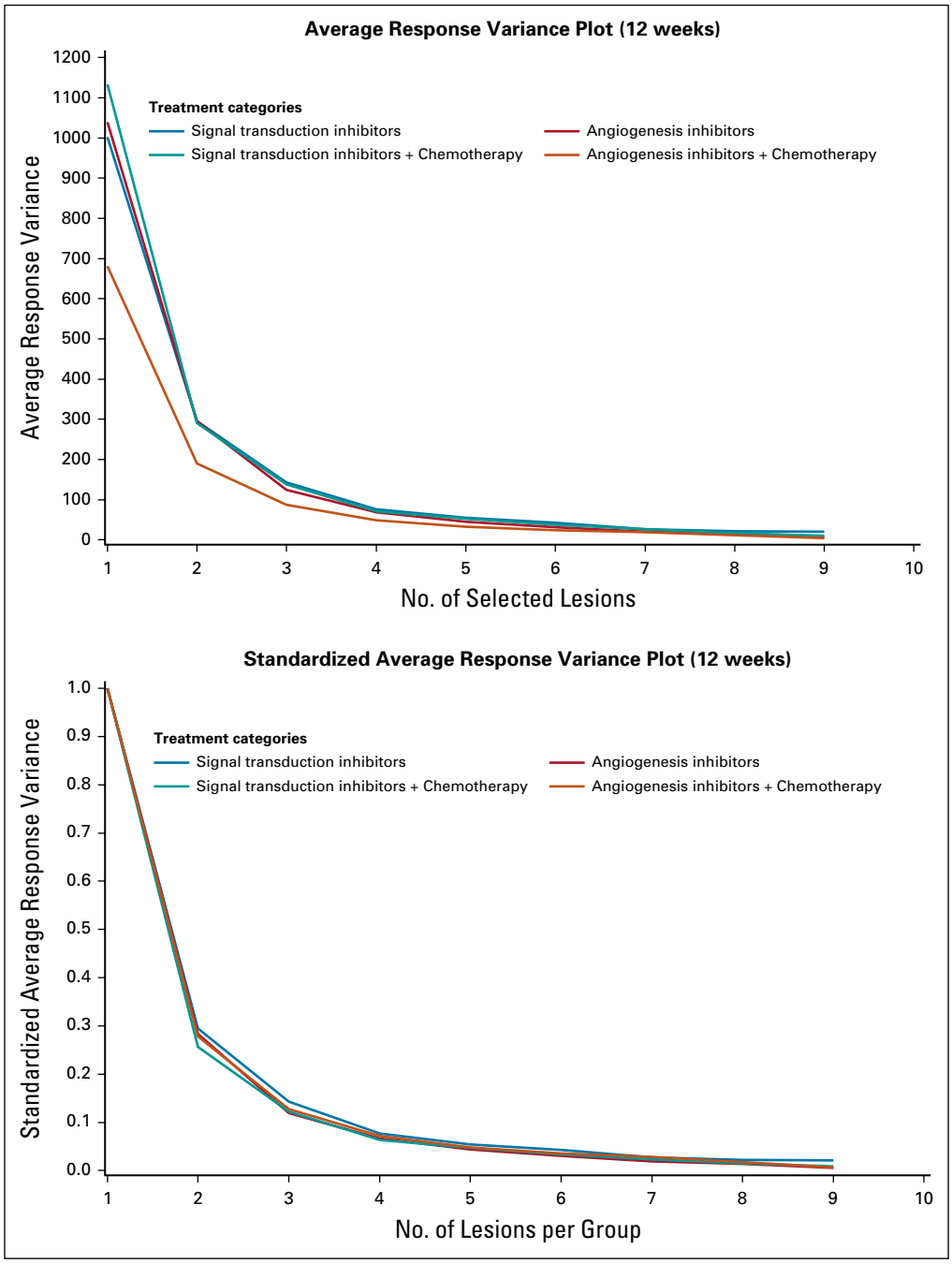

FIG A5. Variability assessments: Variance plots of Percentage change from baseline to week 12 by type of TCA.

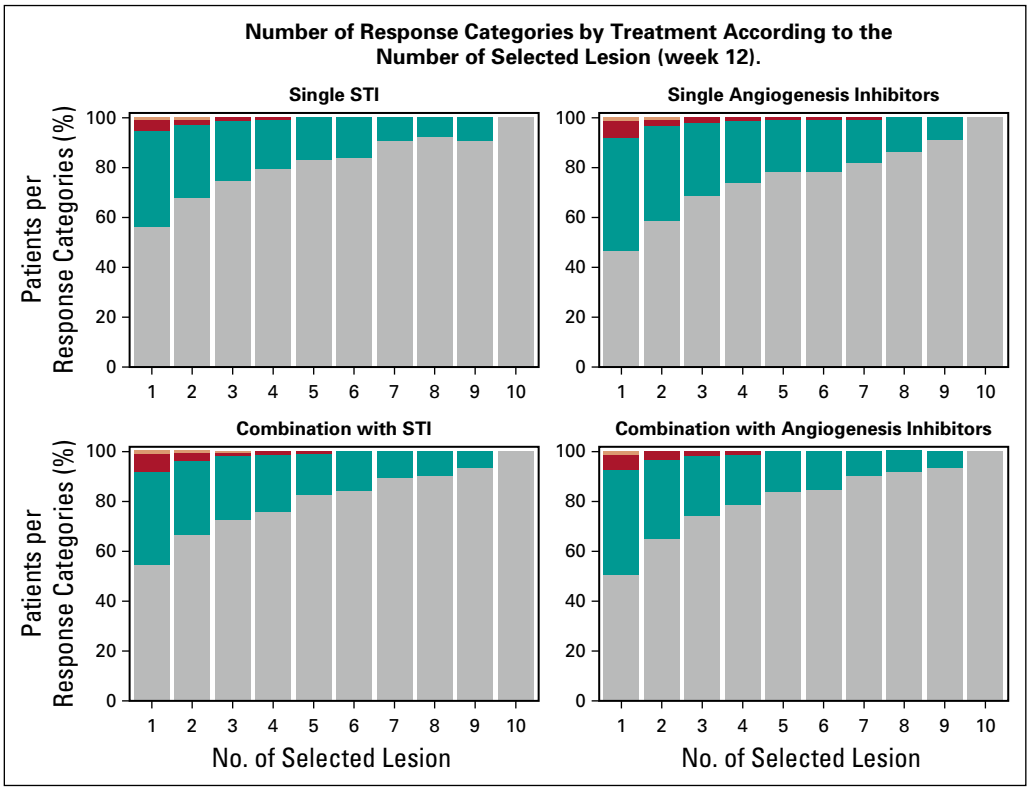

FIG A6. Variability assessment: Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three.

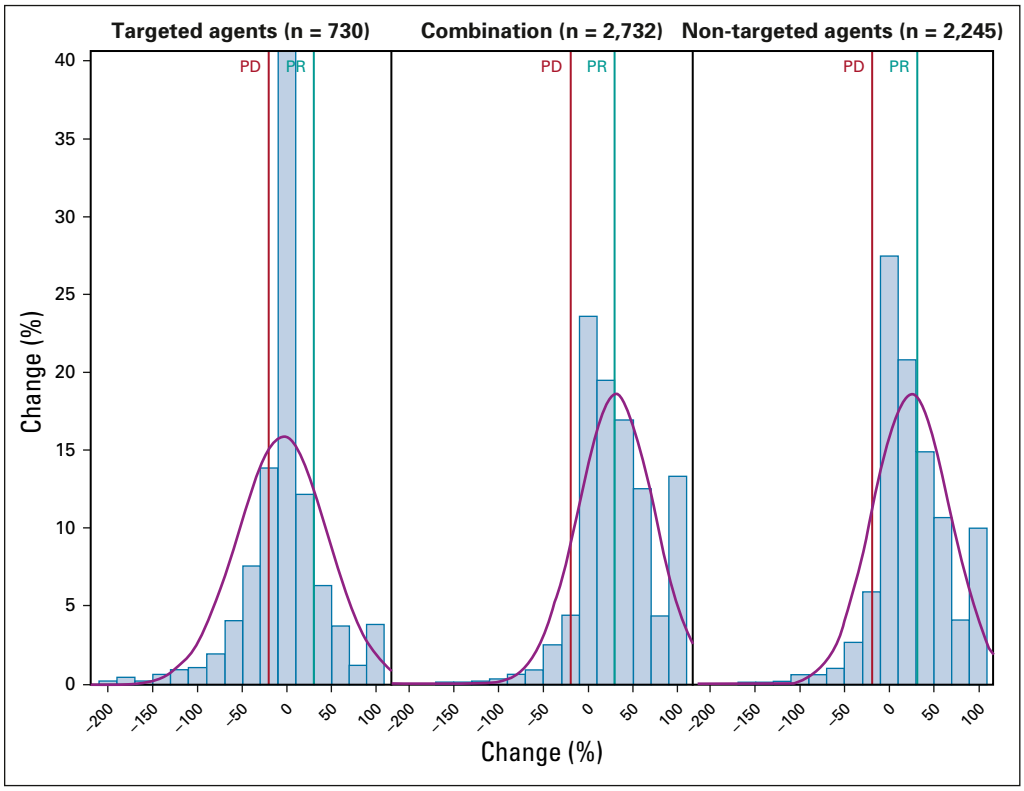

FIG A7. Variability assessments: Lung Cancer - Percentage change from baseline to week 12 by treatment category.

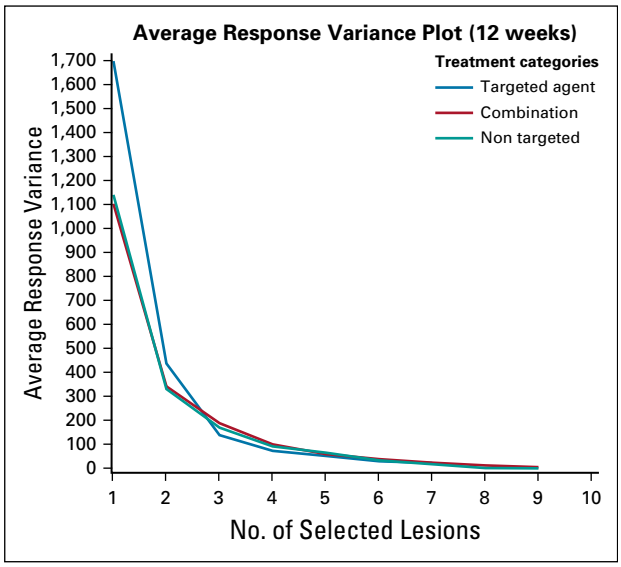

FIG A8. Variability assessments: Lung Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

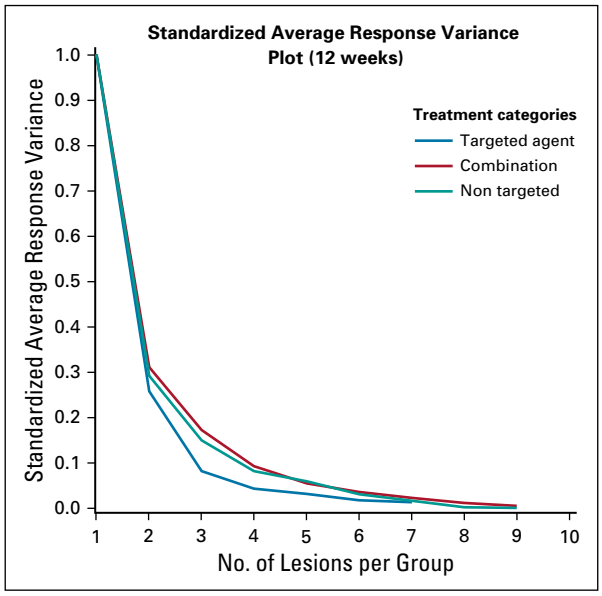

FIG A9. Variability assessments: Lung Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

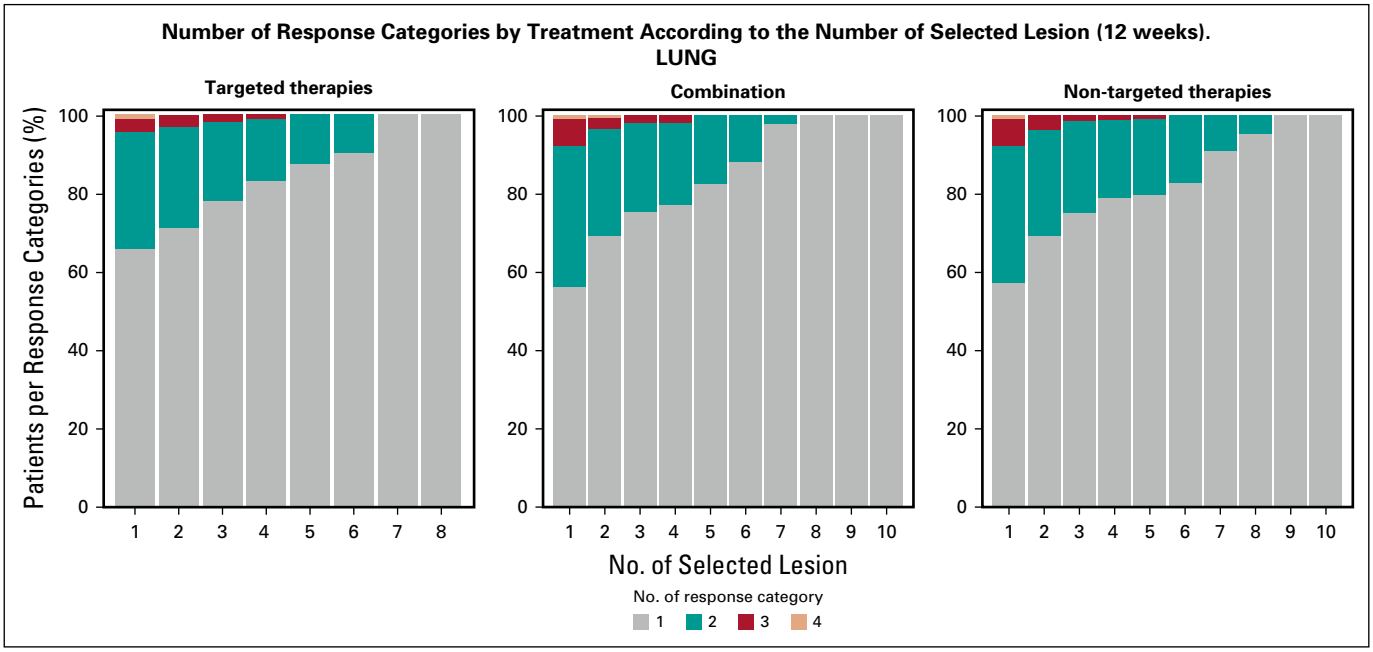

FIG A10. Variability assessment - Lung Cancer: Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three.

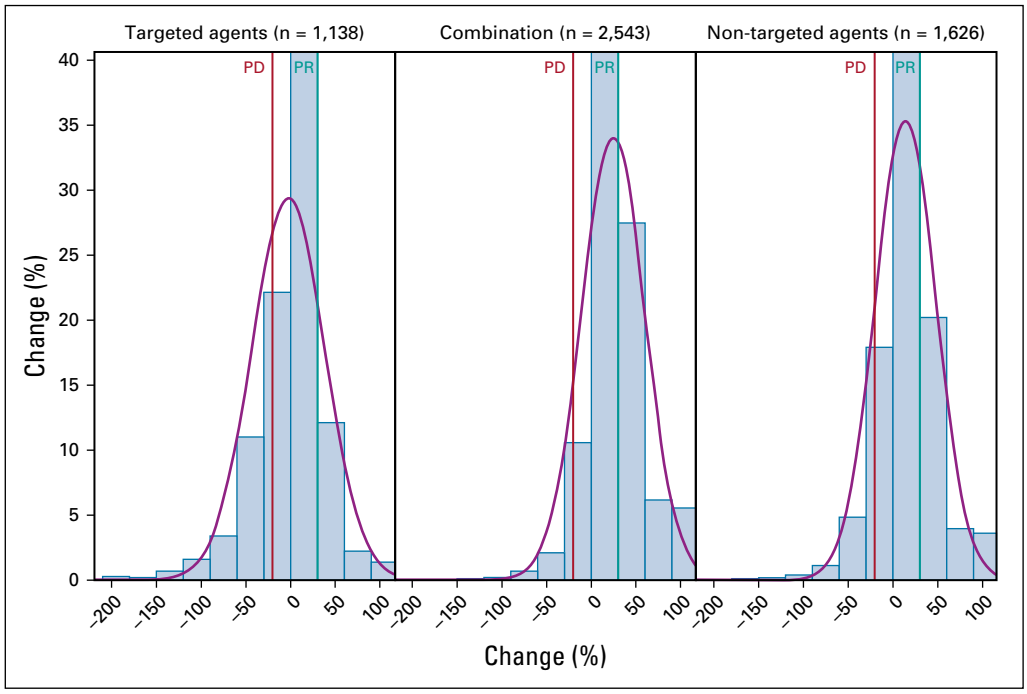

FIG A11. Variability assessments: Colon cancer - Percentage change from baseline to week 12 by treatment category.

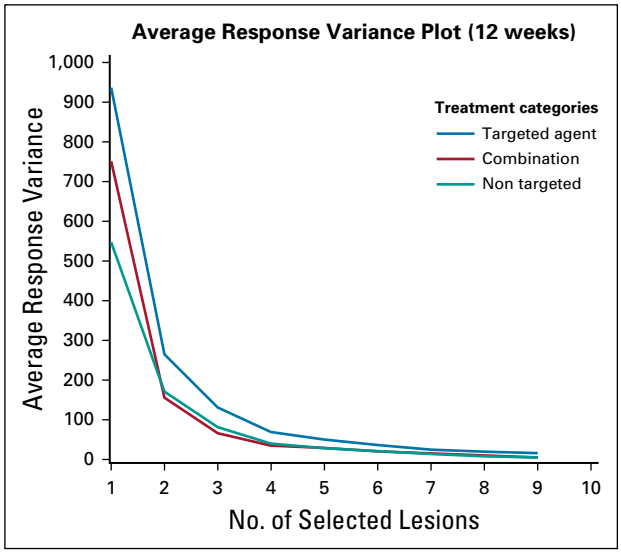

FIG A12. Variability assessments: Colon Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

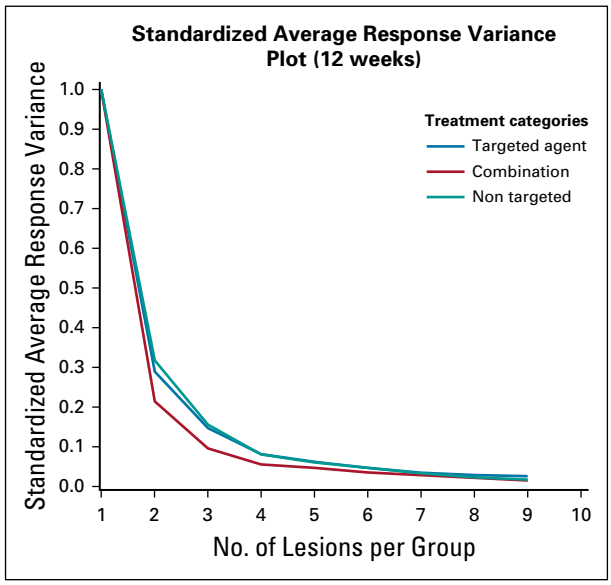

FIG A13. Variability assessments: Colon Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

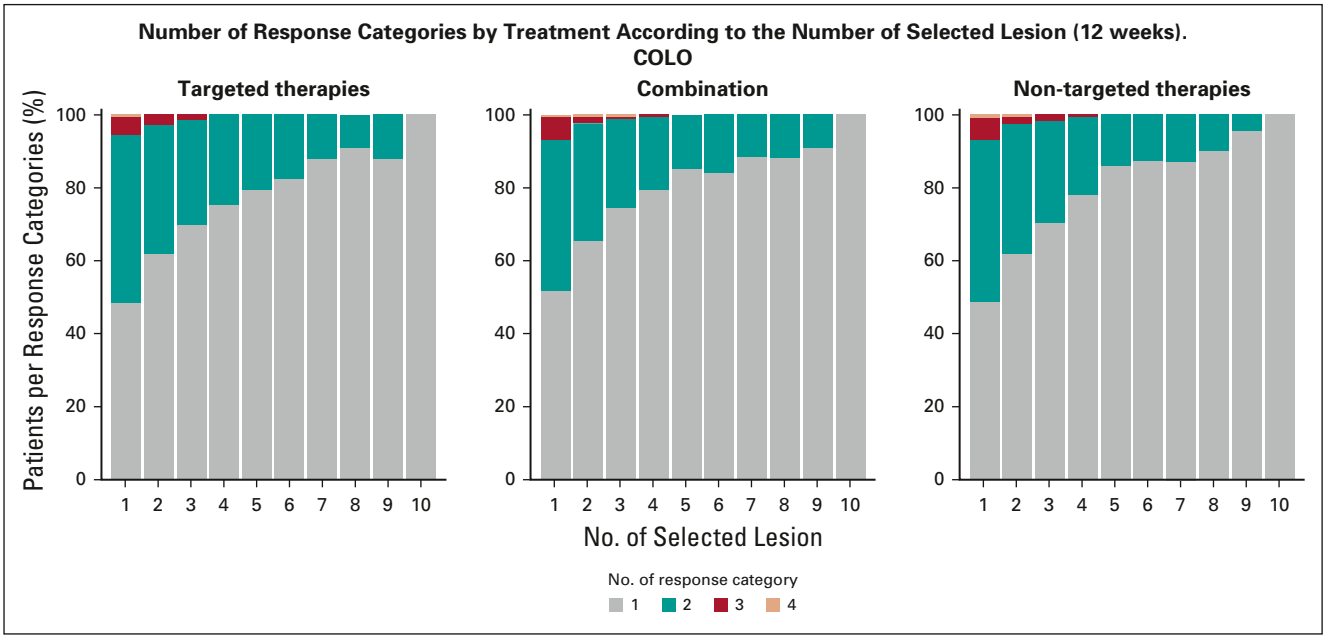

FIG A14. Variability assessment - Colon Cancer: Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three.

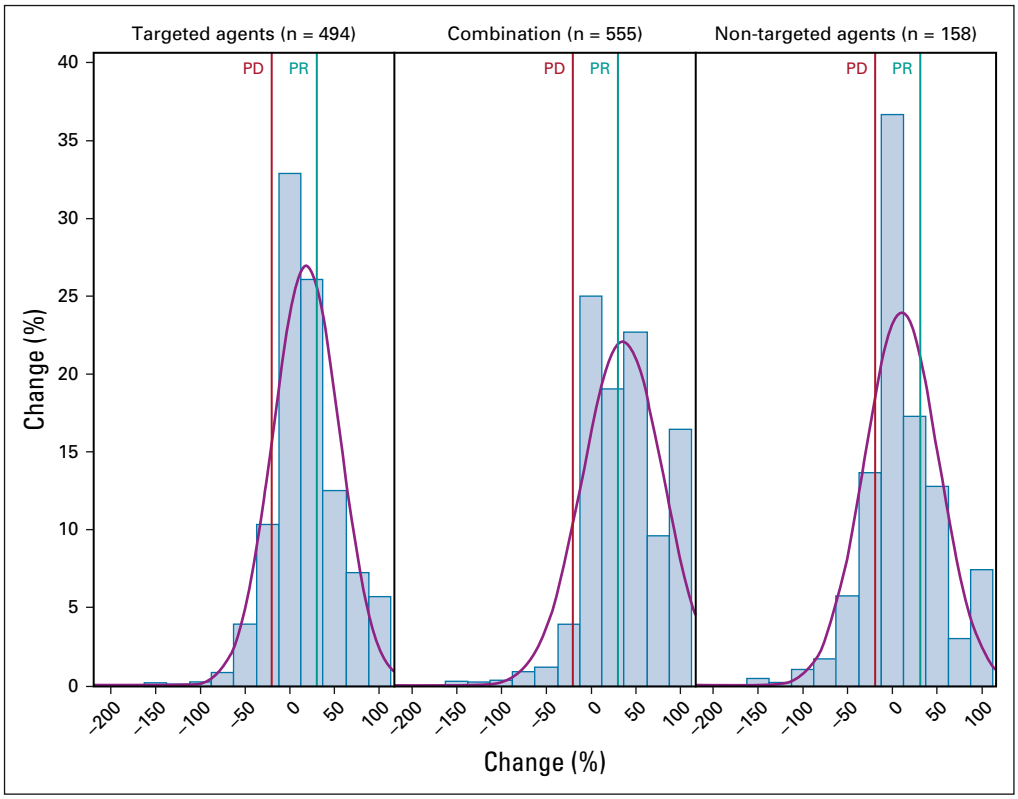

FIG A15. Variability assessments: Breast Cancer - Percentage change from baseline to week 12 by treatment category.

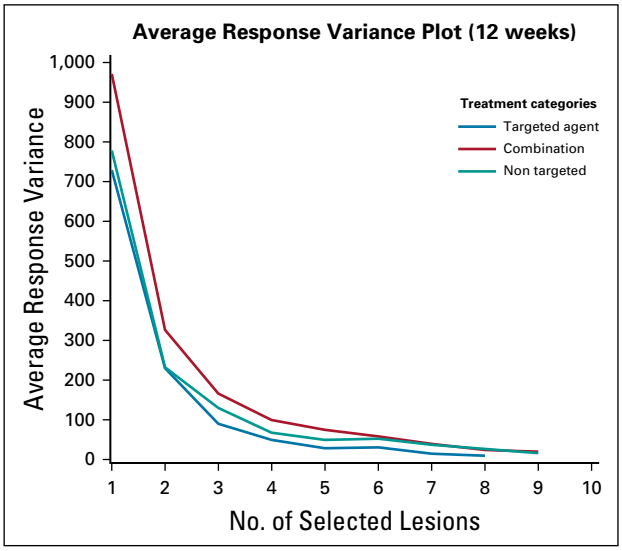

FIG A16. Variability assessments: Breast Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

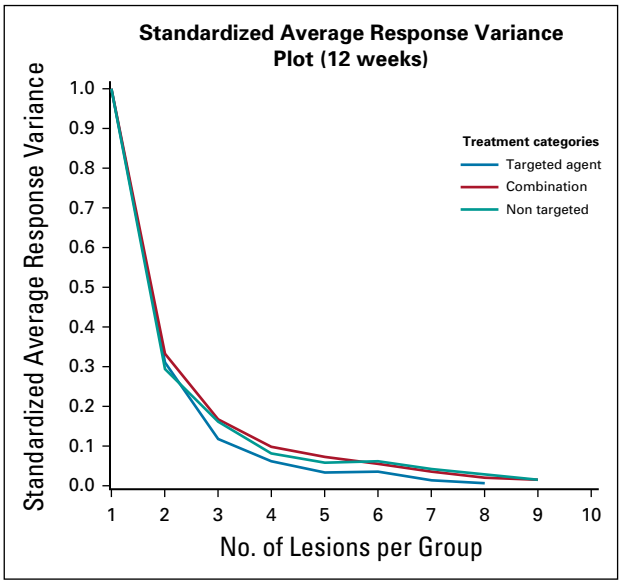

FIG A17. Variability assessments: Breast Cancer - Variance plots of Percentage change from baseline to week 12 by treatment category.

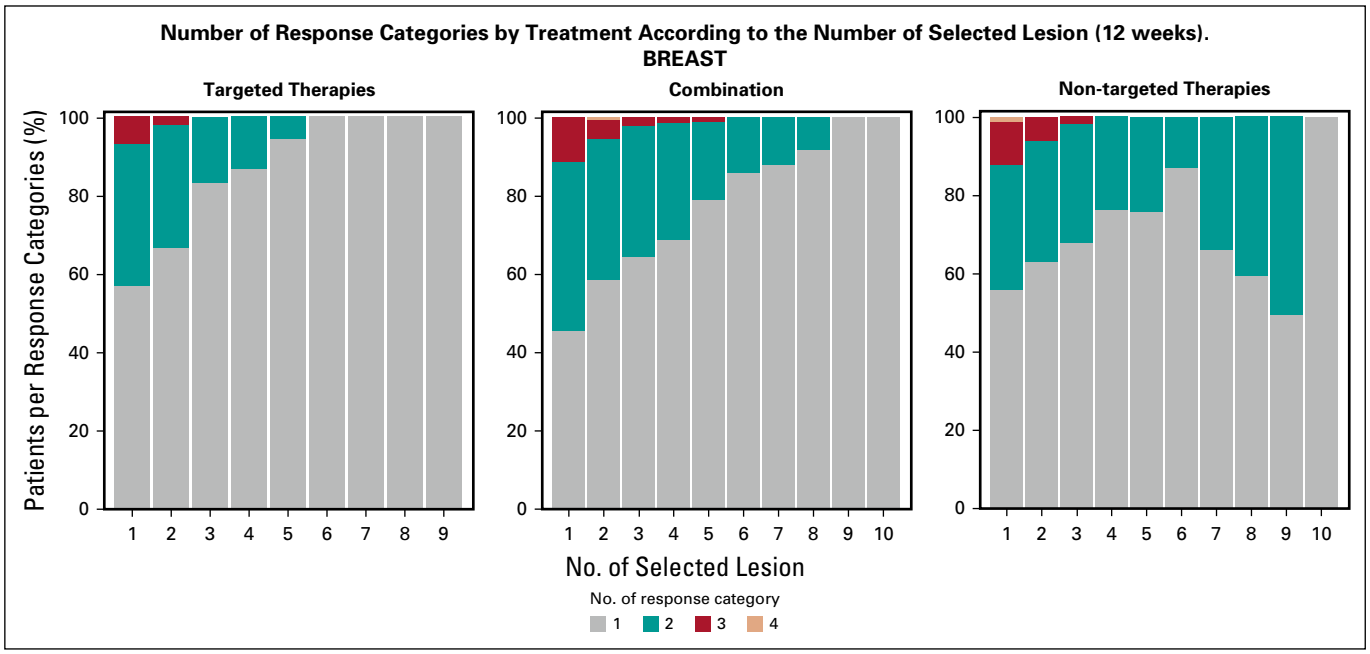

FIG A18. Variability assessment - Breast Cancer: Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three.

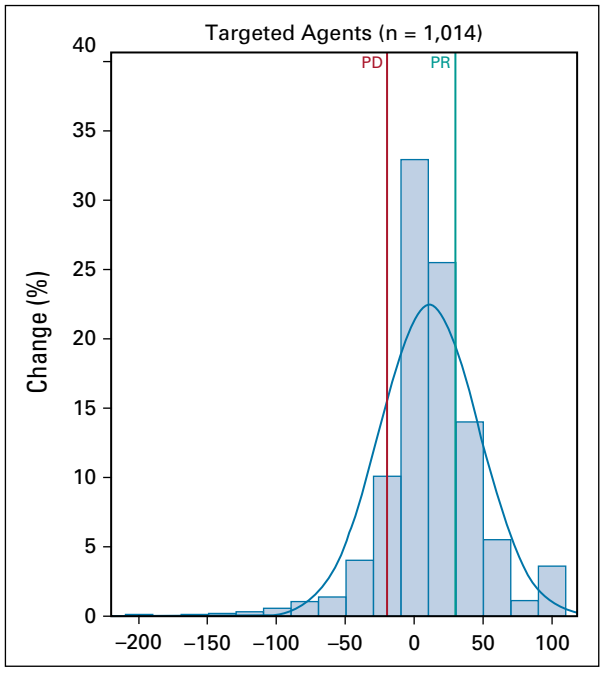

FIG A19. Variability assessments: GIST - Percentage change from baseline to week 12 by treatment category.

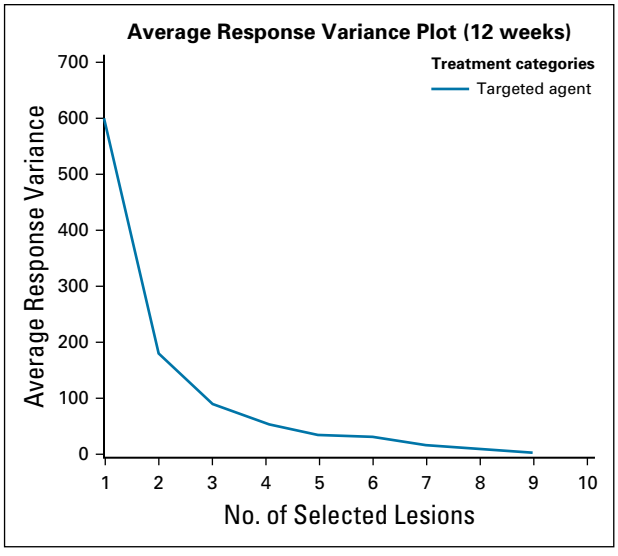

FIG A20. Variability assessments: GIST - Variance plots of Percentage change from baseline to week 12 by treatment category.

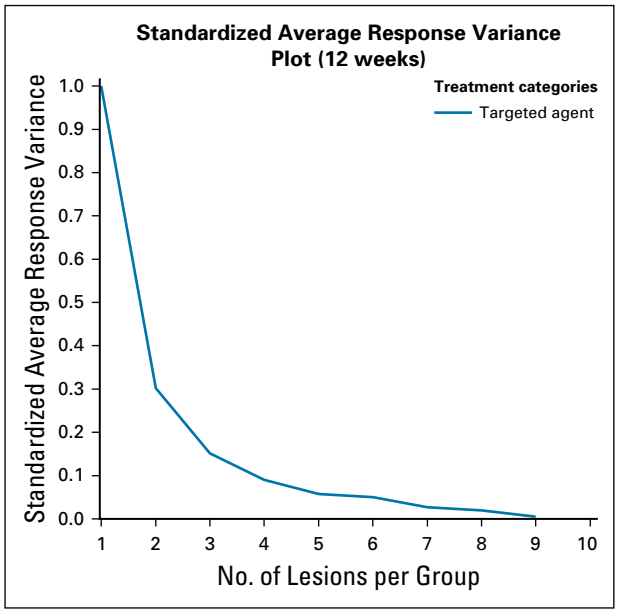

FIG A21. Variability assessments: GIST - Variance plots of Percentage change from baseline to week 12 by treatment category.

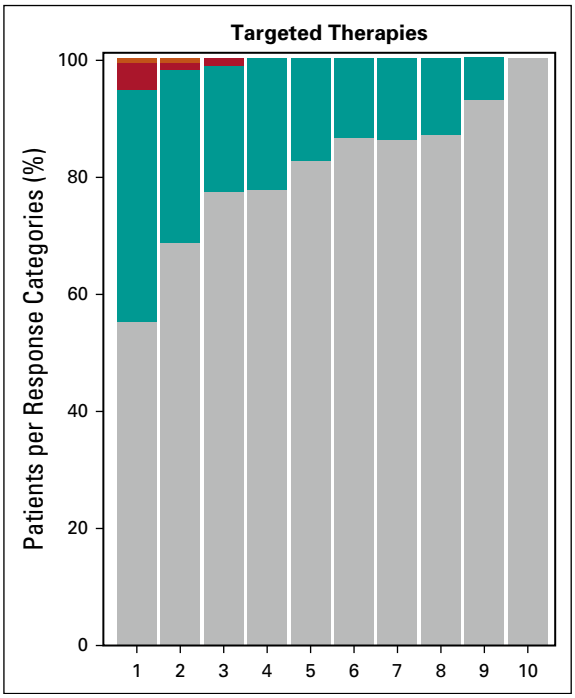

FIG A22. Variability assessment - GIST: Response categories (at 12 weeks) by number of selected target lesions: number of different response categories a patient could be classified in on the basis of all possible selections of target lesions by number of selected lesions. The number of response categories for all possible combinations of target lesions in a patient per RECIST 1.1 outcome was assessed. By number of selected target lesions, we then determined how many different response categories could be assigned to a patient. For example, for a patient with five lesions (two with individual outcome of a partial response, two with stable disease, and one with progressive disease), the number of response categories for one selected lesion is three.

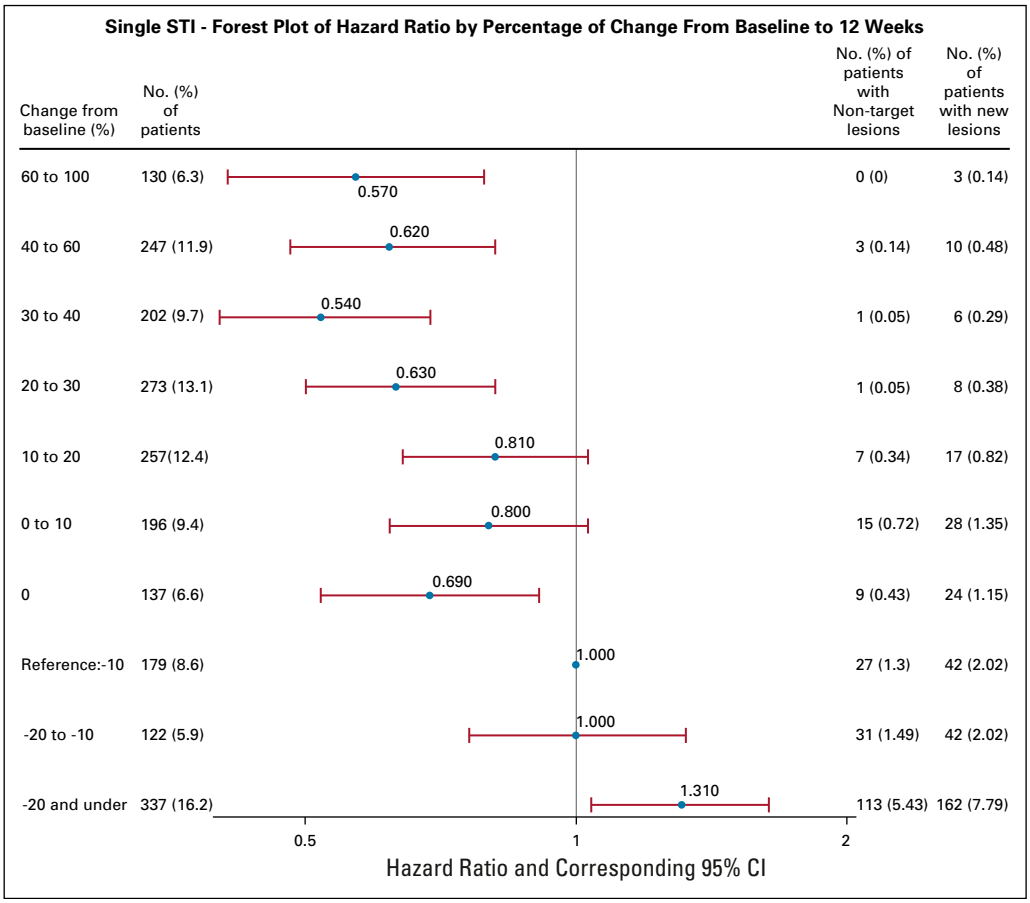

FIG A23. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

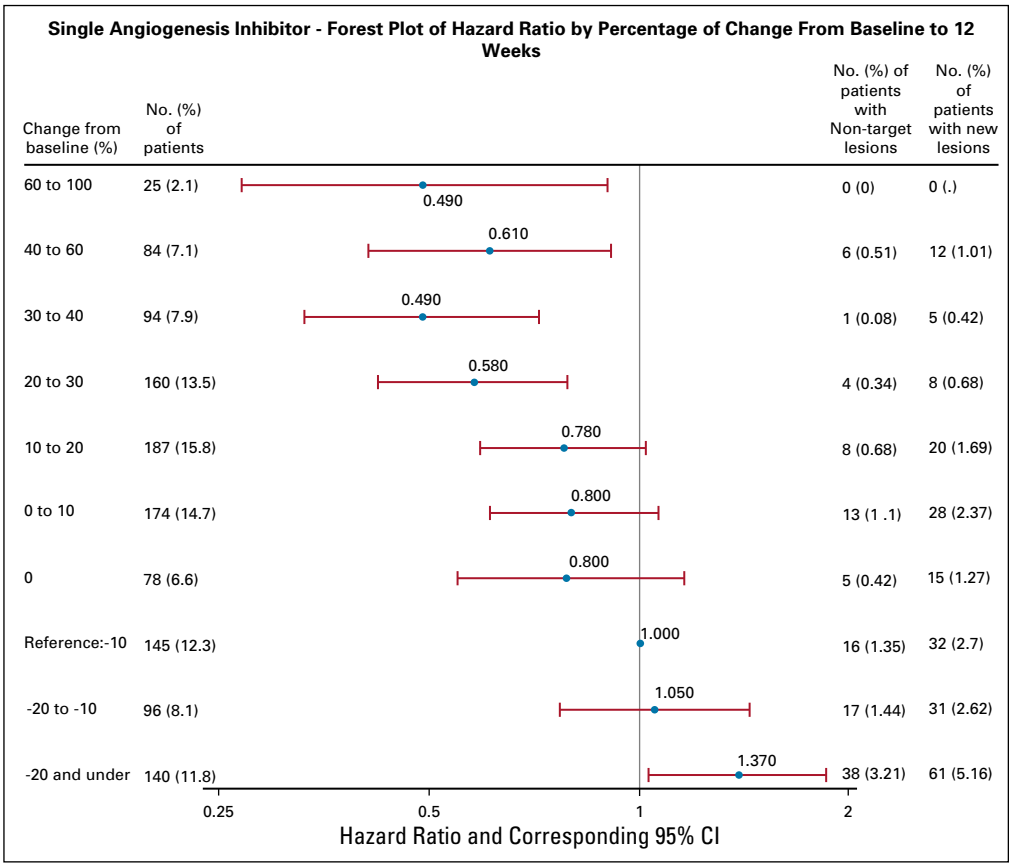

FIG A24. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

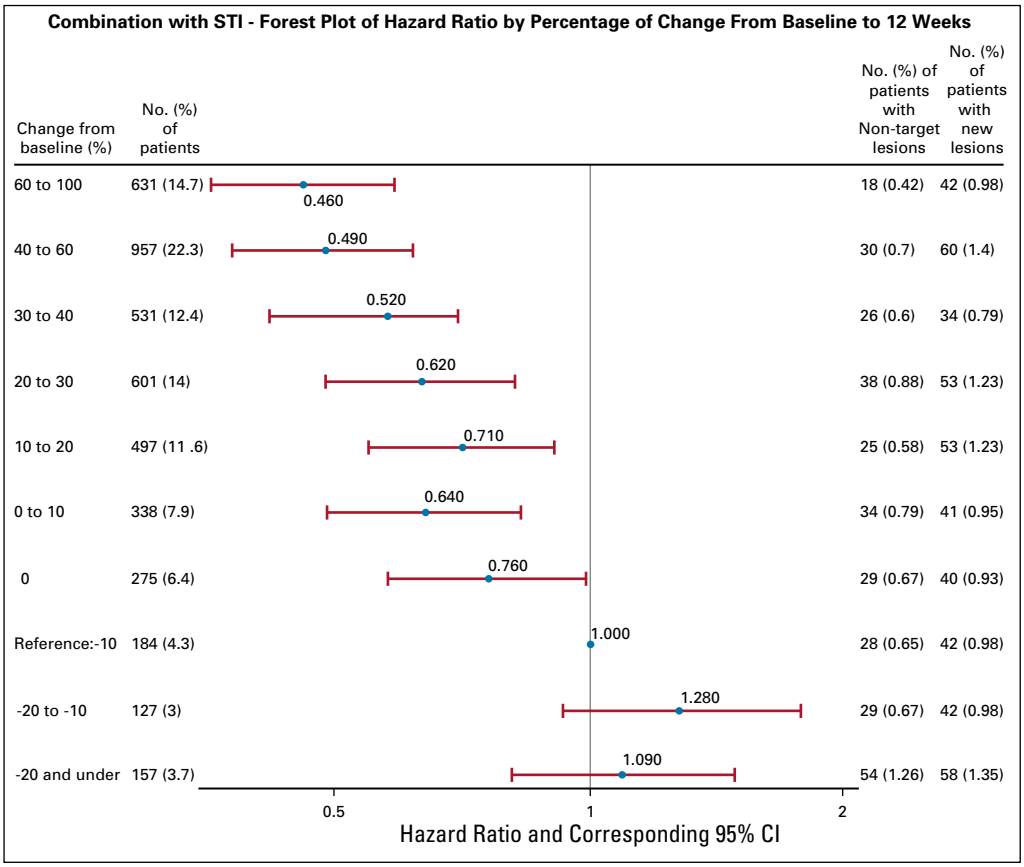

FIG A25. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

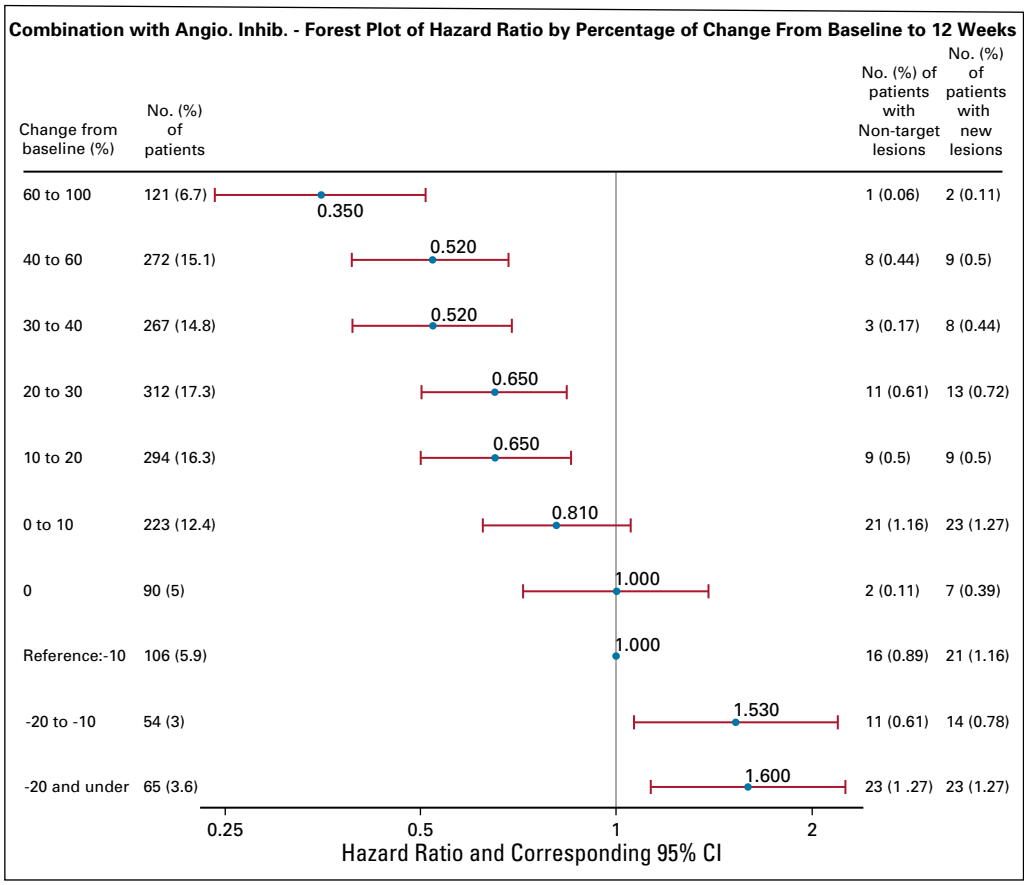

FIG A26. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

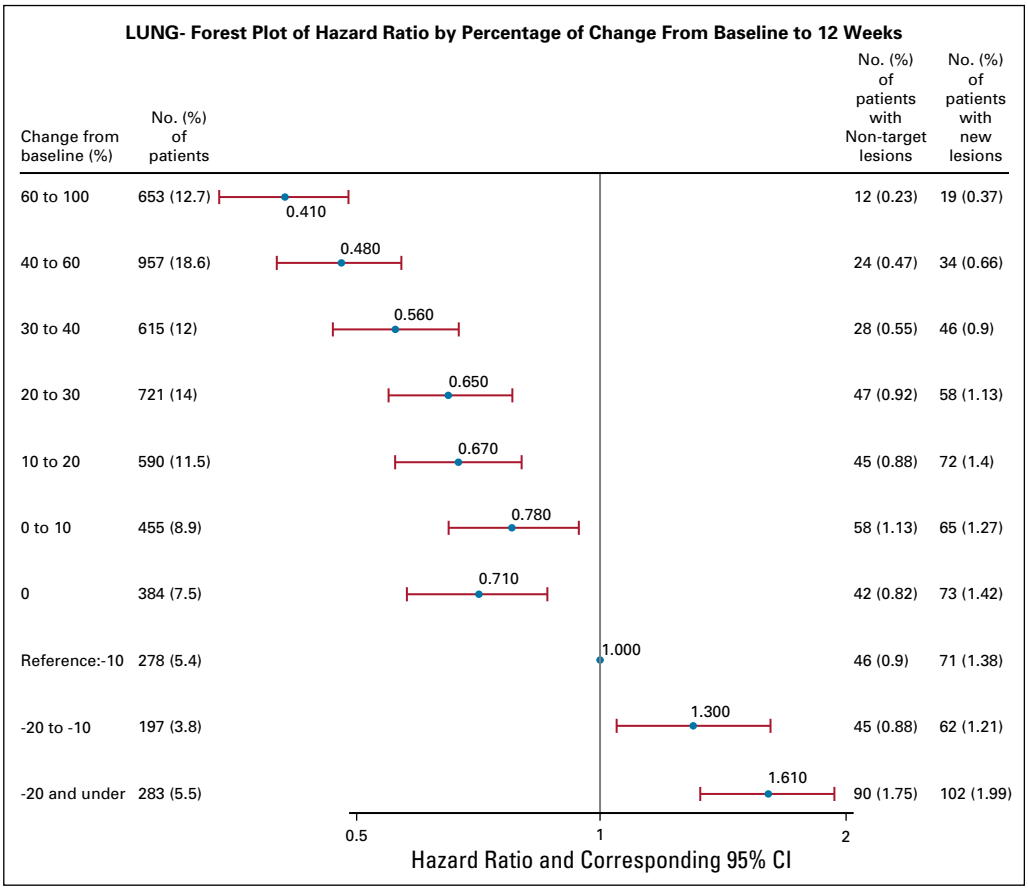

FIG A27. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

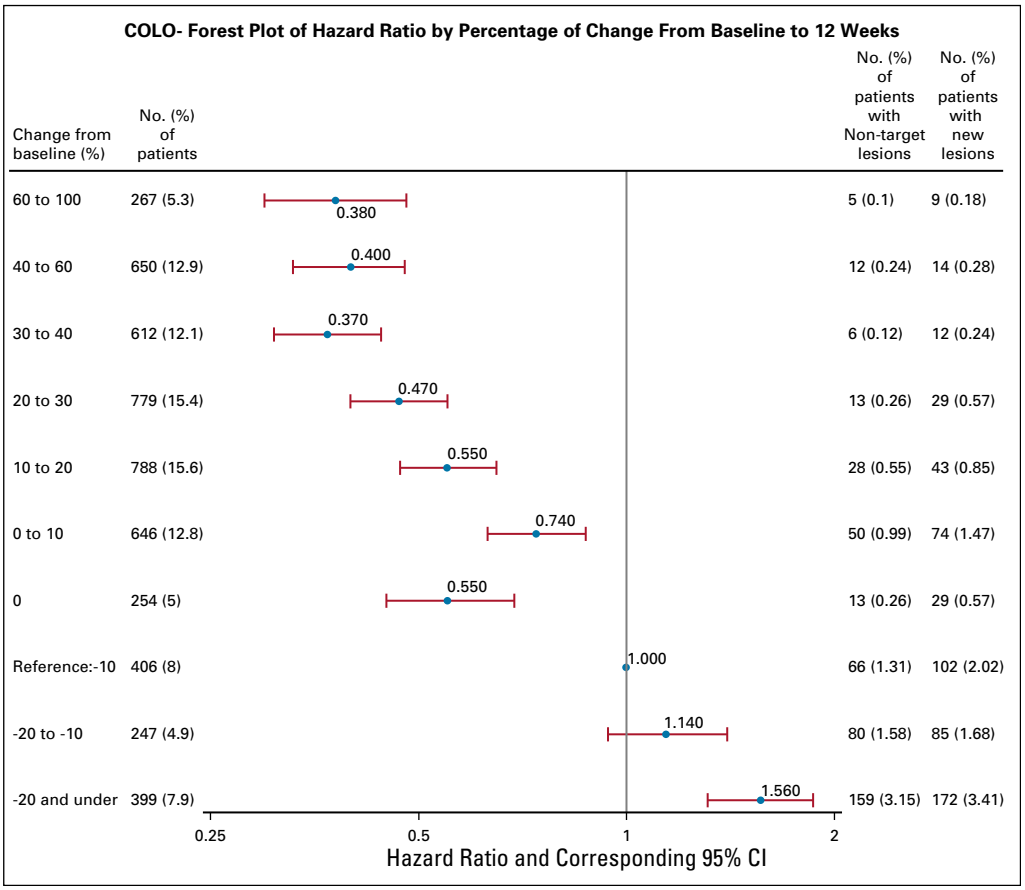

FIG A28. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

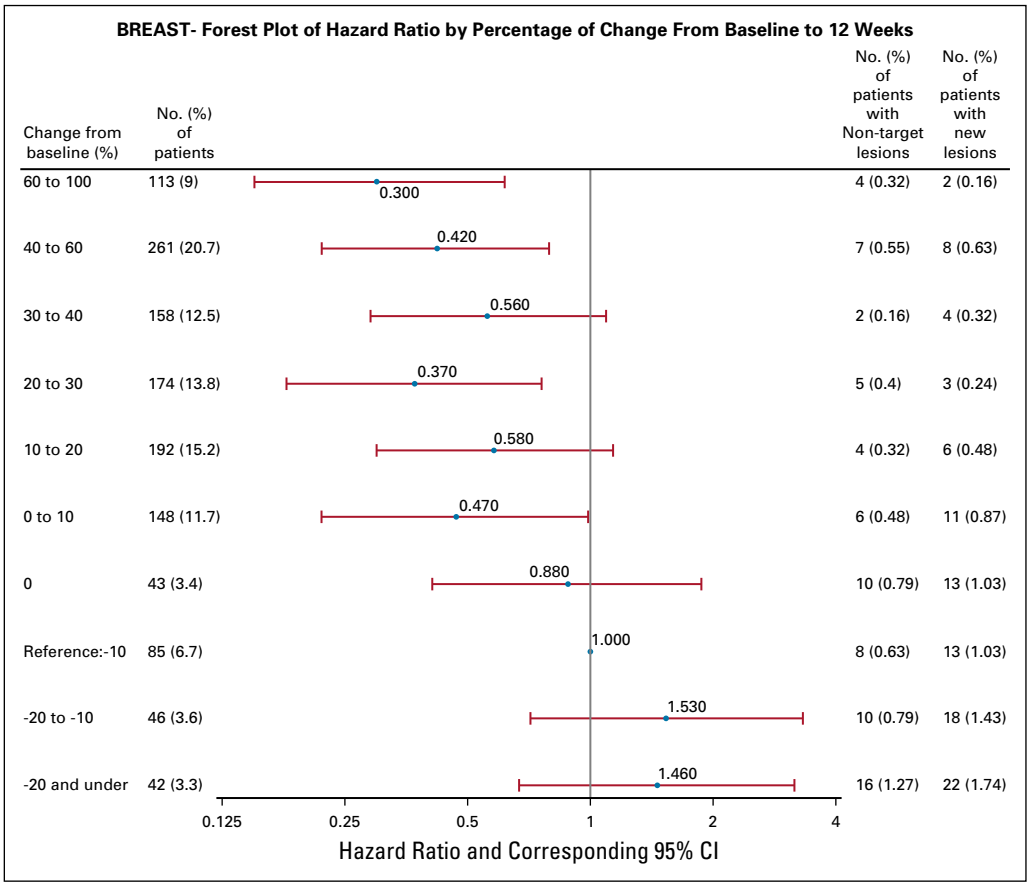

FIG A29. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

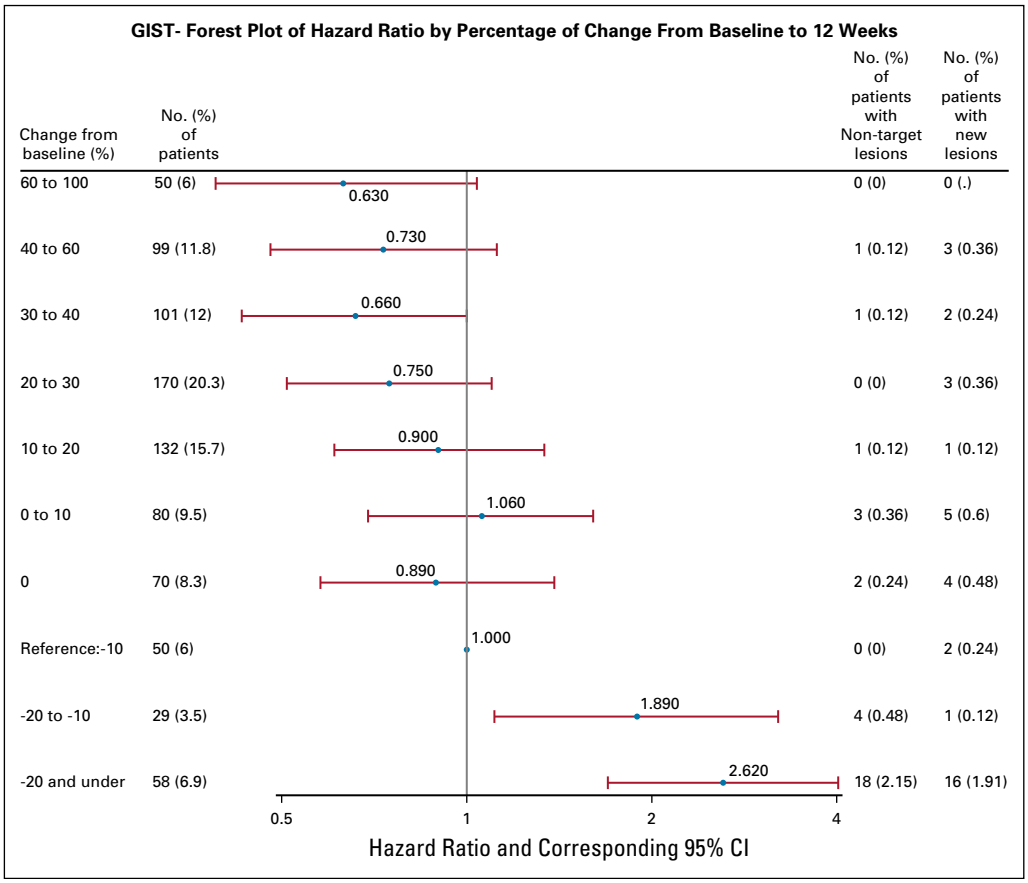

FIG A30. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

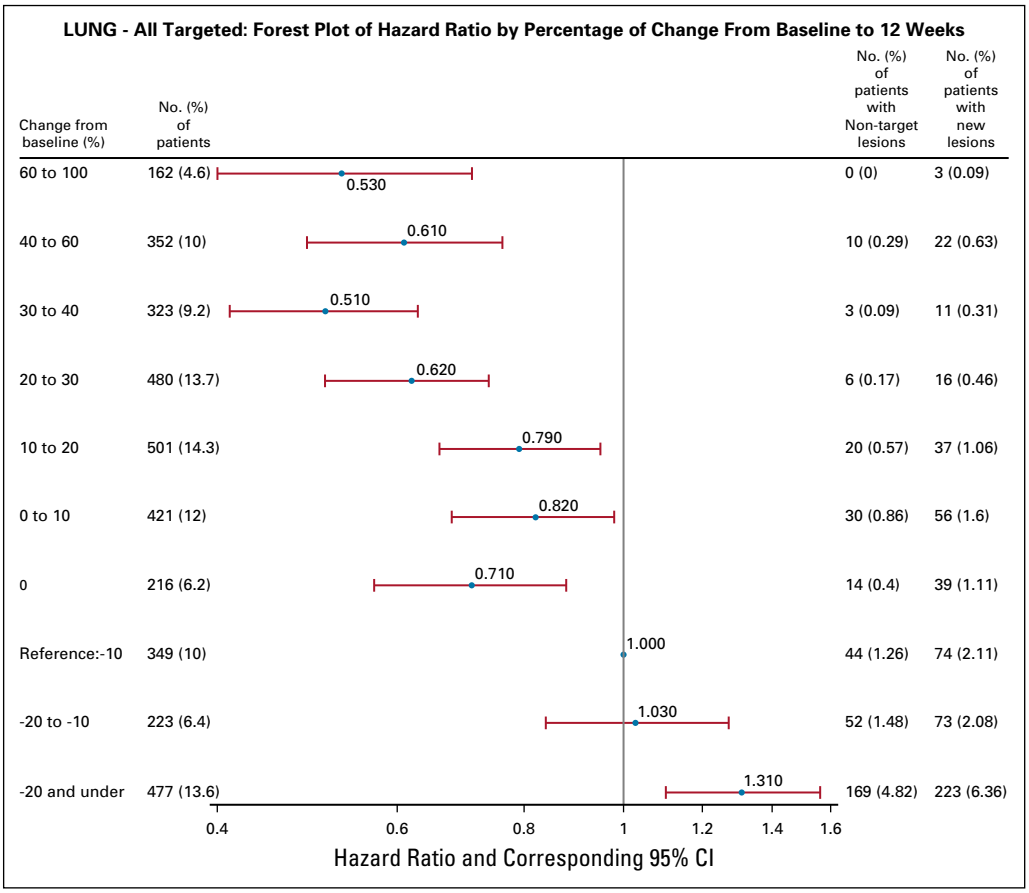

FIG A31. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

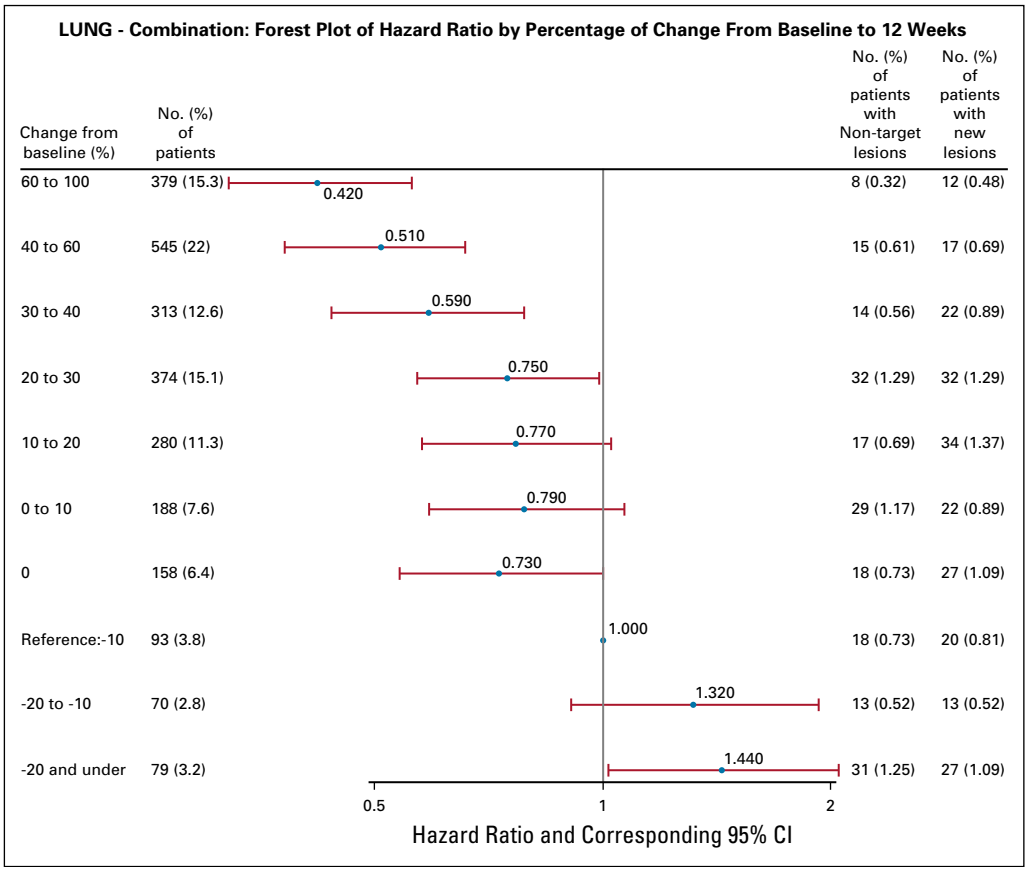

FIG A32. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

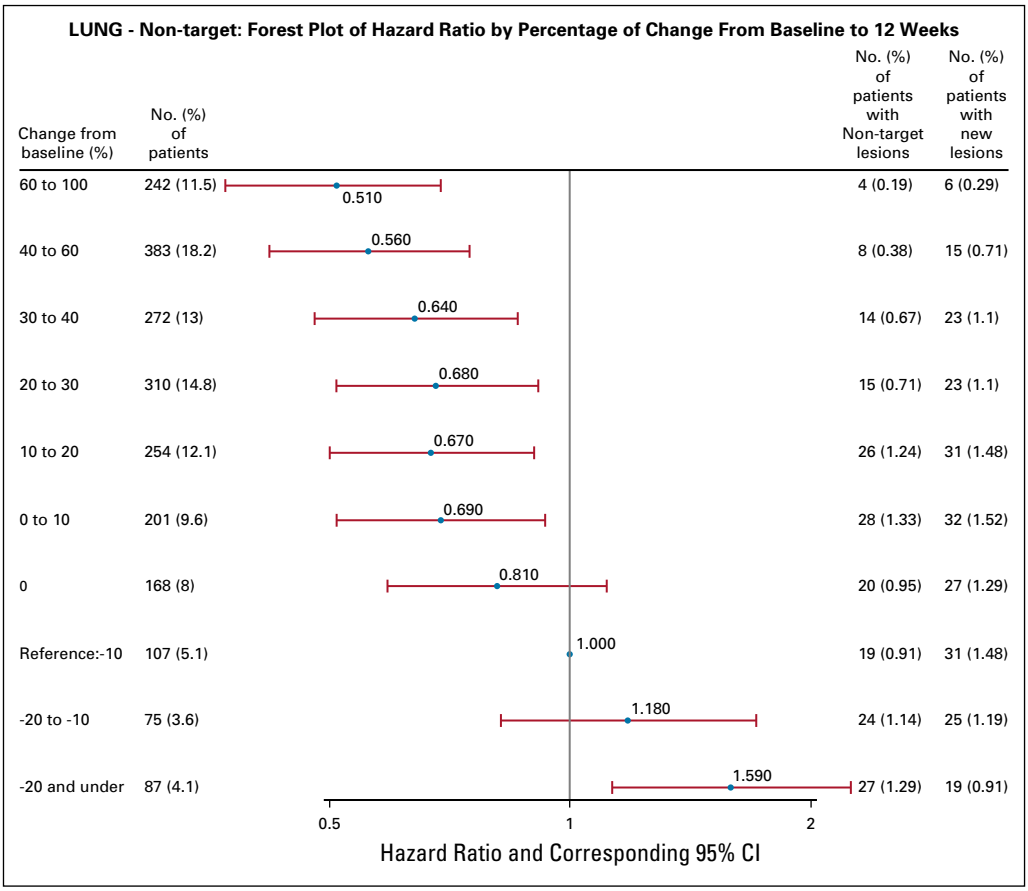

FIG A33. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

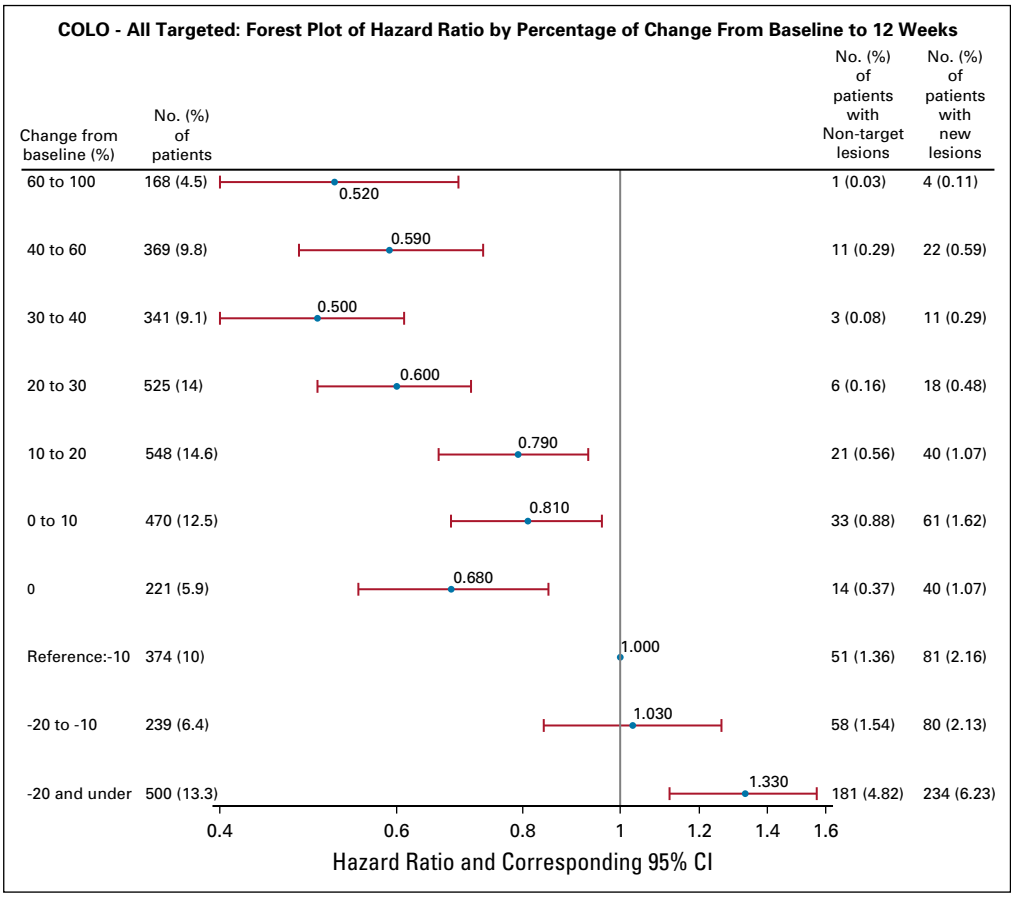

FIG A34. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

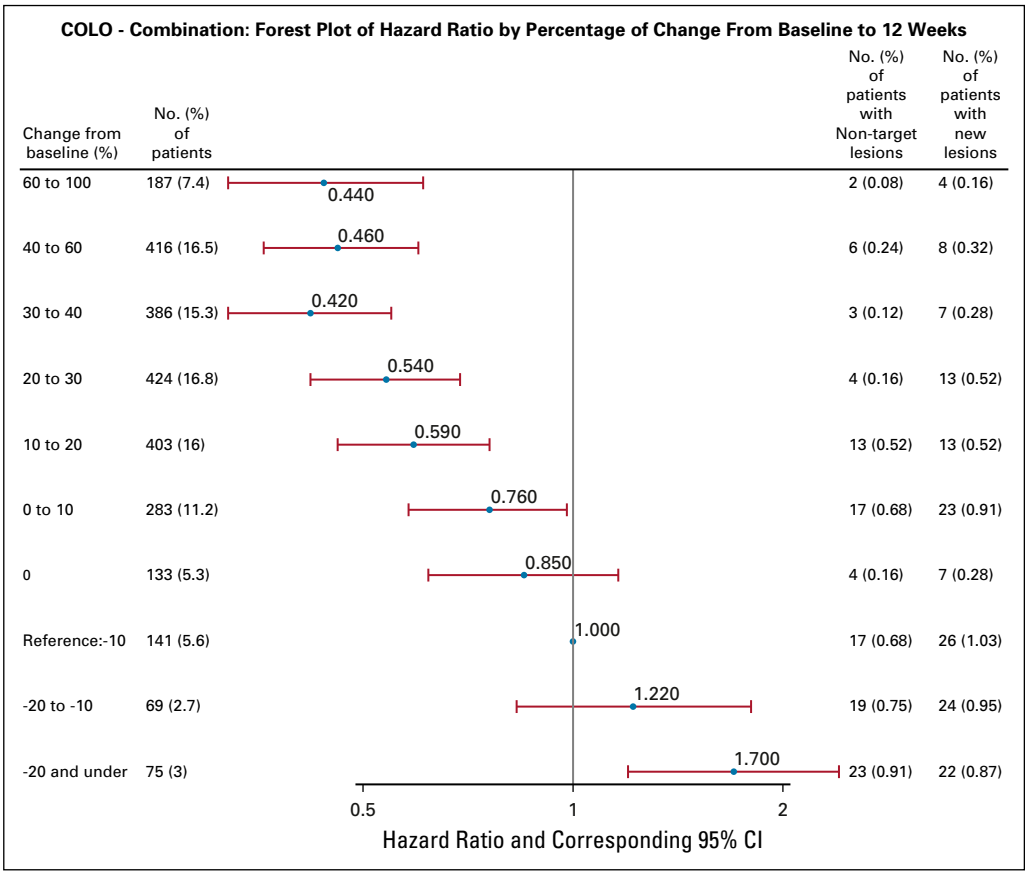

FIG A35. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

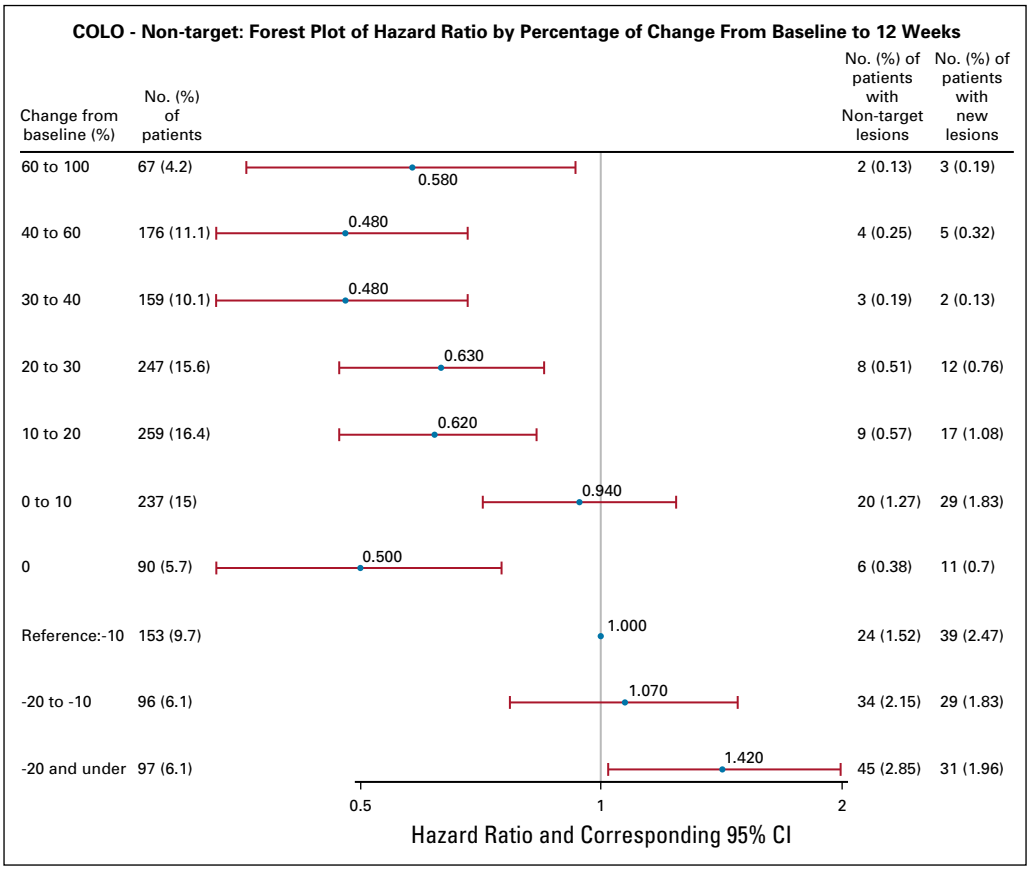

FIG A36. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

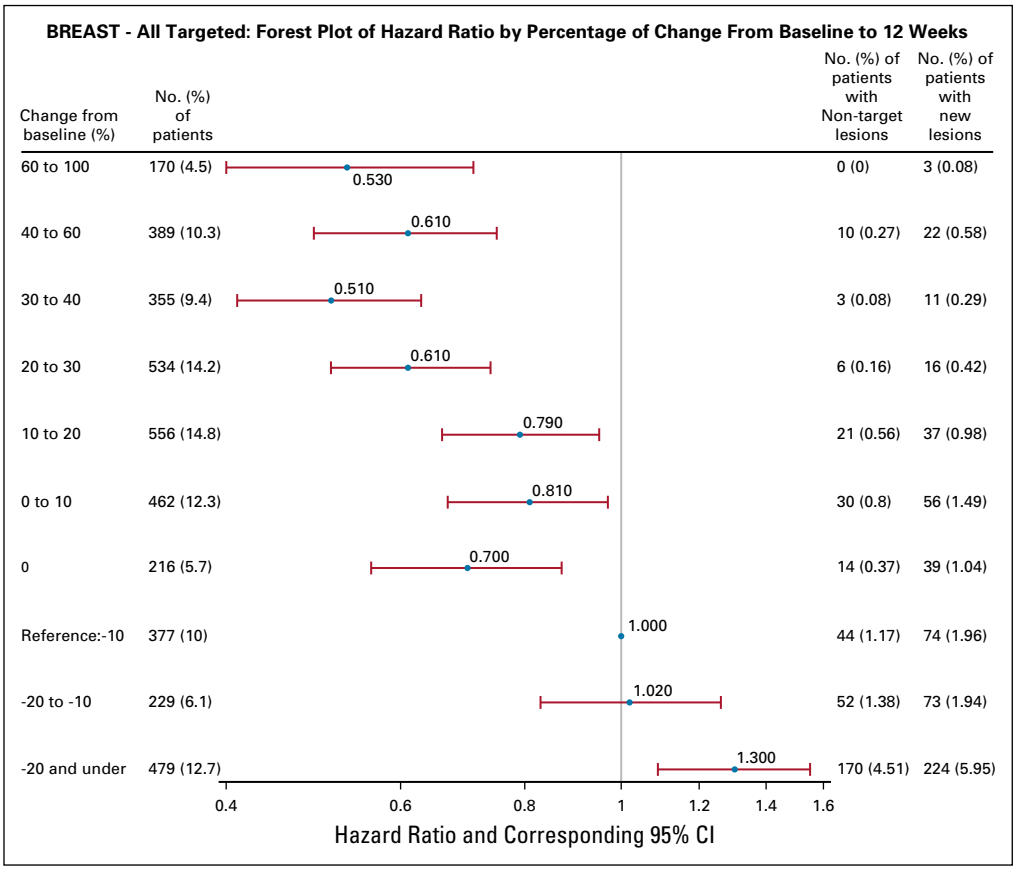

FIG A37. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

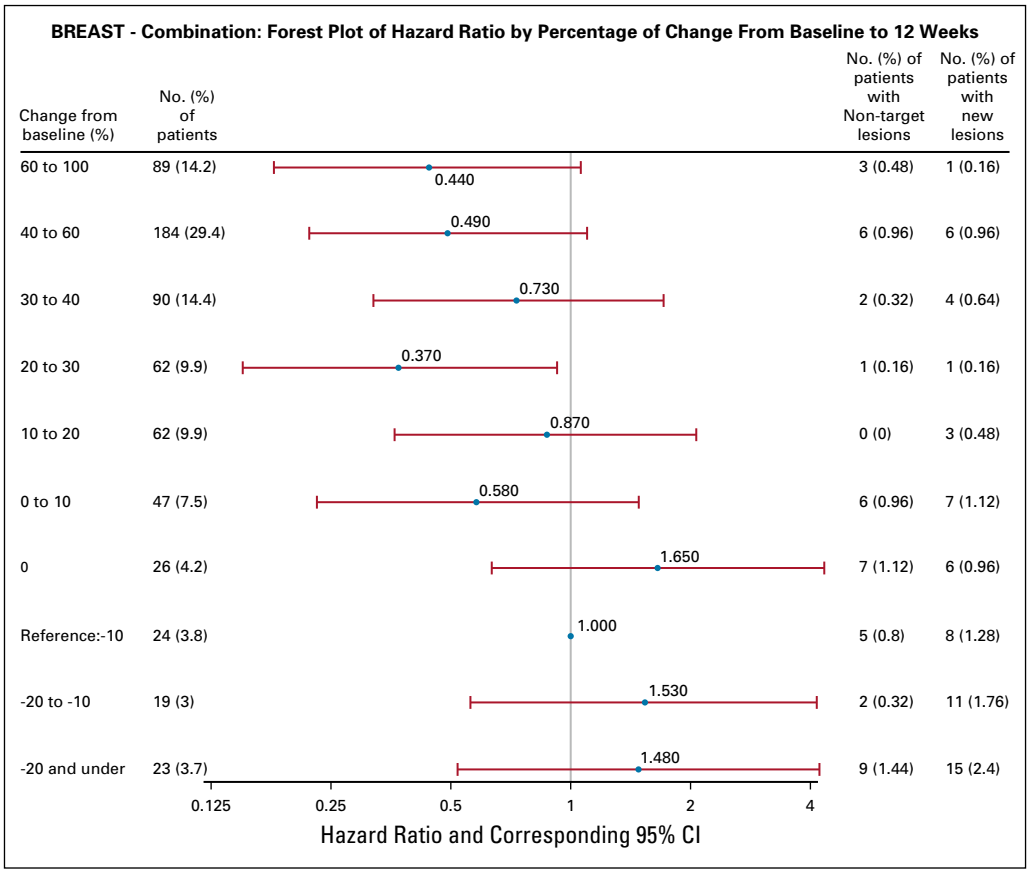

FIG A38. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

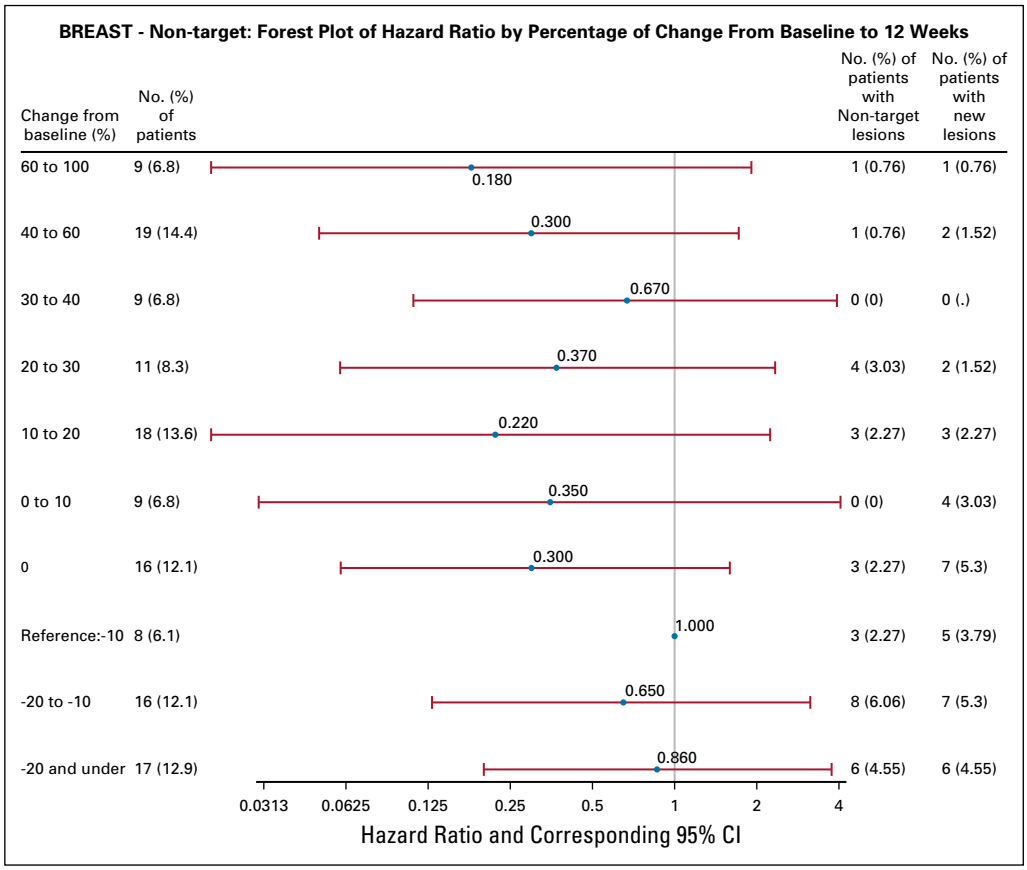

FIG A39. Forest plots of a landmark analysis at 12 weeks of survival by percentage change from baseline of the sum of target lesions up to 12 weeks. Models stratified by study and adjusted for baseline sum of diameters, occurrence of new lesions, and progression of nontarget lesions.

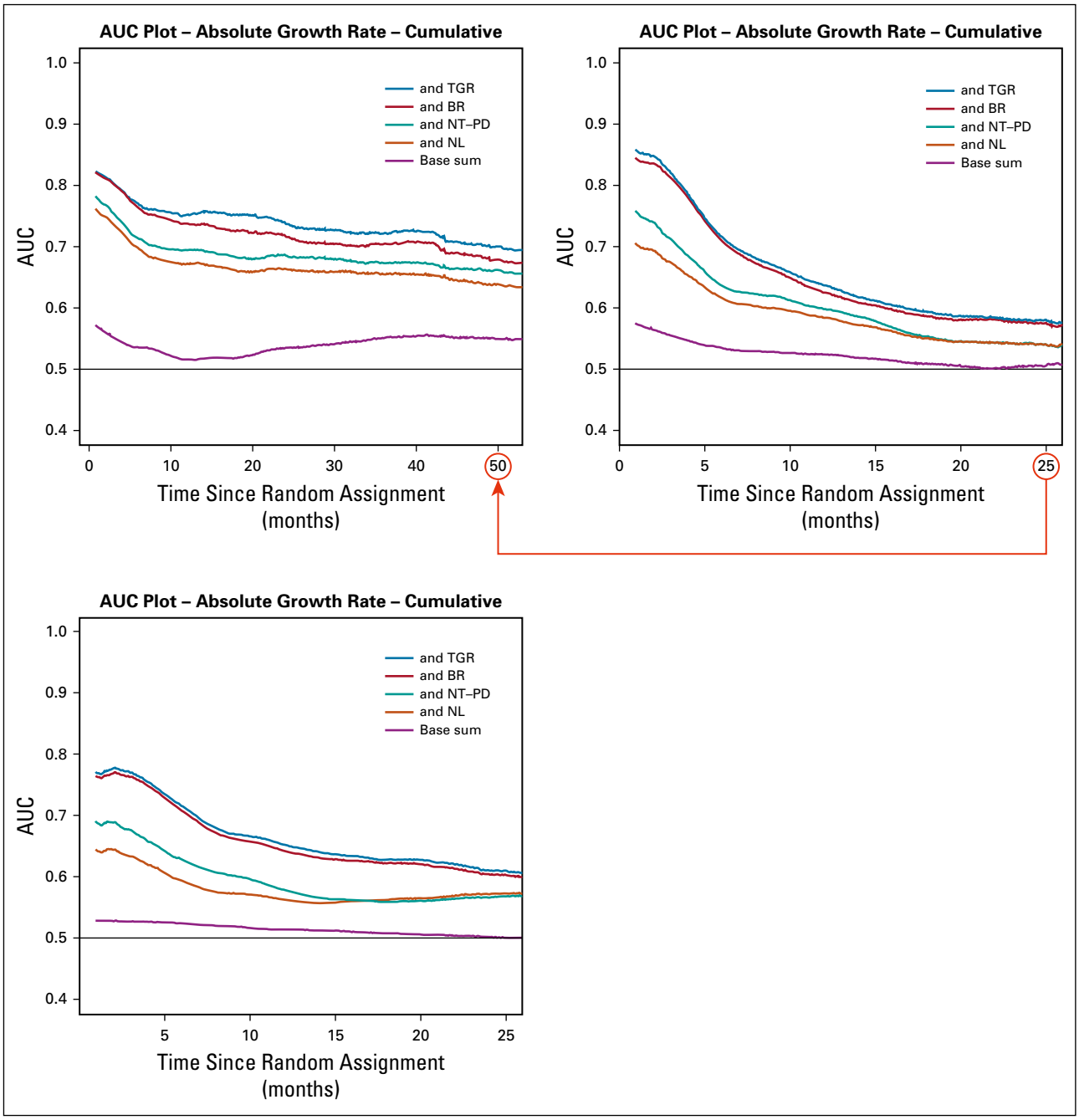

FIG A40. Time-dependent survival analysis: cumulative contributions to the area under the curve (AUC) of the different components of progression. (A) TCAs, (B) Chemotherapy, (C) TCA and chemotherapy. Abbreviation: TCA = targeted cancer agent.

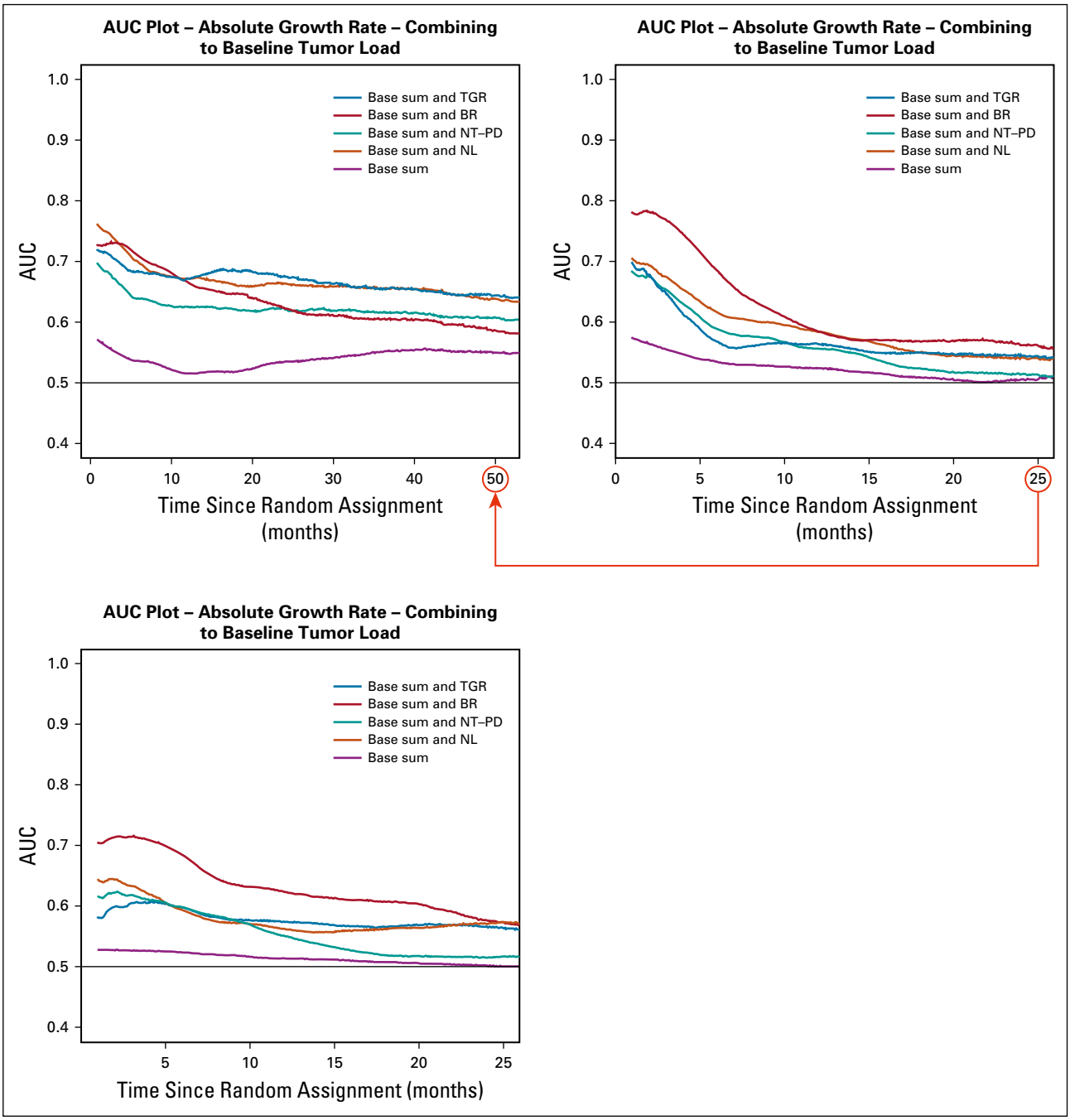

FIG A41. Time-dependent survival analysis: separate contributions to the area under the curve (AUC) of the different components of progression. (A) TCAs, (B) Chemotherapy, (C) TCA and chemotherapy. Abbreviation: TCA = targeted cancer agent.

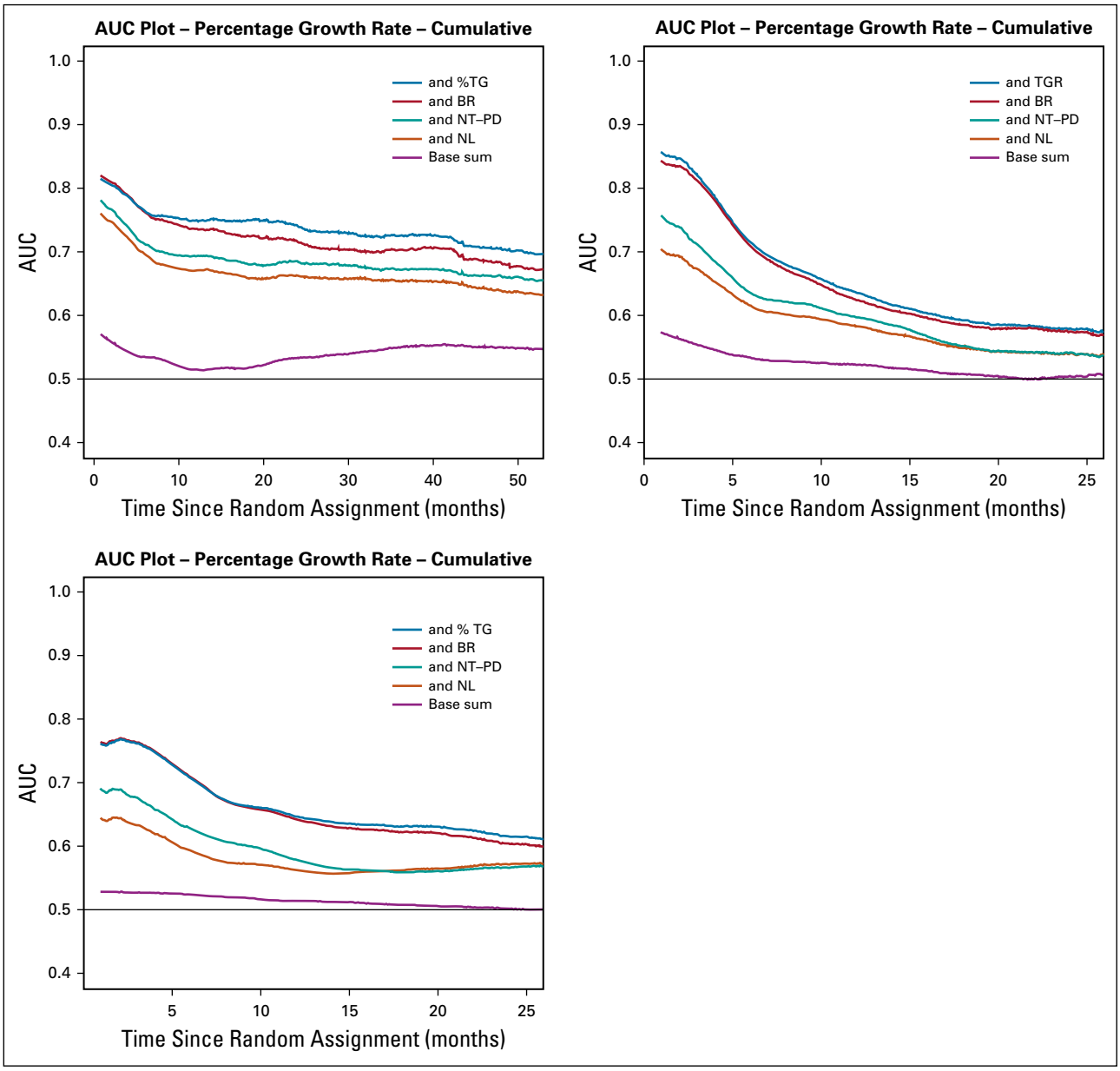

FIG A42. Time-dependent survival analysis: cumulative contributions to the area under the curve (AUC) of the different components of progression. (A) TCAs, (B) Chemotherapy, (C) TCA and chemotherapy. Abbreviation: TCA = targeted cancer agent".

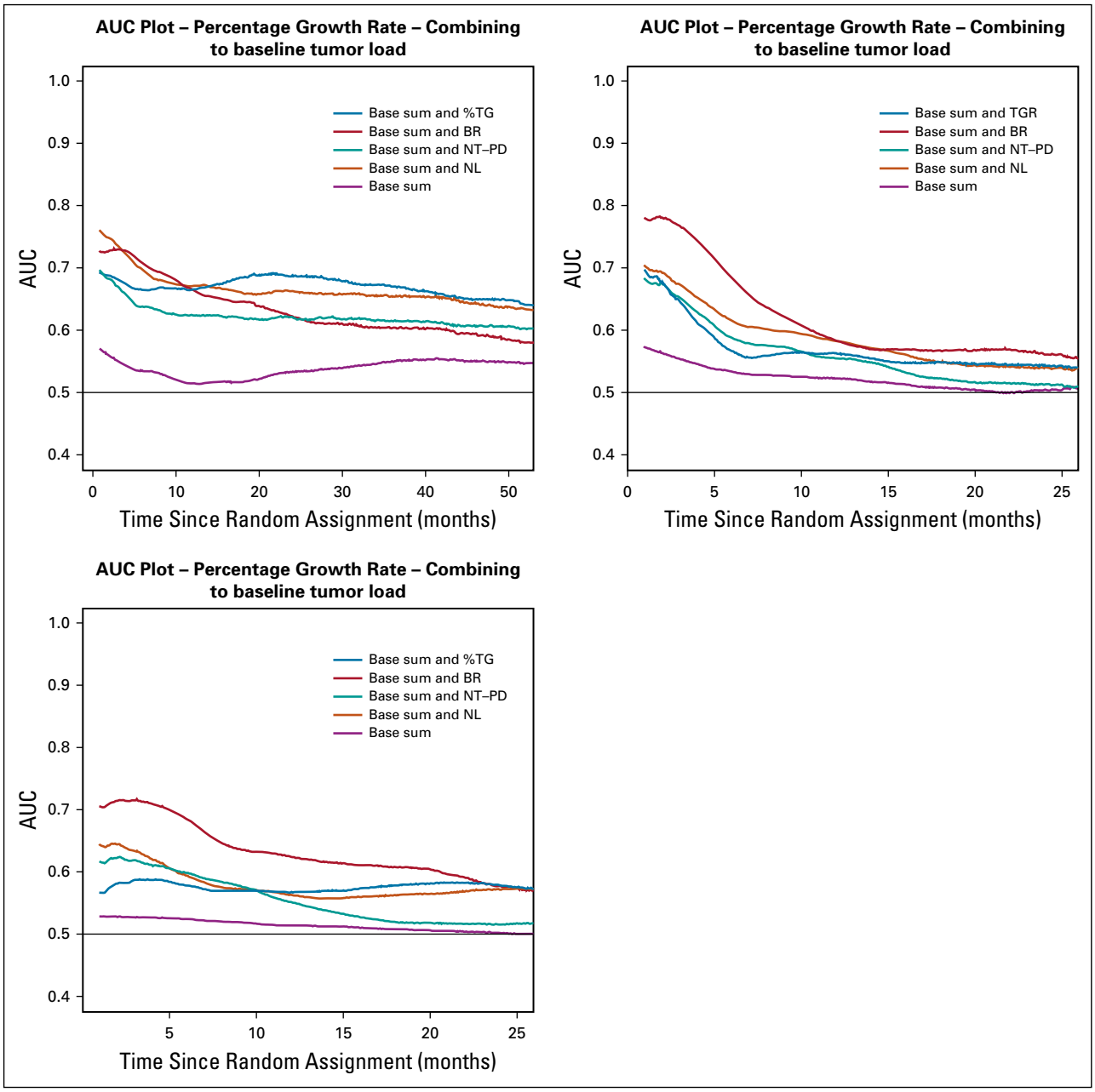

FIG A43. Time-dependent survival analysis: separate contributions to the area under the curve (AUC) of the different components of progression. (A) TCAs, (B) Chemotherapy, (C) TCA and chemotherapy. Abbreviation: TCA = targeted cancer agent".

TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
Amgen (1)	NCT00254267	2004-2005	II	GIST	Motesanib (AMG 706)	Yes	138	1.0	No survival information	Benjamin RS et al: Cancer Chemother Pharmacol 68:69-77, 2011
Amgen (2)	NCT00113763	2004-2005	III	CRC	Panitumumab plus BSC *v* BSC alone	Yes	463	1.0		Van Cutsem E, et al: J Clin Oncol 25: 1658-1664, 2007
DCCG CAIRO 2	NCT00208546	2005-2006	III	CRC	Capecitabine plus oxaliplatin plus bevacizumab *v* capecitabine plus oxaliplatin plus bevacizumab plus cetuximab	Yes	738	1.0		Tol J et al: N Engl J Med 360:563-572, 2009
ECOG E1302	NCT00088907	2004-2008	III	Head and neck	Docetaxel plus placebo *v* docetaxel plus gefitinib	No	255	1.0		Argiris A et al: J Clin Oncol 31:1405-1414, 2013
ECOG E1500	NCT00028028	2002-2007	II	SCLC	Temsirolimus (CCI-779) 25 mg/wk *v* temsirolimus 250 mg/wk	No	87	1.0		Pandya KJ et al: J Thorac Oncol 2: 1036-1041, 2007
ECOG E2501	NCT00064350	2004-2007	II	NSCLC	Step 1: sorafenib If stable disease ≥ step 2: sorafenib *v* placebo If PD on placebo ≥ step 3: cross-over	No	333	1.0		Wakelee HA et al: J Thorac Oncol 7: 1574-1582, 2012
ECOG E6200	NCT00025350	2001	II	CRC	Gefitinib 250 mg/d *v* 500 mg/d	No	113	1.0		Rothenberg ML et al: J Clin Oncol 23: 9265-9274, 2005
EORTC 62005	NCT00685828	2001-2002	III	GIST	Imatinib mesylate 400 mg *v* imatinib mesylate 800 mg	No	946	1.0		Verweij J et al: Lancet 364:1127-1134, 2004
EORTC 62043	NCT00297258	2005-2007	II	STS	Pazopanib	Yes	142	1.0		Sleijfer S et al: J Clin Oncol 27:3126-3132, 2009

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TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
EORTC 62072	NCT00753688	2008-2010	III	STS	Pazopanib *v* placebo	Yes	369	1.0		van der Graaf WT et al: Lancet 379: 1879-1886, 2012
Genentech 2107	NCT00109070	2000-2003	III	CRC	Bevacizumab plus irinotecan plus fluorouracil plus leucovorin (arm stopped after interim analysis) *v* placebo plus irinotecan plus fluorouracil plus leucovorin *v* bevacizumab plus fluorouracil plus leucovorin	Yes	923	1.0		Hurwitz HI et al: J Clin Oncol 23:3502-3508, 2005
Genentech 2298	NCT00047736	2001-2002	III	NSCLC	Erlotinib plus paclitaxel plus carboplatin *v* placebo plus paclitaxel plus carboplatin	No	1,079	1.0	Protocol specified that tumor assessment details were only collected on the first 400 patients	Herbst RS et al: J Clin Oncol 23:5892-5899, 2005
Genentech OAM4558g	NCT00854308	2009-2010	II	NSCLC	MetMAb plus erlotinib *v* placebo plus erlotinib	Yes	67	1.0	No survival information	Spigel DR et al: J Clin Oncol 29, 2011 (suppl; abstr 7505)
GSK EGF30008	NCT00073528	2003-2006	III	Breast	Lapatinib plus letrozole *v* letrozole plus placebo	No	1,286	1.0		Johnston S et al: J Clin Oncol 27: 5538-5546, 2009
GSK EGF100151	NCT00078572	2004-2005	III	HER2-positive breast cancer	Capecitabine plus lapatinib *v* capecitabine	Yes	324	1.0*		Geyer CE et al: N Engl J Med 355:2733-2743, 2006
GSK VEG105192	NCT00334282	2006-2007	III	Renal cell carcinoma	Pazopanib *v* placebo	Yes	435	1.0		Sternberg CN et al: J Clin Oncol 28: 1061-1068, 2010
Intact 1-AZ	NCT00006048	2000-2001	III	NSCLC	Gefitinib 500 mg/d plus gemcitabine plus cisplatin *v* gefitinib 250 mg/d plus gemcitabine plus cisplatin	No	1,093	1.0		Giaccone G et al: J Clin Oncol 22:777-784, 2004

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TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
Intact 2-AZ	NCT00006049	2000-2001	III	NSCLC	Gefitinib 500 mg/d plus paclitaxel plus carboplatin *v* gefitinib 250 mg/d plus paclitaxel plus carboplatin	No	1,037	1.0		Herbst RS et al: J Clin Oncol 22:785-794, 2004
Merck EMR62202-013	NCT00154102	2004	III	CRC	Fluorouracil and folinic acid plus irinotecan plus cetuximab *v* fluorouracil/folinic acid plus irinotecan	No	1,198	Modified WHO criteria		Van Cutsem E et al: N Engl J Med 360: 1408-1417, 2009
Merck EMR62202-047	NCT00125034	2005	II	CRC	Fluorouracil and folinic acid plus oxaliplatin plus cetuximab *v* fluorouracil/folinic acid plus oxaliplatin	Yes	337	Modified WHO criteria		Bokemeyer C et al: J Clin Oncol 27:663-671, 2009
Merck EMR200027-051	NCT00463788	2007	II	Breast	Cetuximab plus cisplatin *v* cisplatin	No	171	1.0		Baselga J et al: J Clin Oncol 31:2586-2592, 2013
Merck EMR200048-052	NCT00678535	2008	III	Gastric	Cetuximab plus capecitabine plus cisplatin *v* capecitabine plus cisplatin	Yes	882	1.0		Lordick F et al: Lancet Oncol 14:490-499, 2013
Merck EMR62202-002	NCT00122460	2004	III	Squamous cell carcinoma of the head and neck	Cetuximab (Erbitux; Eli Lilly, Indianapolis, IN) plus cisplatin or carboplatin plus fluorouracil *v* cisplatin or carboplatin plus fluorouracil	No	434	Modified WHO criteria		Vermorken JB et al: N Engl J Med 359: 1116-1127, 2008

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TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
Merck EMR62202-046	NCT00148798	2004	III	NSCLC	Cisplatin or vinorelbine plus cetuximab *v* cisplatin or vinorelbine	Yes	1,110	Modified WHO criteria		Pirker R et al: Lancet 373:1525-1531, 2009
Merck EMR62202-505	NCT00778830	2009	II	CRC	FOLFIRI plus cetuximab (Erbitux) *v* FOLFOX plus cetuximab	Yes	289	1.0		Cheng A-L et al: J Clin Oncol 31, 2013 (suppl; abstr e14501)
NCIC CTG CO.20	NCT00640471	2008-2011	III	(Wild-type *K-RAS*) CRC	Cetuximab plus brivanib alaninate (BMS-582664) *v* cetuximab plus placebo	No	750	1.0		Siu LL et al: J Clin Oncol 31:2477-2484, 2013
NCIC CTG BR.18	NCT00006229	2000-2002	III	NSCLC	Rebimastat plus paclitaxel plus carboplatin *v* placebo plus paclitaxel plus carboplatin	No	774	1.0		Leighl NB et al: J Clin Oncol 23:2831-2839, 2005
NCIC CTG BR.20	NCT00066313	2003-2006	II	SCLC	Vandetanib (ZD6474) *v* placebo	No	107	1.0		Arnold AM et al: J Clin Oncol 25:4278-4284, 2007
NCIC CTG BR.21	NCT00026325	2001-2003	III	NSCLC	Erlotinib *v* placebo	No	731	1.0		Shepherd FA et al: N Engl J Med 353: 123-132, 2005
NCIC CTG BR.24	NCT00245154	2005-2008	II/III (stop at phase II)	NSCLC	Cediranib (AZD2171) plus paclitaxel plus carboplatin *v* placebo plus paclitaxel plus carboplatin	Yes	296	1.0		Goss GD et al: J Clin Oncol 28:49-55, 2010
NCIC CTG BR.29	NCT00795340	2008-2011	III	NSCLC	Cediranib plus paclitaxel plus carboplatin *v* placebo plus paclitaxel plus carboplatin	Yes	306	1.1		Laurie SA et al: Eur J Cancer 50:706-712, 2014

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TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
NCIC CTG CO.17	NCT00079066	2003-2005	III	EGFR-positive CRC	Cetuximab plus BSC *v* BSC	No	572	1.0		Jonker DJ et al: N Engl J Med 357: 2040-2048, 2007
NCIC CTG IND.202	NCT01152788	2010-2013	II	Melanoma	(Recombinant) interleukin-21 *v* dacarbazine	Yes	60	1.1	Immunotherapy arm will not be used	Petrella TM et al: J Clin Oncol 31, 2013 (suppl; abstr 9032)
NCIC CTG IND.184	NCT00389974	2007-2009	II	Cervical carcinoma	Sunitinib	Yes	19	1.0		Mackay HJ et al: Gynecol Oncol 116:163-167, 2010
NCIC CTG IND.185	NCT00388037	2007-2012	II	Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma	Sunitinib	Yes	31	1.0		Biagi JJ et al: Ann Oncol 22:335-340, 2011
NCIC CTG MA.31	NCT00667251	2008-2012	III	HER2-positive breast cancer	Taxane-based chemotherapy with trastuzumab *v* taxane-based chemotherapy with lapatinib	No	652	1.0		Gelmon KA et al: J Clin Oncol 30, 2012 (suppl; abstr LBA671)
NCIC CTG PA.03		2001-2003	III	Pancreatic cancer	Erlotinib plus gemcitabine *v* gemcitabine plus placebo	No	569	1.0		Vickers MM et al: Eur J Cancer 48:1434-1442, 2012
Pfizer A6181006	NCT00077974	2004	II	Renal cell carcinoma	Sunitinib	Yes	106	1.0		Motzer RJ et al: JAMA 295:2516-2524, 2006
Pfizer A6181004	NCT00075218	2003-2005	III	GIST	Sunitinib plus BSC *v* placebo plus BSC	Yes	103	1.0	Because of potential issues with regard to privacy of patient data sharing, these data contain only the targeted treatment arm and only data from US citizens	Demetri GD et al: Lancet 368:1329-1338, 2006
Pfizer A6181034	NCT00083889	2004-2005	III	Renal cell carcinoma	Sunitinib *v* interferon alfa	Yes	347	1.0	Immunotherapy arm will not be used	Motzer RJ et al: N Engl J Med 356: 115-124, 2007

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TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
Pfizer A6181111	NCT00428597	2007-2009	III	Pancreatic islet cell	Sunitinib plus BSC *v* placebo plus BSC	Yes	6	1.0	Because of potential issues with regard to privacy of patient data sharing, these data contain only the targeted treatment arm and only data from US citizens	Raymond E et al: N Engl J Med 364:501-513, 2011 [Erratum: N Engl J Med 364: 1082, 2011]
Pfizer A6181120	NCT00676650	2008-2010	III	Prostate	Sunitinib plus prednisone *v* placebo plus prednisone	No	96	1.0	Because of potential issues with regard to privacy of patient data sharing, these data contain only the targeted treatment arm and only data from US citizens	Michaelson MD et al: J Clin Oncol 32:76-82, 2014
Pfizer A6181170	NCT00699374	2008-2010	III	Liver	Sunitinib *v* sorafenib	Yes	29	1.0	Because of potential issues with regard to privacy of patient data sharing, these data contain only the targeted treatment arm and only data from US citizens	Cheng AL et al: J Clin Oncol 31: 4067-4075, 2013
Pfizer B1771006	NCT00631371	2008-2010	III	Renal cell carcinoma	Bevacizumab plus temsirolimus *v* bevacizumab plus interferon alfa	Yes	58	1.0	Because of potential issues with regard to privacy of patient data sharing, these data contain only the targeted treatment arm and only data from US citizens Immunotherapy arm will not be used	Rini BI et al: J Clin Oncol 32: 752-759, 2014

(continued on following page)

TABLE A1. Phase II and III Trials With Clinical Data From Patients Treated With TCAs or TCAs Plus Chemotherapy Compounds (continued)

Trial Data Provider and Trial No.	ClinicalTrials.gov Identifier	Year (Randomization)	Phase	Disease	Study Treatment	Measurable Disease Required at Baseline?	Available for Analysis	Version of RECIST Used	Comments	Reference
Roche BO16411	NCT00883779	2001-2002	III	NSCLC	Erlotinib plus cisplatin plus gemcitabine *v* placebo plus cisplatin plus gemcitabine	No	1,172	1.0		Gatzemeier U et al: J Clin Oncol 25: 1545-1552, 2007
Roche BRIM2		2009-2010	II	Melanoma	Vemurafenib	No	132	1.1		Sosman JA et al: N Engl J Med 366: 707-714, 2012
Roche BRIM3	NCT01006980	Jan-Dec 2010	III	Melanoma	Vemurafenib *v* dacarbazine	No	625	1.1		Chapman PB et al: N Engl J Med 364: 2507-2516, 2011
Roche EURTAC	NCT00446225	2007-2011	III	NSCLC	Erlotinib *v* chemotherapy (different regimens)	No	173	1.0		Rosell R et al: Lancet Oncol 13:239-246, 2012
Sanofi	NCT00561470	2007-2010	III	CRC	Aflibercept (Zaltrap; Regeneron Pharmaceuticals, Tarrytown, NY) plus FOLFIRI *v* placebo plus FOLFIRI	No	1,216	1.0		Van Cutsem E et al: J Clin Oncol 30: 3499-3506, 2012
SWOG 0438	NCT00281957	2008-2009	II	Melanoma	Sorafenib plus temsirolimus *v* sorafenib plus tipifarnib	Yes	109	1.0		Margolin KA et al: Clin Cancer Res 18: 1129-1137, 2012

Abbreviations: BSC, best supportive care; CRC, colorectal carcinoma; DCCG, Dutch Colorectal Cancer Group; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; GIST, GI stromal tumor; GSK, GlaxoSmithKline; HER2, human epidermal growth factor receptor 2; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; NSCLC, non–small-cell lung cancer; PD, progressive disease; SCLC, small-cell lung cancer; STS, soft tissue sarcoma; TCA, targeted cancer agent.

*Modified to include lesions with a 15- to 19-mm diameter with other method than spiral computed tomography.

TABLE A2. Targeted Cancer Agents in the Warehouse

Class	Compounds
Hormone therapy	Letrozole
Signal transduction inhibitors	Cetuximab, erlotinib, gefitinib, trastuzumab, lapatinib, sunitinib, temsirolimus, vemurafenib, imatinib, tipifarnib, vandetanib, panitumumab
Angiogenesis inhibitors	Motesanib, rebimastat, sunitinib, cediranib, brivanib alaninate, sorafenib, bevacizumab, pazopanib, aflibercept

TABLE A3. Lesion Site Classification

Category	Composition of the Category
Lymph node	All nodal masses, paratracheal nodes, carinal, hilary mass, iliac adenopathy, hilum node, axillary mass, mediastinum node (if mediastinum alone in the description, go to lymph node category)
Lung/pleura	All lesions in the lung and the pleura
Liver	All lesions in the liver
Bone	Lesions that involve bone, rib, vertebra
Brain	Lesions that involve the CNS
Skin/soft tissue	Lesions that involve skin, abdominal wall, chest wall, iliac mass, psoas mass, buttock/gluteus, umbilicus, sacral mass, cutaneous/subcutaneous mass, supraclavicular mass, soft tissue, extremities (arms and legs), neck, pararenal space, muscle mass, flank, mediastinum mass, diaphragm, subphrenia, arteries or veins, breast, mass in the fat
Large-volume metastasis	Pelvis, omentum, peritoneum, retroperitoneum
Kidney	All lesions that involve the kidney
GI	Colon, rectum, stomach, small bowel, duodenum, cecum, colic mass, esophagus, other GI, bowel, intestines
Other viscera	Lesions that involve the spleen, heart, bladder, thyroid and any other glands, prostate, mesentery, ascites
Adrenal and suprarenal	Lesions that involve the adrenal gland and the suprarenal region
Pancreas	All lesions that involve the pancreas
Gynecologic	Ovary, uterus, fallopian tubes
Head and neck	All head and neck lesions
Other/unclassified	All lesions that are not clear enough to be classified

NOTE. Lesions with measurements for which there was not enough information provided on the site of occurrence to allow classification in one of the 15 categories were not taken into account in the analysis. This concerned one or more lesions in 404 patients (1.7%) of 23,259. This did not necessarily result in the patient not being taken into account in the analysis provided that measurements on other eligible target lesions were available. Secondly, the data were checked for consistency of reporting of site of lesions. For 287 patients (1.2%) of 23,259, there was at least one inconsistency in the reporting of the site of the lesion throughout the different measurements. Measurements were set to missing for those in whom the site did not correspond with the site reported at baseline.

TABLE A4. Analysis Dataset: Type of Treatment by Disease

Tumor Type	Treatment Category, No. (%)				
	Single TCA (n = 4,416)	TCA Plus Chemotherapy (n = 6,933)	Chemotherapy (n = 5,113)	Two TCAs (n = 760)	Total (N = 17,222)
Lung	739 (16.7)	2,746 (39.6)	2,271 (44.4)	0 (0.0)	5,756 (33.4)
Colon	845 (19.1)	2,645 (38.2)	1,639 (32.1)	306 (40.3)	5,435 (31.6)
Breast	370 (8.4)	675 (9.7)	159 (3.1)	364 (47.9)	1,568 (9.1)
GI stromal tumor	1,043 (23.6)	0 (0.0)	0 (0.0)	0 (0.0)	1,043 (6.1)
Gastric	0 (0.0)	382 (5.5)	370 (7.2)	0 (0.0)	752 (4.4)
Skin/melanoma	411 (9.3)	0 (0.0)	225 (4.4)	80 (10.5)	716 (4.2)
Renal cell	529 (12.0)	0 (0.0)	0 (0.0)	10 (1.3)	539 (3.1)
Head and neck	0 (0.0)	267 (3.9)	245 (4.8)	0 (0.0)	512 (3.0)
Pancreas	6 (0.1)	218 (3.1)	204 (4.0)	0 (0.0)	428 (2.5)
Soft tissue sarcoma	360 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	360 (2.1)
Gynecologic	48 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	48 (0.3)
Prostate	42 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	42 (0.2)
Liver	23 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	23 (0.1)

Abbreviation: TCA, targeted cancer agent.

TABLE A5. Analysis Dataset: Description of TCAs

Treatment Category	NCI Classification	Patients (N = 17,222)
Single TCA	Hormone therapy	370
	Signal transduction inhibitors	2,604
	Angiogenesis inhibitors	1,442
TCA Plus Chemotherapy	Signal transduction inhibitors plus chemotherapy	4,682
	Angiogenesis inhibitors plus chemotherapy	1,931
	Signal transduction inhibitors plus angiogenesis inhibitors plus chemotherapy*	320
Chemotherapy	Nontargeted agent	5,113
Two TCAs	Hormone therapy plus signal transduction inhibitors	364
	Signal transduction inhibitors plus angiogenesis inhibitors	396

Abbreviations: NCI, National Cancer Institute; TCA, targeted cancer agent.

*The combination is from the Dutch Colorectal Cancer Group CAIRO2 study. One of the two arms is a combination of chemotherapy and two targeted agents: arm 1, bevacizumab plus chemotherapy; arm 2, bevacizumab plus cetuximab plus chemotherapy.

TABLE A6. Analysis Dataset: Extent of Disease at Baseline

	Baseline Sum of Diameters (in mm) Divided by No. of Target Lesions at Baseline			
Tumor Type	**Median**	**Range**	**Q1-Q3**	**Mean (SD)**
Breast (n = 1,568)	20.0	4.0-168.0	16.0-32.0	25.50 (15.58)
Lung (n = 5,756)	30.0	0.0-780.0	20.5-42.5	34.53 (23.25)
Colon (n = 5,435)	29.2	0.0-400.0	19.5-44.0	35.09 (24.86)
GIST (n = 1,043)	52.0	8.0-752.0	32.0-76.0	61.33 (46.76)
Renal cell (n = 539)	24.5	2.0-193.0	17.0-34.0	28.69 (19.17)
Prostate (n = 42)	18.0	8.0-96.0	12.0-28.0	22.95 (15.38)
Liver (n = 23)	28.0	12.0-96.0	20.0-56.0	38.61 (22.45)
Pancreas (n = 428)	36.0	8.0-160.0	24.0-48.0	37.91 (18.99)
Gynecologic (n = 48)	24.0	8.0-80.0	18.0-34.0	27.75 (15.36)
Skin/melanoma (n = 716)	24.0	8.0-436.0	16.0-36.0	30.45 (24.14)
Soft tissue sarcoma (n = 360)	38.5	3.3-318.0	21.8-66.2	50.58 (41.14)
Head and neck (n = 512)	28.0	8.0-100.0	20.0-40.0	32.09 (16.46)
Gastric (n = 752)	20.0	4.0-160.0	16.0-32.0	26.04 (16.71)

NOTE. Summary statistics of average lesion size (in millimeters) of target lesions by tumor type. With a median of 52 mm at baseline, patients with a GIST seem to have the largest reported baseline tumor load.

Abbreviations: GIST, GI stromal tumor; Q, quartile; SD, standard deviation.

TABLE A7. Analysis Dataset: Site of Target Lesions at Baseline

Tumor Type and Lesion Site	No. (%)
Lung	
Lung/pleura	7,150 (48.0)
Lymph nodes	5,046 (33.9)
Liver	1,171 (7.9)
Colon	
Liver	12,100 (60.1)
Lung/pleura	3,298 (16.4)
Lymph nodes	2,871 (14.3)
Breast	
Lymph nodes	1,887 (38.6)
Liver	1,349 (27.6)
Lung/pleura	900 (18.4)
GIST	
Liver	1,735 (54.0)
Skin/soft tissue	711 (22.1)
Large volume metastasis	437 (13.6)
Skin/melanoma	
Lymph nodes	519 (26.1)
Lung	438 (22.0)
Liver	322 (16.2)
Renal cell	
Lung/pleura	832 (36.9)
Lymph nodes	660 (29.3)
Liver	240 (10.7)
Gastric	
Lymph nodes	1,470 (52.6)
Liver	931 (33.3)
Lung/pleura	97 (3.5)
Head and neck	
Lymph node	467 (36.5)
Lung	379 (29.6)
Primary tumor/recurrence	243 (19.0)
Pancreas	
Liver	491 (46.7)
Pancreas	370 (35.2)
Lymph nodes	118 (11.2)
Soft tissue sarcoma	
Lung	571 (47.5)
Skin/soft tissues	225 (18.7)
Liver	160 (13.3)
Prostate	
Lymph nodes	112 (73.7)
Lung/pleura	10 (6.6)
Liver	7 (4.6)
Large volume metastasis	7 (4.6)
Gynecologic	
Lymph nodes	70 (40.9)
Large volume metastasis	53 (31.0)
Liver	15 (8.8)
Liver	
Liver	49 (77.8)
Lung/pleura	4 (6.3)
Adrenal and suprarenal	3 (4.8)

(continued in next column)

TABLE A7. Analysis Dataset: Site of Target Lesions at Baseline (continued)

NOTE. N = 54,073 target lesions.
Abbreviation: GIST, GI stromal tumor.

TABLE A8. Analysis Dataset: Period Covered by the Tumor Measurement Assessments

	Time to Last Assessment (months)			
Category	**Median**	**Range**	**Q1-Q3**	**Mean (SD)**
Treatment category				
Single TCA (n = 4,416)	5.5	0.7-134.0	2.6-12.7	11.88 (17.37)
TCA plus chemotherapy (n = 6,933)	6.0	0.7-94.9	3.4-9.4	7.30 (5.54)
Chemotherapy (n = 5,113)	4.9	0.7-37.4	2.8-7.7	5.76 (3.96)
Two TCAs (n = 760)	5.9	0.7-45.7	3.0-11.4	8.80 (8.00)
Tumor type				
Breast (n = 1,568)	7.7	0.9-49.7	3.5-13.7	9.95 (8.42)
Lung (n = 5,756)	4.6	0.7-60.9	2.6-7.1	5.42 (3.76)
Colon (n = 5,435)	6.5	0.7-94.9	3.6-10.1	7.65 (5.62)
GIST (n = 1,043)	19.3	0.8-134.0	6.2-40.9	28.32 (27.61)

Abbreviations: GIST, GI stromal; Q, quartile; SD, standard deviation; TCA, target cancer agent.

TABLE A9. Analysis Dataset: Survival by Tumor Type and Treatment Category

Category	No. of Patients (N = 17,049)	Observed No. of Events	Median Time, Months (95% CI)
Tumor type			
Breast	1,568	249	NR
Lung	5,700	3,391	12.25 (11.79 to 12.58)
Colon	5,435	2,863	21.32 (20.27 to 22.08)
GIST	929	647	46.85 (43.14 to 52.11)
Renal cell	539	279	25.46 (21.36 to 30.29)
Prostate	42	22	16.95 (11.66 to 23.16)
Liver	23	13	16.79 (8.94 to NR)
Pancreas	428	356	7.16 (6.34 to 7.66)
Gynecologic	48	27	8.87 (5.75 to 10.12)
Skin/melanoma	713	201	7.95 (7.56 to 9.40)
Soft tissue sarcoma	360	237	11.70 (10.97 to 14.32)
Head and neck	512	232	16.59 (15.80 to 17.58)
Gastric	752	145	22.24 (21.09 to 24.87)
Treatment category			
Single TCA	4,243	2,419	18.14 (17.18 to 19.78)
TCA plus chemotherapy	6,933	3,492	19.61 (18.92 to 20.30)
Chemotherapy	5,113	2,443	16.56 (15.93 to 17.22)
Two TCAs	760	308	15.70 (13.86 to 19.02)

NOTE. For 170 patients (114 from the Amgen 1 study, 56 from the Genentech OAM4558g study, all in single target agent category), no survival information was available. In addition, for three patients from the Roche BRIM3 study, no survival information was available beyond baseline.

Abbreviations: GIST, GI stromal tumor; NR, not reached; TCA, targeted cancer agent.

TABLE A10. Variability Assessments: Patients in Subgroups of Interest Considered for the Analyses

	Tumor Type					
Treatment Category	Lung	Colon	Breast	GIST	Other	All
TCA (single and two)	730	1,138	494	1,014		4,833
Single STI						2,555
Single AI						1,393
TCA plus chemotherapy (all)	2,732	2,543	555			6,688
With Single STI						4,534
With Single AI						1,875
Chemotherapy	2,245	1,626	158			5,068
Total	5,707	5,307	1,207	1,014		16,589

Abbreviations: AI, angiogenesis inhibitor; GIST, GI stromal tumor; STI, signal transduction inhibitor; TCA, targeted cancer agent.

TABLE A11. Variability Assessments: Summary Statistics: Percentage Change From Baseline to Week 12 by Treatment Category

	Treatment Category			
Percentage Change	**TCA (n = 14,963)**	**TCA Plus Chemotherapy (n = 19,465)**	**Chemotherapy (n = 14,728)**	**Total (N = 49,156)**
Median	6.2	25.0	14.3	15.9
Range	−590.0-100.0	−1,009.9-100.0	−1,140.0-100.0	−1,140.0-100.0
Q1-Q3	−7.7-30.0	0.0-50.0	0.0-40.0	0.0-41.2
Mean (SD)	8.03 (42.84)	27.28 (41.10)	17.57 (42.91)	18.51 (42.93)

NOTE. The combination category contains more responders than the other treatment categories. The distribution of the percentage change in this category is wider, which shows that there is more variability in the percentage change observed in lesions treated with combined therapies.

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A12. Variability Assessments: Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Treatment Category

	Treatment Category			
Variance	**TCA (n = 4,833)**	**TCA Plus Chemotherapy (n = 6,688)**	**Chemotherapy (n = 5,068)**	**Total (N = 16,589)**
Median	259.1	293.7	312.5	286.3
Range	0.0-174,050.0	0.0-487,548.5	0.0-47,845.6	0.0-487,548.5
Q1-Q3	68.4-826.3	73.6-918.0	78.9-980.9	72.5-901.9
Mean (SD)	984.61 (4,009.52)	969.68 (7,398.67)	937.83 (2,294.09)	964.73 (5,324.79)
No. of patients	3,756	4,980	3,692	12,428

NOTE. Patients with only one potential target lesion did not contribute to this analysis because it was not possible to calculate variance. The mean per-patient variance seems to be higher in the TCA and combination categories than in the exclusively nontargeted agents.

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A13. Variability Assessments: Patients Who Contributed to the Variability Assessment

	Treatment Category, No. (%)			
No. of Selected Lesions	**TCA**	**TCA Plus Chemotherapy**	**Chemotherapy**	**Total, No. (%)**
1	3,756 (37.1)	4,980 (39.0)	3,692 (38.2)	12,428 (38.2)
2	2,635 (26.0)	3,232 (25.3)	2,438 (25.2)	8,305 (25.5)
3	1,694 (16.7)	1,999 (15.6)	1,571 (16.3)	5,264 (16.2)
4	1,022 (10.1)	1,273 (10.0)	972 (10.1)	3,267 (10.0)
5	487 (4.8)	625 (4.9)	479 (5.0)	1,591 (4.9)
6	265 (2.6)	331 (2.6)	259 (2.7)	855 (2.6)
7	155 (1.5)	179 (1.4)	135 (1.4)	469 (1.4)
8	81 (0.8)	106 (0.8)	77 (0.8)	264 (0.8)
9	35 (0.3)	52 (0.4)	37 (0.4)	124 (0.4)

Abbreviation: TCA, targeted cancer agent.

TABLE A14. Variability Assessments: Summary Statistics: Percentage Change From Baseline to 12 Weeks by Type of Targeted Cancer Agent

	Class of TCA				
Percentage Change	STIs (n = 7,369)	AIs (n = 4,990)	STIs Plus Chemotherapy (n = 12,435)	AIs Plus Chemotherapy (n = 6,216)	Total* (N = 31,010)
Median	5.4	5.3	28.6	18.5	16.7
Range	−590.0-100.0	−484.4-100.0	−1,009.9-100.0	−500.0-100.0	−1,009.9-100.0
Q1-Q3	−8.9-33.3	−8.0-26.8	0.0-55.6	0.0-38.9	0.0-42.9
Mean (SD)	7.86 (45.88)	6.90 (40.16)	30.44 (43.74)	21.45 (35.25)	19.48 (43.39)

Abbreviations: AI, angiogenesis inhibitor; Q, quartile; SD, standard deviation; STI, signal transduction inhibitor; TCA, targeted cancer agent.
*Number of lesions.

TABLE A15. Variability Assessments: Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Type of TCA

	Class of TCA				
Variance	STIs (n = 2,555)	AIs (n = 1,393)	STIs Plus Chemotherapy (n = 4,534)	AIs Plus Chemotherapy (n = 1,875)	Total (N = 10,357)
Median	247.9	269.0	358.9	209.4	281.4
Range	0.0-174,050.0	0.0-57,994.0	0.0-487,548.5	0.0-87,708.3	0.0-487,548.5
Q1-Q3	55.1-831.9	83.4-811.1	85.5-1,055.5	66.5-677.1	72.0-8,91.2
Mean (SD)	1,001.54 (4,590.44)	1,039.55 (3,393.99)	1,133.59 (9,063.47)	681.17 (2,498.63)	996.16 (6,435.21)
No. of patients	1,943	1,154	3,176	1,578	7,851

NOTE. Patients with only one potential target lesion did not contribute to this analysis because it was not possible to calculate variance.
Abbreviations: AI, angiogenesis inhibitor; Q, quartile; SD, standard deviation; STI, signal transduction inhibitor; TCA, targeted cancer agent.

TABLE A16. Variability Assessments: Patients Who Contributed to the Variability Assessment

	Class of TCA, No. (%)				
No. of Selected Lesions	STIs	AIs	STIs Plus Chemotherapy	AIs Plus Chemotherapy	Total, No. (%)
1	1,943 (40.4)	1,154 (32.1)	3,176 (40.2)	1,578 (36.4)	7,851 (38.0)
2	1,287 (26.7)	885 (24.6)	1,948 (24.7)	1,126 (25.9)	5,246 (25.4)
3	786 (16.3)	615 (17.1)	1,196 (15.1)	719 (16.6)	3,316 (16.1)
4	446 (9.3)	417 (11.6)	770 (9.7)	459 (10.6)	2,092 (10.1)
5	180 (3.7)	230 (6.4)	386 (4.9)	227 (5.2)	1,023 (5.0)
6	89 (1.8)	143 (4.0)	207 (2.6)	117 (2.7)	556 (2.7)
7	52 (1.1)	83 (2.3)	113 (1.4)	63 (1.5)	311 (1.5)
8	23 (0.5)	48 (1.3)	70 (0.9)	35 (0.8)	176 (0.9)
9	8 (0.2)	22 (0.6)	35 (0.4)	17 (0.4)	82 (0.4)

Abbreviations: AI, angiogenesis inhibitor; STI, signal transduction inhibitor; TCA, targeted cancer agent.

TABLE A17. Variability Assessments: Lung Cancer Summary Statistics: Percentage Change From Baseline to Week 12 by Treatment Category

	Treatment Category			
Percentage Change	**TCA (n = 1,731)**	**TCA Plus Chemotherapy (n = 6,447)**	**Chemotherapy (n = 5,390)**	**Total* (N = 13,568)**
Median	0.0	27.3	20.0	20.0
Range	−590.0-100.0	−510.0-100.0	−500.0-100.0	−590.0-100.0
Q1-Q3	−20.0-13.0	0.0-54.6	0.0-49.3	0.0-50.0
Mean (SD)	−4.92 (50.12)	30.43 (42.82)	24.13 (42.70)	23.42 (45.18)

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.
*Number of lesions.

TABLE A18. Variability Assessments: Lung Cancer - Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Treatment Category

	Treatment Category			
Variance	**TCA (n = 730)**	**TCA Plus Chemotherapy (n = 2,732)**	**Chemotherapy (n = 2,245)**	**Total (N = 5,707)**
Median	320.7	477.0	480.9	447.9
Range	0.0-174,050.0	0.0-87,708.3	0.0-45,000.0	0.0-174,050.0
Q1-Q3	62.2-1,163.1	108.6-1,255.7	112.3-1,285.8	104.1-1,257.8
Mean (SD)	1,698.84 (8,854.63)	1,105.14 (3,326.30)	1,141.67 (2,429.29)	1,189.58 (4,122.76)
No. of observations	441	1,826	1,469	3,736

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A19. Variability Assessments: Patients With Lung Cancer Who Contributed to the Variability Assessment

	Treatment Category, No. (%)			
No. of Selected Lesions	**TCA**	**TCA Plus Chemotherapy**	**Chemotherapy**	**Total, No. (%)**
1	441 (44.1)	1,826 (49.2)	1,469 (46.7)	3,736 (47.5)
2	268 (26.8)	991 (26.7)	827 (26.3)	2,086 (26.5)
3	150 (15.0)	464 (12.5)	437 (13.9)	1,051 (13.4)
4	83 (8.3)	226 (6.1)	208 (6.6)	517 (6.6)
5	33 (3.3)	112 (3.0)	106 (3.4)	251 (3.2)
6	20 (2.0)	54 (1.5)	58 (1.8)	132 (1.7)
7	6 (0.6)	25 (0.7)	24 (0.8)	55 (0.7)
8	0 (0.0)	11 (0.3)	11 (0.3)	22 (0.3)
9	0 (0.0)	6 (0.2)	5 (0.2)	11 (0.1)

Abbreviation: TCA, targeted cancer agent.

TABLE A20. Variability Assessments: Colorectal Cancer Summary Statistics: Percentage Change From Baseline to Week 12 by Treatment Category

	Treatment Category			
Percentage Change	**TCA (n = 4,074)**	**TCA Plus Chemotherapy (n = 8,817)**	**Chemotherapy (n = 6,106)**	**Total* (N = 18,997)**
Median	0.0	21.4	11.2	13.5
Range	−364.3-100.0	−1,009.9-100.0	−315.0-100.0	−1,009.9-100.0
Q1-Q3	−18.2-19.2	0.0-41.7	0.0-33.3	0.0-34.8
Mean (SD)	−2.82 (40.76)	23.74 (35.19)	14.01 (33.89)	14.92 (37.47)

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.
*Number of lesions.

TABLE A21. Variability Assessments: Colorectal Cancer - Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Treatment Category

	Treatment Category			
Variance	**TCA (n = 1,138)**	**TCA Plus Chemotherapy (n = 2,543)**	**Chemotherapy (n = 1,626)**	**Total (N = 5,307)**
Median	226.3	175.0	192.7	190.1
Range	0.0-53,891.3	0.0-487,548.5	0.0-19,348.3	0.0-487,548.5
Q1-Q3	67.5-776.7	54.5-503.8	61.9-539.7	59.7-555.5
Mean (SD)	937.26 (2,931.78)	751.04 (10,577.11)	547.52 (1,157.16)	728.09 (7,435.74)
No. of patients	983	2,158	1,413	4,554

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A22. Variability Assessments: Patients With Colorectal Cancer Who Contributed to the Variability Assessment

	Treatment Category, No. (%)			
No. of Target Lesions	**TCA**	**TCA Plus Chemotherapy**	**Chemotherapy**	**Total, No. (%)**
1	983 (33.5)	2,158 (34.4)	1,413 (31.5)	4,554 (33.3)
2	750 (25.5)	1,595 (25.4)	1,091 (24.4)	3,436 (25.1)
3	523 (17.8)	1,089 (17.4)	806 (18.0)	2,418 (17.7)
4	332 (11.3)	735 (11.7)	576 (12.9)	1,643 (12.0)
5	169 (5.8)	329 (5.2)	283 (6.3)	781 (5.7)
6	86 (2.9)	179 (2.9)	155 (3.5)	420 (3.1)
7	56 (1.9)	100 (1.6)	84 (1.9)	240 (1.8)
8	26 (0.9)	59 (0.9)	49 (1.1)	134 (1.0)
9	11 (0.4)	30 (0.5)	23 (0.5)	64 (0.5)

Abbreviation: TCA, targeted cancer agent.

TABLE A23. Variability Assessments: Breast Cancer Summary Statistics: Percentage Change From Baseline to Week 12 by Treatment Category

	Treatment Category			
Percentage Change	**TCA (n = 1,190)**	**TCA Plus Chemotherapy (n = 1,810)**	**Chemotherapy (n = 469)**	**Total (N = 3,469)**
Median	13.7	35.7	0.0	21.4
Range	−155.7-100.0	−420.0-100.0	−150.0-100.0	−420.0-100.0
Q1-Q3	−2.7-38.2	0.0-64.4	−8.2-33.3	0.0-53.9
Mean (SD)	18.17 (37.03)	35.54 (45.17)	10.42 (41.64)	26.19 (43.24)

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A24. Variability Assessments: Breast Cancer - Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Treatment Category

	Treatment Category			
Variance	**TCA (n = 494)**	**TCA Plus Chemotherapy (n = 555)**	**Chemotherapy (n = 158)**	**Total (N = 1,207)**
Median	394.9	443.0	368.5	419.1
Range	0.0-7,097.5	0.0-27,888.7	0.0-4,470.4	0.0-27,888.7
Q1-Q3	86.1-954.4	118.1-1,111.2	40.3-1,164.2	92.2-1,054.8
Mean (SD)	727.36 (977.57)	970.59 (2,180.04)	776.73 (1,012.96)	854.04 (1,688.99)
No. of patients	330	433	112	875

Abbreviations: Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A25. Variability Assessments: Patients With Breast Cancer Who Contributed to the Variability Assessment

	Treatment Category, No. (%)			
No. of Target Lesions	**TCA**	**TCA Plus Chemotherapy**	**Chemotherapy**	**Total, No. (%)**
1	330 (47.4)	433 (34.5)	112 (36.0)	875 (38.7)
2	205 (29.5)	304 (24.2)	79 (25.4)	588 (26.0)
3	103 (14.8)	204 (16.3)	52 (16.7)	359 (15.9)
4	41 (5.9)	147 (11.7)	34 (10.9)	222 (9.8)
5	13 (1.9)	81 (6.5)	16 (5.1)	110 (4.9)
6	2 (0.3)	43 (3.4)	6 (1.9)	51 (2.3)
7	1 (0.1)	25 (2.0)	5 (1.6)	31 (1.4)
8	1 (0.1)	14 (1.1)	4 (1.3)	19 (0.8)
9	0 (0.0)	4 (0.3)	3 (1.0)	7 (0.3)

Abbreviation: TCA, targeted cancer agent.

TABLE A26. Variability Assessments: GIST Cancer Summary Statistics: Percentage Change From Baseline to 12 Weeks by Treatment Category

Percentage Change	TCA (N = 3,042)
Median	9.1
Range	−350.0-100.0
Q1-Q3	−2.2-28.6
Mean (SD)	10.88 (35.55)

Abbreviations: GIST, GI stromal tumor; Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A27. Variability Assessments: GIST - Distribution of the Per-Patient Variance of the Percentage Change from Baseline to Week 12, by Treatment Category

Variance	TCA (N = 1,014)
Median	172.5
Range	0.0-57,994.0
Q1-Q3	43.5-541.9
Mean (SD)	601.09 (2,269.79)
No. of patients	802

Abbreviations: GIST, GI stromal tumor; Q, quartile; SD, standard deviation; TCA, targeted cancer agent.

TABLE A28. Variability Assessments: Patients With GIST Cancer Who Contributed to the Variability Assessment

No. of Target Lesions	TCA, No. (%)
1	802 (39.5)
2	531 (26.2)
3	307 (15.1)
4	197 (9.7)
5	101 (5.0)
6	45 (2.2)
7	24 (1.2)
8	15 (0.7)
9	6 (0.3)

Abbreviations: GIST, GI stromal tumor; TCA, targeted cancer agent.

TABLE A29. Time-Dependent Model With Tumor Growth Rate by Treatment Category

	TCA (n = 5,003)		TCA Plus Chemotherapy (n = 6,933)		Chemotherapy (n = 5,113)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.02 (1.02 to 1.03)	< .001 (1)	1.03 (1.02 to 1.03)	< .001 (1)	1.03 (1.03 to 1.04)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	2.14 (1.97 to 2.33)		1.77 (1.65 to 1.90)		1.79 (1.64 to 1.96)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.65 (1.51 to 1.80)		1.44 (1.33 to 1.57)		1.41 (1.29 to 1.55)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.71 (0.63 to 0.80)		0.68 (0.60 to 0.76)		0.61 (0.54 to 0.69)	
15-30	0.55 (0.49 to 0.63)		0.59 (0.53 to 0.66)		0.51 (0.45 to 0.58)	
30-50	0.44 (0.38 to 0.50)		0.43 (0.39 to 0.48)		0.41 (0.36 to 0.46)	
50-70	0.35 (0.30 to 0.42)		0.33 (0.29 to 0.38)		0.35 (0.30 to 0.41)	
70-100	0.33 (0.27 to 0.42)		0.28 (0.24 to 0.33)		0.26 (0.21 to 0.33)	
CR	0.29 (0.22 to 0.39)		0.29 (0.25 to 0.35)		0.25 (0.19 to 0.33)	
Slope: estimated rate of weekly increase, mm/wk						
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	1.09 (0.98 to 1.21)		0.98 (0.90 to 1.06)		0.86 (0.78 to 0.95)	
2-5	1.67 (1.48 to 1.88)		1.42 (1.28 to 1.58)		1.16 (1.03 to 1.31)	
5	2.94 (2.51 to 3.44)		1.88 (1.59 to 2.23)		1.46 (1.22 to 1.76)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; TCA, targeted cancer agent.

TABLE A30. Time-Dependent Model with Tumor Growth Rate by Type of TCA

	STIs (n = 2,545)		AIs (n = 1,328)		STIs Plus Chemotherapy (n = 4,682)		AIs Plus Chemotherapy (n = 1,931)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.02 (1.02 to 1.03)	< .001 (1)	1.02 (1.02 to 1.03)	< .001 (1)	1.03 (1.02 to 1.04)	< .001 (1)	1.03 (1.02 to 1.04)	< .001 (1)
New lesions								
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	2.27 (2.03 to 2.54)		1.57 (1.42 to 1.73)		2.03 (1.80 to 2.29)		2.04 (1.76 to 2.37)	
Response of nontarget lesions								
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.67 (1.49 to 1.88)		1.49 (1.34 to 1.66)		1.47 (1.29 to 1.68)		1.61 (1.36 to 1.91)	
Best percentage change from baseline								
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.73 (0.62 to 0.87)		0.66 (0.56 to 0.77)		0.57 (0.47 to 0.69)		0.72 (0.59 to 0.87)	
15-30	0.52 (0.43 to 0.62)		0.65 (0.56 to 0.76)		0.44 (0.37 to 0.53)		0.63 (0.50 to 0.79)	
30-50	0.44 (0.37 to 0.52)		0.49 (0.42 to 0.57)		0.32 (0.26 to 0.38)		0.49 (0.38 to 0.64)	
50-70	0.37 (0.30 to 0.45)		0.38 (0.33 to 0.45)		0.25 (0.20 to 0.31)		0.34 (0.24 to 0.49)	
70-100	0.34 (0.26 to 0.44)		0.34 (0.28 to 0.41)		0.17 (0.12 to 0.24)		0.36 (0.21 to 0.63)	
CR	0.33 (0.24 to 0.45)		0.33 (0.27 to 0.41)		0.19 (0.12 to 0.29)		0.19 (0.08 to 0.48)	
Slope: estimated rate of weekly increase, mm/wk								
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	1.23 (1.07 to 1.41)		0.91 (0.82 to 1.01)		1.00 (0.88 to 1.15)		0.99 (0.82 to 1.19)	
2-5	1.97 (1.68 to 2.30)		1.18 (1.02 to 1.36)		1.64 (1.37 to 1.96)		1.35 (1.08 to 1.69)	
5	3.46 (2.84 to 4.21)		1.94 (1.57 to 2.40)		1.59 (1.17 to 2.15)		2.54 (1.84 to 3.51)	

Abbreviations: AI, angiogenesis inhibitor; CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; STI, signal transduction inhibitor.

TABLE A31. Time-Dependent Model with Tumor Growth Rate by Tumor Type

	Lung Cancer (n = 5,700)		Colon Cancer (n = 5,435)		Breast Cancer (n = 1,568)		GIST (n = 929)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.03 (1.03 to 1.04)	< .001 (1)	1.02 (1.02 to 1.03)	< .001 (1)	1.03 (1.03 to 1.04)	< .001 (1)	1.02 (1.01 to 1.03)	< .001 (1)
New lesions								
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.69 (1.57 to 1.83)		1.82 (1.69 to 1.97)		1.79 (1.64 to 1.96)		2.66 (2.25 to 3.15)	
Response of nontarget lesions								
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.67 (1.54 to 1.81)		1.31 (1.20 to 1.43)		1.41 (1.29 to 1.55)		1.68 (1.42 to 2.00)	
Best percentage change from baseline								
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.62 (0.55 to 0.69)		0.68 (0.61 to 0.76)		0.61 (0.54 to 0.69)		0.67 (0.49 to 0.92)	
15-30	0.58 (0.52 to 0.65)		0.48 (0.42 to 0.54)		0.51 (0.45 to 0.58)		0.56 (0.42 to 0.75)	
30-50	0.45 (0.40 to 0.50)		0.36 (0.32 to 0.41)		0.41 (0.36 to 0.46)		0.49 (0.38 to 0.63)	
50-70	0.36 (0.32 to 0.41)		0.29 (0.25 to 0.33)		0.35 (0.30 to 0.41)		0.37 (0.28 to 0.49)	
70-100	0.28 (0.24 to 0.33)		0.25 (0.20 to 0.30)		0.26 (0.21 to 0.33)		0.32 (0.23 to 0.44)	
CR	0.29 (0.23 to 0.36)		0.24 (0.20 to 0.30)		0.25 (0.19 to 0.33)		0.36 (0.25 to 0.52)	
Slope: estimated rate of weekly increase, mm/wk								
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	0.82 (0.76 to 0.89)		0.94 (0.86 to 1.03)		0.86 (0.78 to 0.95)		2.04 (1.67 to 2.48)	
2-5	1.19 (1.08 to 1.32)		1.47 (1.31 to 1.65)		1.16 (1.03 to 1.31)		3.34 (2.61 to 4.27)	
5	1.65 (1.42 to 1.93)		1.79 (1.51 to 2.11)		1.46 (1.22 to 1.76)		7.61 (5.48 to 10.57)	

Abbreviations: AI, angiogenesis inhibitor; CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; STI, signal transduction inhibitor.

TABLE A32. Time-Dependent Model with Tumor Growth Rate for Lung Cancer Patients by Treatment Category

	TCA (n = 683)		TCA Plus Chemotherapy (n = 2,746)		Chemotherapy (n = 2,271)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.06 (1.04 to 1.08)	< .001 (1)	1.03 (1.02 to 1.04)	< .001 (1)	1.06 (1.04 to 1.07)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.86 (1.55 to 2.23)		1.59 (1.42 to 1.79)		1.69 (1.49 to 1.91)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	2.05 (1.63 to 2.57)		1.77 (1.57 to 1.98)		1.46 (1.27 to 1.66)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.73 (0.56 to 0.94)		0.64 (0.53 to 0.76)		0.52 (0.43 to 0.62)	
15-30	0.53 (0.39 to 0.71)		0.63 (0.54 to 0.74)		0.48 (0.40 to 0.58)	
30-50	0.50 (0.33 to 0.76)		0.43 (0.36 to 0.50)		0.41 (0.35 to 0.49)	
50-70	0.35 (0.22 to 0.58)		0.34 (0.28 to 0.40)		0.34 (0.28 to 0.42)	
70-100	0.40 (0.21 to 0.75)		0.27 (0.21 to 0.34)		0.24 (0.18 to 0.32)	
CR	0.46 (0.23 to 0.90)		0.27 (0.20 to 0.36)		0.29 (0.20 to 0.43)	
Slope: estimated rate of weekly increase, mm/wk						
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	0.66 (0.54 to 0.82)		0.87 (0.77 to 0.98)		0.86 (0.75 to 0.99)	
2-5	0.98 (0.75 to 1.27)		1.18 (1.02 to 1.37)		1.21 (1.03 to 1.42)	
5	1.65 (1.06 to 2.56)		1.76 (1.41 to 2.21)		1.31 (1.02 to 1.69)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease.

TABLE A33. Time-Dependent Model with Tumor Growth Rate for Colorectal Cancer Patients by Treatment Category

	TCA (n = 1,151)		TCA Plus Chemotherapy (n = 2,645)		Chemotherapy (n = 1,639)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.04 (1.03 to 1.05)	< .001 (1)	1.02 (1.01 to 1.03)	< .001 (1)	1.03 (1.02 to 1.04)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.60 (1.37 to 1.87)		1.89 (1.69 to 2.12)		1.88 (1.61 to 2.18)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	0.013 (1)	1.00	0.001 (1)
PD	1.48 (1.26 to 1.74)		1.20 (1.04 to 1.38)		1.30 (1.11 to 1.52)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.52 (0.42 to 0.64)		0.76 (0.63 to 0.92)		0.68 (0.56 to 0.83)	
15-30	0.37 (0.29 to 0.46)		0.51 (0.42 to 0.62)		0.52 (0.42 to 0.65)	
30-50	0.30 (0.23 to 0.39)		0.39 (0.32 to 0.47)		0.34 (0.26 to 0.44)	
50-70	0.25 (0.16 to 0.39)		0.30 (0.24 to 0.36)		0.32 (0.24 to 0.44)	
70-100	0.19 (0.07 to 0.51)		0.26 (0.21 to 0.34)		0.27 (0.18 to 0.43)	
CR	0.30 (0.10 to 0.96)		0.28 (0.22 to 0.37)		0.22 (0.14 to 0.36)	
Slope: estimated rate of weekly increase, mm/wk						
0	1.00	< .001 (3)	1.00	< .001 (3)	1.00	< .001 (3)
0-2	0.58 (0.47 to 0.72)		1.13 (0.99 to 1.28)		0.87 (0.72 to 1.05)	
2-5	0.93 (0.75 to 1.16)		2.06 (1.73 to 2.47)		1.17 (0.94 to 1.47)	
5	1.20 (0.91 to 1.60)		1.95 (1.42 to 2.69)		1.43 (1.02 to 2.00)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease.

TABLE A34. Time-Dependent Model with Tumor Growth Rate for Breast Cancer Patients by Treatment Category

	TCA* (n = 734)		TCA Plus Chemotherapy (n = 675)		Chemotherapy (n = 159)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)			1.06 (1.03 to 1.08)	< .001 (1)	0.99 (0.93 to 1.04)	.622 (1)
New lesions						
No			1.00	< .001 (1)	1.00	.002 (1)
Yes			2.71 (1.95 to 3.75)		4.00 (1.69 to 9.47)	
Response of nontarget lesions						
No PD			1.00	.279 (1)	1.00	.740 (1)
PD			1.20 (0.86 to 1.67)		1.17 (0.47 to 2.87)	
Best percentage change from baseline						
0			1.00	< .001 (6)	1.00	.160 (6)
0-15			0.45 (0.25 to 0.81)		0.64 (0.17 to 2.39)	
15-30			0.51 (0.29 to 0.88)		0.34 (0.10 to 1.20)	
30-50			0.47 (0.30 to 0.74)		0.29 (0.08 to 1.06)	
50-70			0.30 (0.18 to 0.49)		0.24 (0.06 to 1.02)	
70-100			0.21 (0.12 to 0.38)		0.39 (0.08 to 1.86)	
CR			0.35 (0.17 to 0.70)		0.24 (0.03 to 2.14)	
Slope: estimated rate of weekly increase, mm/wk						
0			1.00	.020 (3)	1.00	.137 (3)
0-2			1.05 (0.75 to 1.46)		0.88 (0.37 to 2.06)	
2-5			1.42 (0.85 to 2.36)		1.26 (0.43 to 3.69)	
5			3.08 (1.44 to 6.56)		9.08 (1.25 to 65.99)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease.
*Too few events to obtain a good fit.

TABLE A35. Time-Dependent Model with Percentage Growth Rate by Treatment Category

	TCA (n = 4,975)		TCA Plus Chemotherapy (n = 6,853)		Chemotherapy (n = 5,068)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.03 (1.03 to 1.03)	< .001 (1)	1.03 (1.03 to 1.03)	< .001 (1)	1.03 (1.03 to 1.03)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	2.18 (2.01 to 2.37)		1.77 (1.65 to 1.91)		1.77 (1.65 to 1.91)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.68 (1.54 to 1.84)		1.47 (1.35 to 1.59)		1.47 (1.35 to 1.59)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.68 (0.61 to 0.77)		0.67 (0.60 to 0.76)		0.67 (0.60 to 0.76)	
15-30	0.53 (0.46 to 0.60)		0.59 (0.52 to 0.65)		0.59 (0.52 to 0.65)	
30-50	0.42 (0.37 to 0.48)		0.43 (0.39 to 0.48)		0.43 (0.39 to 0.48)	
50-70	0.33 (0.27 to 0.39)		0.33 (0.29 to 0.38)		0.33 (0.29 to 0.38)	
70-100	0.29 (0.23 to 0.36)		0.27 (0.23 to 0.32)		0.27 (0.23 to 0.32)	
CR	0.33 (0.23 to 0.45)		0.32 (0.26 to 0.38)		0.32 (0.26 to 0.38)	
Change from nadir, %						
0	1.00	< .001 (4)	1.00	.002 (4)	1.00	.278 (4)
0-20	1.15 (1.03 to 1.29)		1.04 (0.95 to 1.14)		1.04 (0.95 to 1.14)	
20-50	1.30 (1.16 to 1.46)		1.13 (1.02 to 1.24)		1.13 (1.02 to 1.24)	
50-100	1.48 (1.28 to 1.70)		1.25 (1.10 to 1.42)		1.25 (1.10 to 1.42)	
≥ 100	2.10 (1.72 to 2.56)		1.25 (1.05 to 1.49)		1.25 (1.05 to 1.49)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease.

TABLE A36. Time-Dependent Model with Percentage Growth Rate by Type of TCA

	STIs (n = 2,526)		AIs (n = 1,323)		STIs Plus Chemotherapy (n = 4,622)		AIs Plus Chemotherapy (n = 1,917)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.03 (1.02 to 1.03)	< .001 (1)	1.04 (1.03 to 1.05)	< .001 (1)	1.03 (1.02 to 1.03)	< .001 (1)	1.04 (1.03 to 1.05)	< .001 (1)
New lesions								
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	2.34 (2.09 to 2.62)		2.08 (1.80 to 2.41)		1.58 (1.42 to 1.74)		2.03 (1.80 to 2.29)	
Response of nontarget lesions								
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	1.71 (1.52 to 1.92)		1.62 (1.37 to 1.91)		1.53 (1.37 to 1.70)		1.51 (1.32 to 1.73)	
Best percentage change from baseline								
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.69 (0.58 to 0.82)		0.66 (0.54 to 0.80)		0.67 (0.57 to 0.78)		0.55 (0.46 to 0.67)	
15-30	0.50 (0.42 to 0.60)		0.57 (0.45 to 0.71)		0.66 (0.57 to 0.77)		0.43 (0.36 to 0.52)	
30-50	0.42 (0.35 to 0.50)		0.44 (0.34 to 0.58)		0.50 (0.43 to 0.57)		0.31 (0.26 to 0.38)	
50-70	0.35 (0.28 to 0.43)		0.31 (0.22 to 0.44)		0.39 (0.33 to 0.45)		0.25 (0.20 to 0.31)	
70-100	0.30 (0.23 to 0.39)		0.31 (0.17 to 0.54)		0.34 (0.28 to 0.41)		0.17 (0.12 to 0.23)	
CR	0.38 (0.27 to 0.54)		0.16 (0.05 to 0.51)		0.34 (0.27 to 0.43)		0.24 (0.16 to 0.37)	
Change from nadir, %								
0	1.00	< .001 (4)	1.00	.012 (4)	1.00	.375 (4)	1.00	.005 (4)
0-20	1.33 (1.14 to 1.55)		0.97 (0.79 to 1.18)		1.02 (0.90 to 1.15)		1.03 (0.88 to 1.20)	
20-50	1.51 (1.30 to 1.75)		1.16 (0.95 to 1.42)		0.95 (0.84 to 1.09)		1.26 (1.08 to 1.48)	
50-100	1.63 (1.36 to 1.95)		1.34 (1.02 to 1.74)		1.10 (0.93 to 1.31)		1.38 (1.11 to 1.71)	
≥ 100	2.43 (1.92 to 3.07)		1.78 (1.10 to 2.86)		1.18 (0.93 to 1.48)		1.17 (0.85 to 1.60)	

Abbreviations: AI, angiogenesis inhibitor; CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; STI, signal transduction inhibitor.

TABLE A37. Time-Dependent Model with Percentage Growth Rate by Tumor Type

	Lung Cancer (n = 5,644)		Colon Cancer (n = 5,383)		Breast Cancer (n = 1,559)		GIST (n = 914)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.04 (1.03 to 1.04)	< .001 (1)	1.03 (1.03 to 1.04)	< .001 (1)	1.06 (1.03 to 1.08)	< .001 (1)	1.02 (1.02 to 1.03)	< .001 (1)
New lesions								
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.69 (1.57 to 1.83)		1.81 (1.67 to 1.96)		2.67 (1.99 to 3.57)		2.78 (2.34 to 3.29)	
Response of nontarget lesions								
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	.382 (1)	1.00	< .001 (1)
PD	1.71 (1.58 to 1.86)		1.36 (1.24 to 1.48)		1.14 (0.85 to 1.55)		1.70 (1.42 to 2.03)	
Best percentage change from baseline								
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.61 (0.55 to 0.69)		0.66 (0.59 to 0.74)		0.52 (0.33 to 0.84)		0.59 (0.43 to 0.82)	
15-30	0.58 (0.52 to 0.64)		0.47 (0.42 to 0.53)		0.52 (0.33 to 0.81)		0.53 (0.40 to 0.71)	
30-50	0.44 (0.40 to 0.49)		0.35 (0.31 to 0.40)		0.44 (0.29 to 0.65)		0.45 (0.35 to 0.58)	
50-70	0.36 (0.32 to 0.41)		0.28 (0.24 to 0.32)		0.28 (0.18 to 0.43)		0.35 (0.26 to 0.46)	
70-100	0.28 (0.24 to 0.34)		0.24 (0.19 to 0.29)		0.21 (0.13 to 0.36)		0.28 (0.20 to 0.39)	
CR	0.31 (0.24 to 0.40)		0.27 (0.22 to 0.34)		0.26 (0.12 to 0.55)		0.54 (0.35 to 0.84)	
Change from nadir, %								
0	1.00	.314 (4)	1.00	.007 (4)	1.00	.794 (4)	1.00	< .001 (4)
0-20	0.93 (0.85 to 1.02)		1.01 (0.91 to 1.12)		1.05 (0.75 to 1.45)		2.35 (1.86 to 2.97)	
20-50	0.96 (0.88 to 1.06)		1.11 (1.00 to 1.24)		1.01 (0.67 to 1.50)		2.69 (2.11 to 3.43)	
50-100	1.02 (0.90 to 1.16)		1.25 (1.09 to 1.44)		1.28 (0.77 to 2.13)		2.81 (2.12 to 3.73)	
≥ 100	1.10 (0.92 to 1.31)		1.18 (0.95 to 1.46)		1.32 (0.74 to 2.36)		4.18 (3.06 to 5.72)	

Abbreviations: CR, complete response; df, degrees of freedom; GIST, GI stromal tumor; HR, hazard ratio; PD, progressive disease.

TABLE A38. Time-Dependent Model with Percentage Growth Rate for Lung Cancer Patients by Treatment Category

	TCA (n = 681)		TCA Plus Chemotherapy (n = 2,714)		Chemotherapy (n = 2,249)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.08 (1.06 to 1.10)	< .001 (1)	1.03 (1.03 to 1.04)	< .001 (1)	1.07 (1.05 to 1.08)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.90 (1.58 to 2.28)		1.62 (1.44 to 1.82)		1.65 (1.45 to 1.87)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
PD	2.10 (1.68 to 2.62)		1.79 (1.59 to 2.01)		1.49 (1.30 to 1.71)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.69 (0.53 to 0.89)		0.64 (0.53 to 0.76)		0.50 (0.42 to 0.61)	
15-30	0.51 (0.38 to 0.69)		0.63 (0.54 to 0.74)		0.46 (0.39 to 0.56)	
30-50	0.49 (0.32 to 0.74)		0.43 (0.37 to 0.50)		0.39 (0.33 to 0.47)	
50-70	0.33 (0.20 to 0.54)		0.34 (0.28 to 0.41)		0.33 (0.27 to 0.40)	
70-100	0.40 (0.21 to 0.74)		0.27 (0.21 to 0.34)		0.23 (0.17 to 0.31)	
CR	0.45 (0.21 to 0.97)		0.29 (0.21 to 0.41)		0.32 (0.20 to 0.50)	
Change from nadir, %						
0	1.00	.036 (4)	1.00	.767 (4)	1.00	.805 (4)
0-20	0.70 (0.55 to 0.89)		0.96 (0.83 to 1.10)		0.96 (0.82 to 1.12)	
20-50	0.75 (0.59 to 0.94)		1.03 (0.89 to 1.18)		0.95 (0.82 to 1.11)	
50-100	0.83 (0.60 to 1.15)		1.04 (0.86 to 1.27)		1.06 (0.86 to 1.31)	
≥ 100	1.07 (0.64 to 1.79)		1.13 (0.87 to 1.48)		1.09 (0.83 to 1.44)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; TCA, targeted cancer agent.

TABLE A39. Time-Dependent Model with Percentage Growth Rate for Colorectal Cancer Patients by Treatment Category

	TCA (n = 1,147)		TCA Plus Chemotherapy (n = 2,612)		Chemotherapy (n = 1,624)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)	1.05 (1.04 to 1.06)	< .001 (1)	1.03 (1.02 to 1.03)	< .001 (1)	1.03 (1.02 to 1.04)	< .001 (1)
New lesions						
No	1.00	< .001 (1)	1.00	< .001 (1)	1.00	< .001 (1)
Yes	1.57 (1.34 to 1.83)		1.89 (1.69 to 2.12)		1.86 (1.60 to 2.17)	
Response of nontarget lesions						
No PD	1.00	< .001 (1)	1.00	.008 (1)	1.00	< .001 (1)
PD	1.56 (1.33 to 1.83)		1.21 (1.05 to 1.40)		1.37 (1.17 to 1.60)	
Best percentage change from baseline						
0	1.00	< .001 (6)	1.00	< .001 (6)	1.00	< .001 (6)
0-15	0.35 (0.28 to 0.45)		0.74 (0.61 to 0.89)		0.67 (0.55 to 0.82)	
15-30	0.28 (0.22 to 0.37)		0.50 (0.42 to 0.61)		0.53 (0.42 to 0.67)	
30-50	0.22 (0.14 to 0.34)		0.39 (0.32 to 0.47)		0.34 (0.26 to 0.44)	
50-70	0.15 (0.05 to 0.41)		0.29 (0.24 to 0.36)		0.33 (0.24 to 0.45)	
70-100	0.96 (0.23 to 3.91)		0.26 (0.20 to 0.33)		0.28 (0.18 to 0.45)	
CR	0.45 (0.21 to 0.97)		0.32 (0.24 to 0.43)		0.25 (0.15 to 0.43)	
Change from nadir, %						
0	1.00	.012 (4)	1.00	< .001 (4)	1.00	.713 (4)
0-20	0.69 (0.55 to 0.86)		1.11 (0.95 to 1.29)		1.00 (0.82 to 1.23)	
20-50	0.74 (0.60 to 0.92)		1.46 (1.24 to 1.70)		0.91 (0.74 to 1.13)	
50-100	0.87 (0.66 to 1.14)		1.61 (1.31 to 1.99)		1.07 (0.81 to 1.40)	
≥ 100	1.02 (0.61 to 1.68)		1.41 (1.06 to 1.87)		0.86 (0.53 to 1.38)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; TCA, targeted cancer agent.

TABLE A40. Time-Dependent Model with Percentage Growth Rate for Breast Cancer Patients by Treatment Category

	TCA* (n = 732)		TCA Plus Chemotherapy (n = 668)		Chemotherapy (n = 159)	
Parameter and Level	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**	**HR (95% CI)**	***P* (df)**
Baseline tumor load (per cm increase)			1.06 (1.04 to 1.09)	< .001 (1)	1.01 (0.96 to 1.06)	.698 (1)
New lesions						
No			1.00	< .001 (1)	1.00	.004 (1)
Yes			2.62 (1.89 to 3.64)		3.48 (1.48 to 8.16)	
Response of nontarget lesions						
No PD			1.00	.317 (1)	1.00	.875 (1)
PD			1.19 (0.85 to 1.66)		1.08 (0.43 to 2.68)	
Best percentage change from baseline						
0			1.00	< .001 (6)	1.00	.356 (6)
0-15			0.44 (0.25 to 0.80)		0.56 (0.15 to 2.09)	
15-30			0.49 (0.28 to 0.84)		0.40 (0.11 to 1.40)	
30-50			0.45 (0.28 to 0.70)		0.33 (0.09 to 1.27)	
50-70			0.27 (0.16 to 0.45)		0.31 (0.07 to 1.31)	
70-100			0.19 (0.10 to 0.35)		0.49 (0.09 to 2.56)	
CR			0.26 (0.11 to 0.58)		0.25 (0.03 to 2.34)	
Change from nadir, %						
0			1.00	.319 (4)	1.00	.627 (4)
0-20			1.05 (0.72 to 1.53)		1.17 (0.44 to 3.12)	
20-50			0.91 (0.57 to 1.44)		1.95 (0.66 to 5.77)	
50-100			1.43 (0.82 to 2.51)		0.53 (0.10 to 2.73)	
≥ 100			1.75 (0.88 to 3.49)		0.84 (0.24 to 2.93)	

Abbreviations: CR, complete response; df, degrees of freedom; HR, hazard ratio; PD, progressive disease; TCA, targeted cancer agent.
*Too few events to obtain a good fit.