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Clinical Cancer Research

Cancer Therapy: Clinical

Tumor Growth Rate Is an Early Indicator of Antitumor Drug Activity in Phase I Clinical Trials

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Abstract

Purpose: Response Evaluation Criteria in Solid Tumors (RECIST) evaluation does not take into account the pretreatment tumor kinetics and may provide incomplete information about experimental drug activity. Tumor growth rate (TGR) allows for a dynamic and quantitative assessment of the tumor kinetics. How TGR varies along the introduction of experimental therapeutics and is associated with outcome in phase I patients remains unknown.

Experimental Design: Medical records from all patients ($N = 253$) prospectively treated in 20 phase I trials were analyzed. TGR was computed during the pretreatment period (reference) and the experimental period. Associations between TGR, standard prognostic scores [Royal Marsden Hospital (RMH) score], and outcome [progression-free survival (PFS) and overall survival (OS)] were computed (multivariate analysis).

Results: We observed a reduction of TGR between the reference versus experimental periods (38% vs. 4.4%; $P < 0.00001$). Although most patients were classified as stable disease (65%) or progressive disease (25%) by RECIST at the first evaluation, 82% and 65% of them exhibited a decrease in TGR, respectively. In a multivariate analysis, only the decrease of TGR was associated with PFS ($P = 0.004$), whereas the RMH score was the only variable associated with OS ($P = 0.0008$). Only the investigated regimens delivered were associated with a decrease of TGR ($P < 0.00001$, multivariate analysis). Computing TGR profiles across different clinical trials reveals specific patterns of antitumor activity.

Conclusions: Exploring TGR in phase I patients is simple and provides clinically relevant information: (i) an early and subtle assessment of signs of antitumor activity; (ii) independent association with PFS; and (iii) it reveals drug-specific profiles, suggesting potential utility for guiding the further development of the investigational drugs. *Clin Cancer Res; 20(1); 246–52. ©2013 AACR.*

Introduction

The introduction of the Response Evaluation Criteria In Solid Tumors (RECIST) system represented a major improvement in the assessment of the tumor response to antineoplastic agents in the setting of clinical trials (1,2). Its criteria are based on the variation of the sum of the longest diameters of selected target lesions over time. However, the ability of RECIST to evaluate recent molecular targeted agents is highly discussed as these drugs may induce tumor density or perfusion changes responsible of long-lasting stabilizations rather than tumor shrinkage (3–6). This is especially relevant because the thresholds that dictate the decision-making for patients are somewhat arbitrary cutoffs on the continuous response scale: −30% for partial response (PR), +20% or occurrence of new lesions for progressive disease, and between these two values for stable disease. A number of alternative methods exploring tumor metabolism (5,7), tumor perfusion (8,9), or the immune component of the response (10) have been proposed to overcome these inadequacies. However, most of them require extra imaging exams [e.g., positron emission tomography with 18-FDG, dynamic contrast enhanced (DCE) ultrasonography] or did not reach the warranted level of evidence to be used in daily practice.

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C. Ferté, M. Fernandez, and A. Hollebecque contributed equally to this work.

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Translational Relevance

In addition to explore the safety profiles of the investigated regimens, phase I trials play a major role in the drug development by revealing the early signs of antitumor activity of the drugs. We evaluated the variation of the tumor growth kinetics [assessed by tumor growth rate (TGR)] across the reference (wash-out period before treatment) and the experimental periods in 201 patients prospectively treated in 20 phase I trials. Although most of the patients were classified as stable disease (65%) or progressive disease (25%) by Response Evaluation Criteria in Solid Tumors (RECIST) at the first tumor evaluation, 82% and 65% of them exhibited a decrease of TGR, respectively. The decrease of TGR was the only independent variable associated with progression-free survival (PFS; multivariate analysis) and was only influenced by the prescribed investigational regimen (multivariate analysis). Such findings suggest the usefulness of TGR profiling to guide the "go/no go" decision-making in early drug development.

We and others have previously reported on the potential value of tumor kinetics in phase I trials to better evaluate tumor response (11–16). In a hypothetical trial testing an active drug, fast growing tumors at inclusion are more likely to be classified as stable disease or progression even if there is an antitumor activity (Supplementary Fig. S1). This would lead to discard the patient from the trial and hamper the drug development. On the opposite, in a non-active drug configuration, patients enrolled with slow-growing tumors are likely to be classified as stable disease (Supplementary Fig. S2) and lead to continue the unnecessary patient exposure to the drug. The analysis of tumor growth rate (TGR) combines the RECIST sums of target lesions and the time between the tumor evaluations. It allows for a dynamic and quantitative evaluation of the tumor kinetics. Still, how the TGR varies along the introduction of experimental therapeutics and is associated with the outcome in phase I patients remains unknown.

Patients and Methods

Patients

The medical records of all consecutive patients ($N = 253$) prospectively enrolled and treated in 20 phase I clinical trials at Gustave Roussy (Villejuif Cedex, France) between July 2008 and June 2012 were analyzed. All the computed tomography scans were independently reviewed by two senior radiologists (C. Dromain and S. Ammari).

Definition of the TGR

Tumor size (D) was defined as the sum of the longest diameters of the target lesions as per the RECIST criteria (1). Let t be the time expressed in months at the tumor evaluation. Assuming the tumor growth follows an exponential law, V_t the tumor volume at time t is equal to $V_t = V_0 \exp(TG.t)$, where V_0 is volume at baseline, and TG is the growth rate. We approximated the tumor volume (V) by $V = 4\,\pi\, R^3/3$, where R, the radius of the sphere, is equal to $D/2$. Consecutively, TG is equal to $TG = 3 \log(Dt/D0)/t$. To report the TGR results in a clinically meaningful way, we expressed TGR as a percent increase in tumor volume during one month using the following transformation: $TGR = 100\ (\exp(TG) - 1)$, where exp(TG) represents the exponential of TG.

We calculated the TGR across clinically relevant treatment periods (Fig. 1): (i) TGR reference assessed during the wash-out period (off-therapy) before the introduction of the experimental drug, (ii) TGR experimental assessed during the first cycle of treatment (i.e., between the drug introduction and the first evaluation, on-therapy). To compute the TGR reference, additional imaging exploring the wash-out period (off-therapy) immediately before the introduction was included when available. As per the RECIST system, patients with nonmeasurable disease only at baseline could not be assessed by TGR. For patients who progressed with new lesions, the TGR was computed on the target lesions only (new lesions not included in the RECIST sum).

Statistical analysis

We performed pairwise comparisons to test the variations of TGR along the treatment sequences using Wilcoxon signed-rank tests. Progression-free survival (PFS) was determined as the time between the date of randomization and the earliest sign of disease progression or death from any cause. Overall survival (OS) was determined as the time between the date of randomization and the death from any cause. The tumor progression was assessed using the RECIST (1,2) at the first treatment evaluation after the onset of the experimental drug. OS and PFS were estimated using the Kaplan–Meier method and compared between treatment groups using the log-rank test. To avoid the potential bias introduced by the fact that responders must live long enough for a response to be observed and for TGR to be

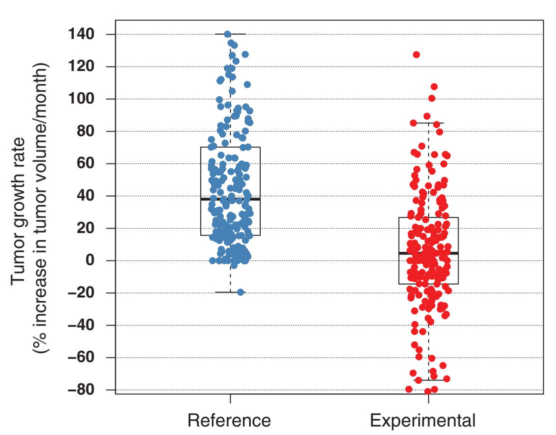

Figure 1. Distribution of TGR across the reference and the experimental periods.

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Table 1. Patients' characteristics

		Patients, *N* (%)
Age, y	Mean (range)	56 (20–77)
Gender	Males	101 (50%)
	Females	100 (50%)
Histological type	Thoracic	35 (17%)
	Colorectal	33 (16%)
	Breast	20 (10%)
	Mesothelioma	17 (8%)
	Genitourinary (renal, bladder, and prostate)	14 (7%)
	Melanoma	10 (5%)
	Noncolorectal GI (upper-GI, pancreas)	17 (8%)
	Head-and-neck cancer	8 (4%)
	Sarcoma	8 (4%)
	Gynecologic (ovarian, endometrial, and cervix)	10 (5%)
	Other (thyroid, carcinoma of unknown origin, adrenocortical carcinoma, etc.)	29 (14%)
Previous lines of chemotherapy (*N*)	0	21 (10%)
	1	22 (11%)
	2	43 (21%)
	3	48 (24%)
	4–8	67 (33%)
Number of metastatic sites (*N*)	0–1	51 (25%)
	2	87 (43%)
	3	52 (26%)
	>4	11 (5%)
RMH prognostic score	0	40 (21%)
	1	83 (44%)
	2	51 (27%)
	3	14 (7%)

Abbreviation: RMH, Royal Marsden Hospital.

measured, all associations between survival and TGR were performed using landmark method (17). As per the different protocols, all the patients had to be evaluated after 6 to 8 weeks of drug exposure. Consequently, we set the landmark point at 56 days. HRs were estimated from Cox proportional hazard models and were adjusted to the standard clinicopathologic prognostic factors, assessed by the Royal Marsden prognostic score (RMH), as previously described (18). All the tests were two-sided and significance was assumed if $P < 0.05$. All the analyses were carried out using the R statistical software (R version 2.15.0, http://www.R-project.org/.), the "survival" R package (version 2.37.4, published by T. Therneau), and controlled by a senior statistician (S. Koscielny).

Results

Description of the cohort

The calculation of TGR for both the reference and TGR experimental periods could be computed in 201 out of 253 patients (79%): 47 patients did not have a tumor evaluation before the baseline, 3 patients exhibited a clinical tumor progression before the first tumor evaluation, and 2 patients stopped because of toxicity before the first evaluation. Patient characteristics are described in Table 1. The distribution of the patients according to the clinical trials ($n = 20$) characteristics is described in Supplementary Table S1.

Variation of TGR across the reference and the experimental periods, according to the RECIST

The distribution of TGR across the reference [median, 38; 95% confidence interval (CI), 0–140] and the experimental periods (median, 4.4; 95% CI, 65–80) is described in Fig. 1. At the first tumor evaluation, whatever the treatment delivered, most evaluable patients (131 patients, 65%) were classified as stable disease according to RECIST criteria (Fig. 2, Table 3), which is not very informative for decision-making and for evaluating the antitumor activity of a drug. Meanwhile, 51 patients (26%) and 19 patients (9%) were classified as progressive disease and PR, respectively. Conversely, we observed that 82% and 65% of the patients initially classified as stable disease and progressive disease exhibited a decrease in TGR, respectively. Overall, there was a significant decrease in the TGR between the reference and the

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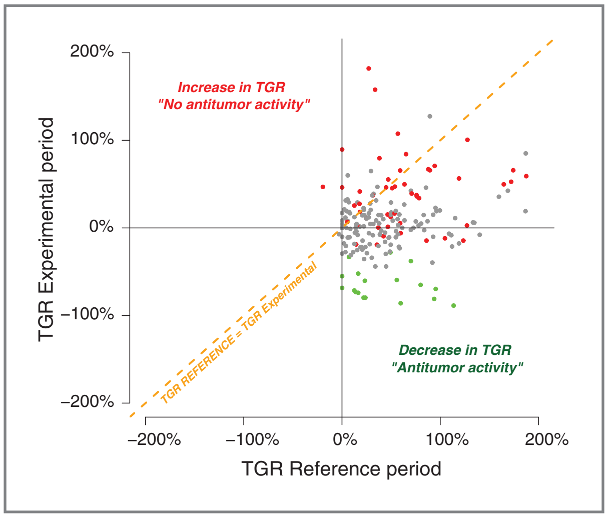

Figure 2. Pairwise comparisons of TGR between the reference and the experimental periods in 201 patients treated in 20 phase I clinical trials (*P* values are computed from Wilcoxon pairwise tests; *n*, the number of samples with pairwise TGR information). Red, gray, and green colors indicate progressive disease, stable disease, and partial response as per RECIST criteria, respectively.

experimental periods in 159 patients (79%; pairwise comparison: Wilcoxon signed-rank test $P < 1e{-}05$; Fig. 2, Supplementary Table S2). Interestingly, we also observed that 20 out of the 28 patients (71%) progressing with new lesions at the first tumor evaluation experienced simultaneously a decrease of TGR, suggesting evidence of drug activity on the target lesions in this subset of patients as well. All together, these results suggest that TGR profiling is able to detect early antitumoral activity in patients receiving an experimental compound as early as in the first drug evaluation period.

The decrease of TGR between the reference and the experimental periods is associated with PFS (multivariate analysis)

We assessed whether the decrease of TGR between the reference and the experimental periods was associated with outcome using the landmark method (Table 2). In a multivariate Cox regression analysis ($n = 157$), the decrease of TGR was significantly associated with PFS (HR, 0.91; 95% CI, 0.85–0.96; $P = 0.004$), but not with OS (HR, 0.95; 95% CI, 0.88–1.04; $P = 0.27$). As such, every 10% decrease in the TGR between the reference and the experimental periods results in a 9% decrease in the progression hazard of progression. Conversely, the RMH prognostic score was nearly associated with PFS (HR, 1.42; 95% CI, 0.96–2.08; $P = 0.08$) and remained strongly associated with OS (HR, 2.53; 95% CI, 1.47–4.34; $P = 0.0008$). To note, the interaction tests between the decrease of TGR and RMH were not significant for PFS ($P = 0.63$) nor for OS ($P = 0.15$). Finally, when adding the tumor volume at baseline (V_0, estimated by the RECIST sum) to the model combining the TGR and the RMH score, V_0 seems to have no effect on survival (HZs consistently very close to 1 and not significant *P* values; data not shown). This confirms that the tumor burden at baseline (V_0 estimated by the RECIST sum) has no or marginal effect on survival when TGR is incorporated in the model. All together, these results reveal that the decrease of TGR is strongly and independently associated with PFS but not with OS. On the opposite, when adjusting for a decrease in TGR, the RMH prognostic score remains the only independent variable associated with OS.

TGR profiling across investigational regimens reveals specific patterns of antitumor activity

Because the decrease of TGR was independently associated with PFS but not with OS, we assumed that the decrease of TGR might be influenced by the investigational regimen. To investigate this hypothesis, we computed a multivariate linear model incorporating the investigational regimen, the RMH prognostic score, the age, the gender, and the number of previous lines of treatment. We empirically restricted our analysis on the trials with a minimum of 8 patients enrolled per trial (12 of 20 trials). Importantly, only the investigational regimen was associated

Table 2. Multivariate Cox regression analysis of the decrease of TGR and the RMH prognostic score for PFS and OS

	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Decrease of tumor growth rate[a]	0.91 0.85–0.96	0.004	0.95 0.88–1.04	0.27
RMH prognostic score low score (0–1) vs. high score (2–3)	1.42 0.96–2.08	0.08	2.53 1.47–4.34	0.0008

NOTE: All the analyses reported are performed with the landmark method (landmark point was set to 56 days, $n = 157$ patients analyzed).
Abbreviation: RMH, Royal Marsden Hospital.
[a]To be clinically meaningful, HRs are computed for 10% variation in TGR. Here, every 10% decrease in TGR between the reference and the experimental periods results in a 9% decrease in the progression hazard.

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Table 3. Distribution of the stage of development, the decrease of TGR, and the tumor response (RECIST) across the different trials

Investigational regimen	Decrease of TGR[a]	RECIST evaluation: Progressive disease (*N*)	RECIST evaluation: Stable disease (*N*)	RECIST evaluation: Partial response (*N*)	Total number of patients (*N*)	Current development status
Trial #1: HSP inhibitor	Not significant	3	5	0	8	Stopped
Trial #2: HSP inhibitor	Not significant	10	11	0	21	Ongoing
Trial #3: Cell-cycle inhibitor	Not significant	3	9	0	12	Stopped
Trial #4: PI3K/Akt/mTOR inhibitor	Not significant	2	7	0	9	Ongoing
Trial #5: Antiangiogenic	Not significant	3	4	1	8	Ongoing
Trial #6: HDAC inhibitor	Not significant	9	11	0	20	Ongoing
Trial #7: PI3K/Akt/mTOR inhibitor	Significant	3	7	2	12	Ongoing
Trial #8: MEK inhibitor	Significant	3	8	2	13	Stopped
Trial #9: Antiangiogenic	Significant	3	9	2	14	Ongoing
Trial #10: HER family inhibitor	Significant	6	11	0	17	Stopped
Trial #11: Antiangiogenic	Significant	3	15	2	20	Ongoing
Trial #12: PI3K/Akt/mTOR inhibitor	Significant	2	14	3	19	Ongoing

[a]Significance of the decrease of TGR between the reference and the experimental period (pairwise comparison, Wilcoxon signed-rank test).

with the decrease of TGR ($P < 0.00001$), accounting for 31% of the explained variance (R^2; Supplementary Table S3, Fig. 3). The TGR analysis (reference vs. experimental periods) across the different clinical trials clearly shows specific patterns of antitumor activity (Fig. 3). Interestingly, we observed that some regimens without objective tumor response by RECIST (e.g., Trial #10: HER family inhibitor) but exhibiting a significant decrease of TGR are now stopped in development (Table 3).

Discussion

Within this study, TGR demonstrates a strong potential for translation in the early drug development setting in several ways: (i) TGR allows for an earlier and more precise detection of signs of antitumor activity as compared with the RECIST criteria, (ii) it is independently associated with PFS in a prospective cohort of phase I patients, (iii) the TGR profiles reveal clear antitumor activity patterns specific to the investigated regimens.

Interestingly, neither the RECIST criteria were developed in the specific early drug development context nor the aims of phase I trials are primarily to evaluate the antitumor efficacy. However, it is notable and logical that the studies exhibiting objective tumor response (as per RECIST) receive more attention from the oncology community and are thus more prone to be further developed. The present study clearly confirms that early signs of antitumor activity (i.e., as soon as at the first planned tumor evaluation) are not well estimated using the conventional RECIST criteria in phase I patients because most of the patients (65%) are classified as stable disease, which is not very informative for assessing a drug efficacy. Furthermore, our study reveals that most of the patients (79%) exhibit signs of antitumor activity, confirming the risk of discarding, at wrong, potentially responder patients and ultimately, potential active drugs.

It is expected that greater tumor shrinkage is correlated with outcome, though this link remains highly debated across tumor types (18–22). Other authors have recently described a correlation between change in tumor response by RECIST—taken as a continuous variable—with OS in the context of phase I trials (23). However, such results were not adjusted for the standard prognostic score (RMH), which has been shown to be highly prognostic for OS (17). Although this study confirmed that the RMH score was the only variable associated with OS, the decrease of TGR was the only independent variable associated with PFS. Additionally, we showed that the investigated regimen is the only variable associated with the decrease of TGR. These results underscore the importance of TGR profiles as a tool for evaluating the antitumor activity of the investigational regimens in phase I trials and for guiding the "go/no go" decision in the early drug development setting. Such findings are nevertheless limited by the retrospective nature of our analyses and warrant further validation.

The TGR assessment is feasible for most patients (79% patients enrolled) and requires minor additional costs, mainly imputable to the retrieval and analysis of the pretreatment imaging. Moreover, TGRs are simple to compute at bedside: web and smartphone applications even exist (e.g., CancerPal). We are releasing within this article a free TGR calculator web tool (http://www.gustaveroussy.fr/doc/tgr_calculator/index_en.html) to help oncologists and clinical researchers to ease its assessment.

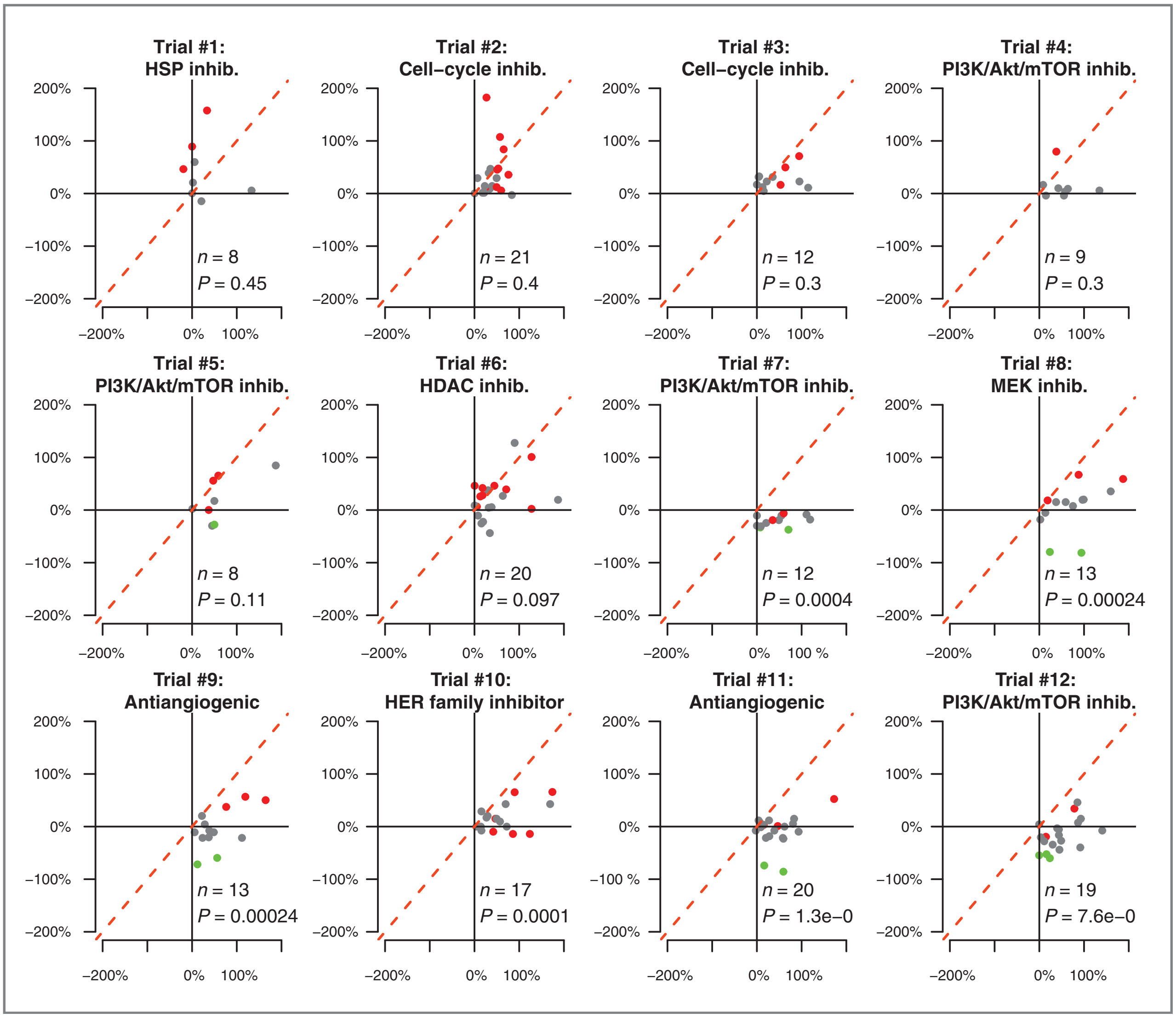

Figure 3. TGR profiling reveals specific patterns of antitumor activity across 12 phase I clinical trials (*P* values are computed from Wilcoxon pairwise tests; *n*, the number of samples with pairwise TGR information; only clinical trials with more than 7 patients were analyzed). Red, gray, and green colors indicate progressive disease, stable disease, and partial response as per RECIST criteria, respectively.

These practical considerations reinforce our belief that translating the TGR into the clinical research could substantially impact the decision-making process in phase I trials, by providing an earlier and precise evaluation of the drug activity of patients and by improving the evaluation of investigational new drugs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Ferté, C. Massard, R. Balheda, C.G. Roca, C. Dromain, J.-C. Soria
Development of methodology: C. Ferté, M. Fernandez, C. Massard, R. Balheda, C.G. Roca
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Ferté, M. Fernandez, A. Hollebecque, C. Massard, R. Balheda, C.G. Roca, C. Dromain, S. Ammari
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Ferté, S. Koscielny, C. Massard, R. Balheda, B.M. Bot, J.-C. Soria
Writing, review, and/or revision of the manuscript: C. Ferté, M. Fernandez, A. Hollebecque, S. Koscielny, A. Levy, C. Massard, R. Balheda, B.M. Bot, C.G. Roca, J.-C. Soria
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Ferté, M. Fernandez, C. Massard, R. Balheda, B.M. Bot, C. Dromain
Study supervision: C. Ferté, S. Koscielny, C. Massard, R. Balheda, C.G. Roca

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