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Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms
A Meta-analysis

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IMPORTANCE The impact of a biomarker-based (personalized) cancer treatment strategy in the setting of phase 1 clinical trials was analyzed.

OBJECTIVE To compare patient outcomes in phase 1 studies that used a biomarker selection strategy with those that did not.

DATA SOURCES PubMed search of phase 1 cancer drug trials (January 1, 2011, through December 31, 2013).

STUDY SELECTION Studies included trials that evaluated single agents, and reported efficacy end points (at least response rate [RR]).

DATA EXTRACTION AND SYNTHESIS Data were extracted independently by 2 investigators.

MAIN OUTCOMES AND MEASURES Response rate and progression-free survival (PFS) were compared for arms that used a personalized strategy (biomarker selection) vs those that did not. Overall survival was not analyzed owing to insufficient data.

RESULTS A total of 346 studies published in the designated 3-year time period were included in the analysis. Multivariable analysis (meta-regression and weighted multiple regression models) demonstrated that the personalized approach independently correlated with a significantly higher median RR (30.6% [95% CI, 25.0%-36.9%] vs 4.9% [95% CI, 4.2%-5.7%]; $P < .001$) and a longer median PFS (5.7 [95% CI, 2.6-13.8] vs 2.95 [95% CI, 2.3-3.7] months; $P < .001$). Targeted therapy arms that used a biomarker-based selection strategy (n = 57 trials) were associated with statistically improved RR compared with targeted therapy arms (n = 177 arms) that did not (31.1% [95% CI, 25.4%-37.4%] vs 5.1% [95% CI, 4.3%-6.0%]; $P < .001$). Nonpersonalized targeted arms had outcomes comparable with those that tested a cytotoxic agent (median RR, 5.1% [95% CI, 4.3%-6.0%] vs 4.7% [95% CI, 3.6%-6.2%]; $P = .63$; respectively; median PFS, 3.3 [95% CI, 2.6-4.0] months vs 2.5 [95% CI, 2.0-3.7] months; $P = .22$). Personalized arms using a "genomic (DNA) biomarker" had higher median RR than those using a "protein biomarker" (42.0% [95% CI, 33.7%-50.9%] vs 22.4% [95% CI, 15.6%-30.9%]; $P = .001$). The median treatment-related mortality was not statistically different for arms that used a personalized strategy vs not (1.89% [95% CI, 1.36%-2.61%] vs 2.27% [95% CI, 1.97%-2.62%]; $P = .31$).

CONCLUSIONS AND RELEVANCE In this meta-analysis, most phase 1 trials of targeted agents did not use a biomarker-based selection strategy. However, use of a biomarker-based approach was associated with significantly improved outcomes (RR and PFS). Response rates were significantly higher with genomic vs protein biomarkers. Studies that used targeted agents without a biomarker had negligible response rates.

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With the recent technologic advances in genomics and understanding of the mechanisms driving the development and progression of cancers, the use of drugs targeting anomalies identified in tumors from patients with cancer has become possible. Indeed, the main objective of "precision" or "personalized" medicine is to select patients (with a protein or genomic biomarker) who might benefit from a specific therapy.

In the past, most drugs were approved by the US Food and Drug Administration (FDA) without a biomarker to select patients likely to benefit, including most cytotoxic chemotherapies and some targeted agents. Currently, more and more targeted agents are in development and strategies to maximize their benefit by selecting patients are also being investigated. There are already successful examples of drugs approved by the FDA with a companion diagnostic test to identify a predictive biomarker, such as vemurafenib for *BRAF* V600E mutation in melanoma,[1] erlotinib for patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations,[2] or crizotinib for patients with metastatic non-small-cell lung cancer whose tumors are anaplastic lymphoma kinase–aberrant.[3] As a consequence of high response rates (RRs) with new paradigms for patient selection, some recent trials leading to FDA approval were nonrandomized, single-arms studies (eg, the recent approval of crizotinib for *ROS-1*-positive tumors in metastatic patients with non-small-cell lung cancer[4]). In addition, we can expect that selecting patients likely to benefit from a treatment might allow studies to be performed in smaller numbers of patients. As an example, in 2006 imatinib was approved as a single agent for the treatment of multiple conditions associated with Abl, Kit, or PDGFR protein tyrosine kinase abnormalities (dermatofibrosarcoma protuberans, myelodysplastic and/or myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome/chronic eosinophilic leukemia) with patient populations matched to drug ranging from 5 to 14 patients.[5,6] The extent to which this strategy is generalizable is the subject of the current analysis.

In this study, we focused our analysis on 346 studies of phase 1 clinical trials of cancer drugs published between January 2011 and December 2013. Phase 1 studies are designed to test a new drug or drug combination in a small group of patients to evaluate safety (through successive dose escalation steps) and to detect response signals (albeit traditionally as secondary end points).

Our goal was to compare patient outcomes between studies that used a personalized approach (selecting patients with a cognate biomarker) with those that did not in the early clinical trial setting.

Key Points

Question Does the use of a biomarker to select patients in phase 1 trials improve efficacy outcomes?

Findings The meta-analysis of 346 phase 1 trial including 13 203 patients found that using a biomarker-based selection strategy was associated with improved response rate (median, 30.6% vs 4.9%) and progression-free survival (median, 5.7 vs 2.95 months). Targeted arms that did not use a biomarker had median response rates comparable with those of the arms that tested a cytotoxic agent.

Meaning A biomarker-based (personalized) approach to phase 1 drug development is associated with improved outcomes, even in a refractory cancer population.

Methods

Search Strategy and Study Selection

A search was conducted using PubMed (http://www.ncbi.nlm.nih.gov/pubmed), using the word "cancer" in the search toolbar. "Clinical Trials, Phase 1," "Publication dates from January 1, 2011, to December 31, 2013," and studies in "Humans" were selected as additional filters. This 3-year period was chosen because we believed this period would include enough personalized and nonpersonalized trials. (The 3-year period was chosen before starting data extraction.) Studies describing combination treatments, supportive care, locoregional treatments, drugs targeting hormonal receptors, as well as cellular, viral, or vaccine therapy trials were excluded. Pediatric studies as well as clinical trials restricted to brain tumors were also excluded (penetrance of blood-brain barrier unknown). Whenever possible, if a study comprised both a biomarker-selected population and a nonselected group (eg, in the case of several histologies included but one had the cognate biomarker as disease characteristic), the data were extracted separately and categorized as personalized and nonpersonalized, respectively. This was the case for 5 studies. eFigure 2 in the Supplement depicts, in diagrammatic form, the study inclusion and/or exclusion steps and the full list of references can be found in the eReferences in the Supplement.

Data Extraction and Categorization

Data extraction was conducted independently by 2 investigators (M.S. and M.Z.) and categorization was validated in frequent meetings in the presence of the moderator (R.K.). To be included, the study had to describe a phase 1 cancer drug trial published between January 1, 2011, and December 31, 2013; evaluate a drug as a single agent; and report adequate efficacy end points (at least RR). All deaths reported by investigators as "possibly," "probably," or "definitely" related to treatment were considered toxicity-related deaths.

For assessment of the RRs, only complete and partial responses (CR and PR, respectively) were considered. Median progression-free survival (PFS) (or time-to treatment progression (TTP) if PFS was not reported) and overall survival (OS) were extracted, as well as their corresponding 95% CIs whenever available.

For the purpose of our analysis we defined personalized therapy when a treatment met one of the following criteria: (1) test for a cognate biomarker used for treatment selection or (2) no cognate biomarker used, but at least 50% of patients are known to harbor the cognate biomarker. Full details of definition for personalized vs nonpersonalized therapies can be found in the eMethods in the Supplement.

Statistical Analysis

We performed a meta-analysis using a random effects model,[7] as this model takes into account for both between and within study heterogeneity. We also performed a multivariable pooled analysis of the RR and PFS data using the weighted least-squares method to account for the size effects. Random effects meta-regression models (linear mixed model) were used to assess the relationship between the estimates and personalized therapy status, adjusted for other potential confounders and/or mediators, as appropriate. Note that the weighted least-squares method under the multivariable pooled analysis can address the potential small sample size bias (publication bias) better, while the random effects meta-regression model is more appropriate for dealing with the between study heterogeneity.[8,9] Both methods were applied such that the results can be compared to provide a robust inference. The data were stratified, and only the significant variables in univariable analysis were included in multivariable analysis (eg, meta-regressions). Nonsignificant covariates were dropped from the model, with the final model containing only significant covariates in the multivariable analyses. Assessment of continuous variables between independent samples was done using a Wilcoxon rank sum test. Two-sided $P \leq .05$ was considered statistically significant. Statistical analyses were performed and reviewed by M.S. and J.J.L. using SPSS software (version 22) and Comprehensive Meta-Analysis software (CMA; version 3). More details about the statistical analysis can be found in the eMethods in the Supplement.

Results

Search Results and Clinical Trial Characteristics

Our initial PubMed search identified 1854 results. After a careful review of the titles, only 440 studies met our selection criteria (described in the Methods section). A comprehensive reading of these 440 studies led to the exclusion of 94 additional studies, resulting in the inclusion of a total of 346 studies published in the designated 3-year time period (January 2011-December 2013) (eFigure 2 in the Supplement).

In total, 351 arms comprising 13 203 patients were included (including 5 studies that were dichotomized into 2 different arms, 1 of which used a biomarker-selection strategy and the other did not). There were 117 arms using a cytotoxic agent, and all except 1 of them were considered nonpersonalized. Conversely, 234 arms used a targeted agent, with 75.6% (177 of 234) being nonpersonalized and 24.4% (57 of 234) being personalized (eTable 1 in the Supplement). Fifty-eight arms were personalized and accrued a total of 2655 patients compared with 293 arms for trials using a nonpersonalized strategy (10 548 patients). Personalized and nonpersonalized arms both had a median number of 30 patients per arm.

In our data set, 184 of the 351 arms (52.4%) had an RR greater than 0% (167 studies had a 0% RR). In a multivariable analysis, the factors that correlated most significantly with an RR greater than 0% were (1) the use of a personalized strategy vs not (86.2% vs 45.7%; $P < .001$); (2) a higher number of patients included in the study (62.7% if more than 30 patients vs 42.9% if 30 or fewer; $P < .001$); and (3) if study drugs were FDA/European Medicines Agency (EMA) approved by the time of the current analysis (75% vs 45.3%; $P < .001$) (eTable2 in the Supplement).

Targeted Agents Subanalysis

Of note, while most of the personalized arms (98.3%) used targeted agents, the majority of the arms using targeted agents used a nonpersonalized approach, that is, they did not select patients using a cognate biomarker (76%). A subanalysis within targeted arms (n = 234 arms) showed that across both a pooled and meta-analysis, targeted arms using a personalized strategy had a statistically higher RR compared with targeted arms that lacked a personalized approach ($P < .001$) (see eTable 3 and eFigure 1A in the Supplement). In addition, personalized arms using targeted agents led, in 86% of cases, to a RR greater than 0% compared with only 49% in nonpersonalized arms using targeted agents ($P < .001$) (see eTable 3 in the Supplement). Of interest, nonpersonalized targeted arms had outcomes comparable with arms that tested a cytotoxic agent (median RR, 5.1% and 4.7%; $P = .63$; respectively; median PFS, 3.3 vs 2.5 months; $P = .22$).

Association of Personalized Therapy With Higher RRs

The meta-analysis demonstrated that the use of a personalized approach (n = 58 arms) led to a median RR of 31% vs 5% when a nonpersonalized strategy was used (n = 293 arms) ($P < .001$). The other variables that correlated with higher RR were hematologic malignant neoplasms vs solid tumors (21% vs 4%; $P < .001$), if the agent was FDA/EMA approved by the time of the current analysis (17% vs 5%; $P < .001$), or the use of a targeted drug (7.8% vs 4.7%; $P = .003$).

In a meta-regression analysis including the previously mentioned variables that were significant ($P \leq .05$), the use of a personalized approach correlated independently with a higher RR, and was the most significant covariable in the model (eTable 4 and eFigure 1B in the Supplement; **Figure 1**). Outliers of response have also been analyzed (eResults in the Supplement).

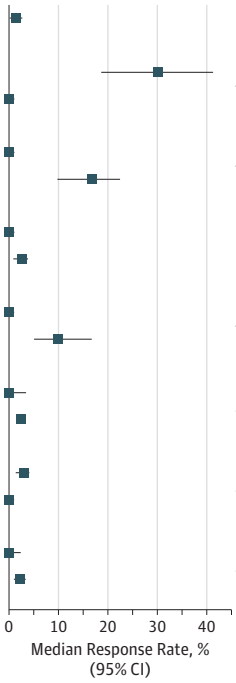
Personalized Therapy Subanalysis

We investigated if there was a difference in outcome when the biomarker was a protein (eg, protein overexpression) vs a genomic alteration. Across the meta-analysis and the pooled-analysis, median RRs were significantly higher (42% vs 22.4% [$P = .001$; meta-analysis]; 42% vs 18% [$P = .008$; pooled analysis]) if the biomarker was a genomic alteration (eTable 6 and eFigure 1C in the Supplement). Of note, the type of targeted drug (small molecule vs antibody) highly correlated with the type of biomarker used ($P < .001$). Indeed, 95% of the personalized studies that used a genomic biomarker (20 of 21 studies) tested a targeted small molecule. In comparison, 35% of the personalized trials that used a protein biomarker tested targeted small molecules (13 of 37 studies), while most tested antibodies (21 of 37 [56.8%]) (the 3 remaining studies were testing a recombinant protein, a nanoparticle, and a cytotoxic drug, respectively). Because only 1 trial with a genomic biomarker was applied to an antibody, a robust multivariate analysis was

Figure 1. Representation of the Response Rate

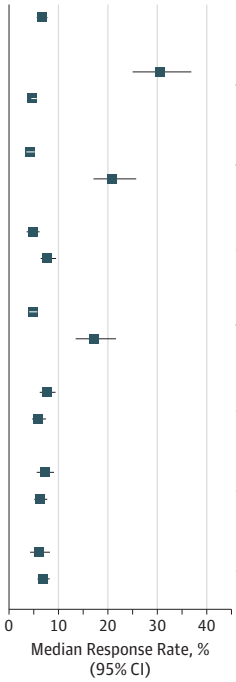
A Response rate (pooled analysis)

Variable	No. of Arms	Median Response Rate, % (95% CI)	*P* Value
Overall	351	1.40 (0.0-2.70)	
Used a personalized strategy			
Yes	58	30.0 (18.6-41.2)	<.001[a]
No	293	0.0 (0.0-1.08)	
Tumor type			
Solid	272	0.0 (0.0-1.15)	<.001[a]
Hematologic	79	16.7 (9.68-22.35)	
Agent class			
Cytotoxic	117	0.0 (0.0-0.98)	.001
Targeted	234	2.5 (1.04-3.80)	
FDA/EMA approved			
No	267	0.0 (0.0-1.08)	<.001[a]
Yes	84	10.0 (5.05-16.70)	
No. of patients per arm			
≤30	182	0.0 (0.0-3.45)	.02
>30	169	2.5 (1.50-3.13)	
Administration route			
Oral	162	2.97 (1.40-4.0)	.007
Systemic	189	0.0 (0.0-1.13)	
No. of treating centers			
Single center	91	0.0 (0.0-2.40)	.04
Multiple centers	260	2.34 (0.98-3.20)	



B Response rate (meta-analysis)

Variable	No. of Arms	Median Response Rate, % (95% CI)	*P* Value
Overall	351	6.56 (5.57-7.72)	
Used a personalized strategy			
Yes	58	30.62 (25.0-36.90)	<.001[a]
No	293	4.89 (4.22-5.66)	
Tumor type			
Solid	272	4.25 (3.48-5.19)	<.001[a]
Hematologic	79	21.02 (17.0-25.71)	
Agent class			
Cytotoxic	117	4.72 (3.60-6.17)	.003
Targeted	234	7.84 (6.46-9.49)	
FDA/EMA approved			
No	267	4.83 (4.04-5.76)	<.001[a]
Yes	84	17.27 (13.60-21.69)	
No. of patients per arm			
≤30	182	7.67 (6.20-9.45)	.11
>30	169	5.94 (4.70-7.48)	
Administration route			
Oral	162	7.23 (5.68-9.16)	.41
Systemic	189	6.32 (5.13-7.76)	
No. of treating centers			
Single center	91	6.0 (4.3-8.2)	.48
Multiple centers	260	6.8 (5.7-8.2)	



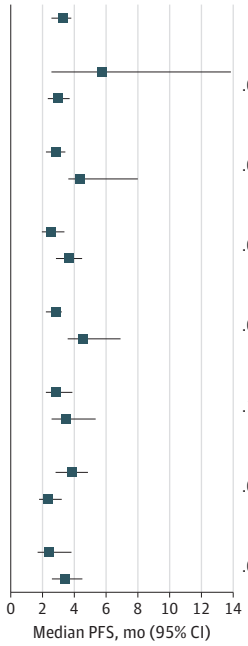
A, Response rate, pooled analysis. B, Response rate, meta-analysis.

[a] These remained significant in the multivariable analysis. Wilcoxon tests were performed for panel A; *P* values for panel B were computed using a mixed-effect analysis model. See also eTables 4 and 5 in the Supplement.

not possible. However, the median RR for the 20 studies of small molecules with a genomic biomarker was 41.4%, while that for the 13 studies of small molecules with a protein biomarker was 25% ($P = .05$), suggesting that genomic biomarkers had a more significant correlation with salutary effects.

Figure 2. Representation of Progression-Free Survival (PFS)

Variable	No. of Arms	Median PFS, mo (95% CI)	P Value
Overall	45	3.23 (2.56-3.80)	
Used a personalized strategy			
Yes	7	5.70 (2.56-13.78)	.049[a]
No	38	2.95 (2.30-3.70)	
Tumor type			
Solid	35	2.80 (2.24-3.43)	.002[a]
Hematologic	10	4.30 (3.62-8.0)	
Agent class			
Cytotoxic	15	2.50 (2.0-3.36)	.09
Targeted	30	3.64 (2.83-4.43)	
FDA/EMA approved			
No	29	2.80 (2.20-3.23)	.007
Yes	16	4.51 (3.57-6.90)	
No. of patients per arm			
≤30	27	2.87 (2.10-3.80)	.13
>30	18	3.47 (2.56-5.31)	
Administration route			
Oral	29	3.80 (2.87-4.84)	.004
Systemic	16	2.34 (1.80-3.23)	
No. of treating centers			
Single center	11	2.40 (1.70-3.80)	.055
Multiple centers	34	3.44 (2.60-4.47)	



P values are for univariable analysis (Wilcoxon test).

[a] These remained significant in the multivariable analysis. See also eTables 4 and 5 in the Supplement.

Association of Personalized Therapy With Longer PFS

We performed a pooled analysis including all the studies that reported a median PFS (n = 45 studies). The following factors were significantly correlated with a longer PFS: (1) the use of a personalized strategy (5.70 vs 2.95 months); (2) hematologic malignant neoplasms vs solid tumors (4.30 vs 2.80 months); (3) drugs that were FDA/EMA approved by the time of the current analysis (4.51 vs 2.80 months), and (4) orally administered agents vs injectables (3.80 vs 2.34 months), all with $P < .05$. In the multivariable analysis (multiple linear regression using a weighted least-squares model), only a personalized strategy and hematologic tumors remained independent predictors of a longer PFS, with $P < .001$ and $P = .02$, respectively (eTable 5, eFigures 1D and 2C in the Supplement; **Figure 2**).

Survival Analysis

Survival were not analyzed owing to insufficient data (data were provided in only 27 of 346 studies [n = 4 were personalized studies]).

Outcome Subanalysis

Stratification by Tumor Type—Solid Tumors vs Hematologic Malignant Neoplasms

We conducted a subanalysis stratifying the studies performed in solid (n = 272) and hematologic malignant neoplasms (n = 79) because this variable significantly correlated with both the RR and PFS. In the meta-analysis, the use of a personalized approach was associated with higher RR in trials investigating solid tumors (24.5% vs 4.5% for a nonpersonalized strategy; $P < .001$). Trials investigating hematologic tumors using a personalized strategy achieved a 24.5% RR vs 13.5% for those that were not personalized; $P < .001$. The pooled analysis also showed a benefit from the use of a personalized therapy, with $P < .001$ (see eTable 7 in the Supplement).

For the PFS analysis, in both solid and hematologic tumors, trials using a personalized approach reached longer PFS (4.1 vs 2.8 months in solid tumors; 13.6 vs 4.0 months in hematologic tumors) although the difference was not statistically significant (see eTable 7 in the Supplement).

Stratification by FDA/EMA Approval

For the RR analysis, 84 studies tested drugs that were approved by regulatory agencies compared with 267 not approved at the time of our analysis. In the meta-analysis and within studies that used an agent later approved by the FDA/EMA, personalized trials achieved a 50% RR vs 8.8% for those that did not ($P < .001$). Among studies that used agents not currently FDA/EMA approved, personalized trials reached a 16.5% RR vs 4.2% ($P < .001$). Comparable results were obtained in the pooled analysis (see eTable 8 in the Supplement). The list of agents and classification can be found in eTable 9 in the Supplement.

For the PFS analysis, within the 16 studies of drugs that have been approved (and had a median PFS reported), personalized trials had a median PFS of 9.7 months vs 3.8 for nonpersonalized trials ($P = .04$) (see eTable 8 in the Supplement).

Mortality Rate Analysis

Results from a meta-analysis established that median treatment-related mortality rate was 1.89% (95% CI, 1.36%-2.61%) for arms that used a personalized strategy vs 2.27% (95% CI, 1.97%-2.62%) for nonpersonalized arms, which was not

statistically different (P = .31). Another meta-analysis concluded that there was no statistical difference between arms that used a cytotoxic agent vs a targeted agent (2.4% [95% CI, 1.9-3.0] vs 2.1% [95% CI, 1.8-2.5]; P = .38).

Discussion

We performed a comprehensive meta-analysis as well as a weighted pooled analysis of phase 1 studies testing single agents within a 3-year period. To our knowledge, this is the largest analysis of its type of phase 1 trials, including 346 trials for a total of 13 203 patients. In our analyses of both RR and PFS, the use of a personalized strategy was the variable that correlated best with significantly improved outcomes in multivariable analysis. In addition, we showed that, within personalized studies, the nature of the biomarker used for patient selection had importance, because patient selection using genomic biomarkers (eg, mutation and/or amplification) was associated with a higher RR than "protein" biomarkers (eg, protein overexpression), with in the meta-analysis. Importantly, targeted agents were not by themselves more effective than cytotoxic agents. Indeed, the median RR for targeted agents developed without a biomarker was only 5.1%, which was comparable with the 4.7% RR for cytotoxic agents. However, biomarker-driven phase 1 trials of targeted agents demonstrated significantly higher median RR of 31.1% (eTable 3 and eFigure 1A in the Supplement). Of interest in this regard, a meta-analysis performed on phase 2 studies demonstrated that targeted drugs used without biomarker selection had significantly poorer outcomes than cytotoxic agents, with a median RR of 4% vs 11.9%, respectively; median PFS of 2.6 vs 3.3 months, respectively (P < .001 for all comparisons); and median OS of 8.7 vs 9.4 months (P < .05).[10] Taken together, these data suggest that the poorest outcomes are associated with the use of targeted agents in a nonpersonalized strategy, while targeted personalized therapy correlated with the best outcomes. Consistent with our results, this meta-analysis as well as one looking at clinical trials leading to FDA approval also concluded that a personalized approach consistently and independently correlated with higher median RR, prolonged median PFS and OS.[10,11] Personalized therapy was safe, as toxic death rates in personalized arms were no different from those in nonpersonalized arms (1.89% vs 2.27%; P = .31). It is interesting that in a previous meta-analysis of 32 149 patients on phase 2 studies,[10] personalized therapy was associated with lower rates of toxic deaths (1.52% vs 2.26%; P < .001).

Other interesting observations also emerged from this analysis. For instance, use of a genomic biomarker had more impact than use of a protein biomarker (median RR = 42% vs 22.4%; P = .001; meta-analysis). The superiority of genomic biomarkers has been reported previously.[10] Because of the direct relevance of proteins to function, it is plausible that, with time, the predictive power of protein markers will be refined. Indeed, with our knowledge and technology expanding, the simple 1-dimensional genomic drivers will soon be supplemented or replaced by multiple profiling tests, including proteomic biomarkers, which are driven by a multitude of genomic contributors.

Also intriguing is that superperformer and/or outlier trials with very high efficacy (RR ≥ 60%) were personalized in 8 of 9 cases, again emphasizing the importance or early biomarker development.

Conducting a meta-analysis using the random-effects model is the most appropriate method to analyze combined and heterogeneous results. While this was possible for the comparison of RRs (the number of responders and sample size were used to compute the analysis), it was not feasible for the PFS analysis because most of the arms reporting median PFS did not include their 95% CIs. For this reason, we also used a weighted pooled analysis for the multiple linear regressions models to account for effect size and potential confounders. Similar to the meta-regression models, the weighted linear regression analysis showed that personalized therapy was independently associated with increased RR and prolonged PFS.

Survival is, of course, a crucial end point for patients. Previous meta-analyses of phase 2 and 3 studies showed that survival was improved with the use of a biomarker-based strategy to select treatment.[10,11] For the phase 1 studies analyzed herein, survival could not be assessed, as it was reported in only a small minority of studies.

Our conclusion that selecting patients with a biomarker is associated with significantly improved outcomes is also consistent with those of several prior studies conducted in various tumors types.[12-20] Additional trials, such as NCI-MATCH and ASCO TAPUR, have recently been launched.[21-27] Even so, not all trials support this approach. SHIVA,[28,29] a randomized clinical trial, showed no benefit for a personalized strategy for treatment assignment. However, this trial may have been hampered by the large number of patients with advanced disease who were treated with single-agent hormone modulators or everolimus, both of which are strategies that have been shown not to work well in this setting.[29]

Because expedited approval pathways that can accelerate drug development often require demonstration of efficacy in early-phase trials, the application of personalized medicine (molecular tumor profiling for matched therapy) is increasingly seen in phase 1 studies.[30,31] Nevertheless, incorporating biomarkers in early-phase drug development has inherent challenges. For instance, because most advanced cancers have multiple genetic aberrations, the sensitivity to a targeted drug can be abrogated by secondary molecular alterations. In addition, the development of companion diagnostics can be expensive, and the value of single gene diagnostics in the era of multigene panels is a matter of debate.

There were several limitations relevant to the present study. First, we included only arms reporting single agents that were published over a limited 3-year period of time (2011-2013), and the omission of certain studies (eg, testing hormonal agents) and nonpublished study results could have lent some bias in favor of any of the variables. Second, we have to acknowledge that the variety of phase 1 study designs (eg, first in humans or not, dose escalation vs expansion) might have introduced heterogeneity in our data set. For instance, it is plausible that patients receiving lower doses during drug escala-

tion might have less robust responses. However, it should be noted that the effect of dose on response is not clear-cut in the era of targeted therapy.[32,33] For cytotoxic chemotherapy, where dose is known to correlate with response, RRs may have been underestimated for patients treated in the dose escalation part of the study.[34] Another limitation was that studies with combination therapy were not analyzed because they would have added an additional layer of difficult-to-dissect heterogeneity to our study. Also, trials with zero RRs typically did not report PFS, and in most studies reporting a PFS, 95% CIs were not available. Another intrinsic limitation arises from the fact that patient follow-up times may vary between trials, producing heterogeneity in the estimation of median PFS.[35] Finally, the low number of studies reporting OS (n = 27) was insufficient for us to analyze survival as an end point of our study.

Conclusions

Next-generation sequencing studies have provided better characterization of the molecular biology of cancer and allowed for analysis of tumor complexity, heterogeneity, progression, and resistance mechanisms.[36] Our study suggests that a biomarker-based selection of patients, even in the phase 1 setting, is associated with significantly better outcomes. On the other hand, treating patients with targeted agents without a biomarker selection strategy produces very low RRs in the early clinical trials setting. These results argue strongly for the enrichment of phase 1 clinical trials with biomarker selection for targeted therapies. However, rigid exclusion based on biomarkers that have not been proven clinically could prove counterproductive in some cases.

ARTICLE INFORMATION

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