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Cancer Therapy: Clinical

Clinical Cancer Research

Patients with Advanced Head and Neck Cancers Have Similar Progression-Free Survival on Phase I Trials and Their Last Food and Drug Administration–Approved Treatment

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Abstract

Purpose: To compare clinical outcomes of metastatic head and neck cancer patients treated in phase I clinical trials with clinical outcomes of those patients who had their last Food and Drug Administration (FDA)–approved therapy in the setting of metastatic disease.

Experimental Design: We retrospectively reviewed the outcomes of 61 consecutive patients with head and neck tumors treated in 36 phase I trials at The University of Texas M.D. Anderson Cancer Center between July 2004 and September 2009.

Results: The most common histology was head and neck squamous cell carcinoma (62%). Median age was 55 years (range, 26-80). Eastern Cooperative Oncology Group performance status was 0 to 1 for 95% of patients. Fifty-nine patients had received FDA-approved drugs as the backbone of their last systemic therapy before inclusion in phase I trials (median, 2 systemic therapies). Progression-free survival (PFS) on phase I trials was not inferior to PFS on their last FDA-approved therapies (12 versus 10.7 weeks, log-rank $P = 0.87$). Fifty-three patients were evaluable for response by Response Evaluation Criteria in Solid Tumors criteria. Four (7%) had partial responses and 16 (26%) had stable disease for ≥4 months. In univariate analysis, number of metastatic sites, lactate dehydrogenase (LDH) levels at baseline, and Royal Marsden Hospital prognosis scores were significant predictors of survival. Only LDH was significant in multivariate analysis (hazard ratio, 6.35; $P \leq 0.0001$).

Conclusions: For patients with heavily pretreated advanced head and neck tumors, PFS on phase I trials is not inferior to PFS with their last FDA-approved therapy. The only significant predictor of survival in the multivariate analysis was baseline LDH. *Clin Cancer Res; 16(15); 4031–7. ©2010 AACR.*

The goals of phase I clinical trials are to identify the maximum tolerated dose of investigational drugs for future phase II studies and to define their safety profiles and pharmacokinetic properties. Critics cite the lack of benefit for patients enrolled in them (1, 2). Studies show that as many as 20% of patients enrolled in phase I trials die within 90 days of study entry, although most of these deaths are due to progressive disease, whereas drug-related mortality is <0.5% (3–5). Clinical benefit from these trials is likely to increase when patient selection is refined so that patients with specific biomarkers are fitted to trials with therapies aimed at those targets. Poor performance status is cited by others as one of the reasons for lack of benefit of these trials (6). In this regard, a prospective study has validated the Royal Marsden Hospital (RMH) prognosis score for patient selection in an attempt to improve this process (7). Other critics have pointed to the culpability of low doses of the agents used for treatment in the lack of efficacy of phase I trials. However, we and others recently showed that patients on low doses do not fare worse than those enrolled in high-dose cohorts (8, 9). Another focus to improve patient selection has been to identify the optimal biological dose of a given therapy for target modulation rather than maximum tolerated dose as an end point with the goal of improving clinical outcome (10).

Our study retrospectively reviewed patients with head and neck tumors treated in the Phase I Clinic at The University of Texas M.D. Anderson Cancer Center. We compared clinical outcome in these trials with that achieved using previous standard Food and Drug Administration (FDA)–approved therapies, and we tested the predictive value of the RMH prognosis score in that context.

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Translational Relevance

Phase I trials were traditionally considered dose-finding studies and patients enrolled in them were rarely expected to derive benefit. This concept is quickly evolving as identification of druggable targets [EML4-ALK and poly(ADP-ribose) polymerase] and therapies directed to these targets have resulted in significant tumor responses in patients treated with them. This success will likely increase the numbers of patients with refractory tumors referred for evaluation in phase I trials. Here, we show that the clinical outcomes in phase I trials were not inferior to outcomes on Food and Drug Administration–approved therapies for patients with advanced head and neck cancers, and we expect that this will increase enrollment of these patients in phase I clinical trials.

Materials and Methods

Patients

We retrospectively reviewed clinical outcomes of 61 consecutive patients with head and neck cancers that were treated in the Phase I Clinic at M.D. Anderson from July 2004 to September 2009. Data were collected from all transcribed notes and radiology reports in the electronic database of these patients. Patient records were reviewed for history, laboratory, and clinical findings at the time of presentation in the Phase I Clinical Trials Program, treatment, and clinical outcomes. Pathology was reviewed by an M.D. Anderson pathologist in all cases. Regimens varied over time and according to protocol availability during the time the patients were seen.

All patients had progressed on systemic therapy for metastatic disease. We collected baseline characteristics that included age, gender, tumor histology, Eastern Cooperative Oncology Group (ECOG) performance status, number of prior systemic therapies for metastatic disease, number of metastatic sites and location of metastatic disease, hemoglobin (g/dL), lactate dehydrogenase (LDH; IU/L), platelets (K/μL), albumin (g/L), progression-free survival (PFS) while on last FDA-approved treatment before inclusion in phase I trial, date of initiation and progression to phase I therapy, best response to this therapy based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and date of death or date lost to follow-up. All studies were done in accordance with M.D. Anderson Institutional Review Board guidelines.

Statistical analyses

Patient characteristics were summarized using median (range) for continuous variables and frequency (percentage) for categorical variables. To test the RMH prognostic score, we classified patients according to these three variables: LDH normal (0) versus LDH >ULN (upper limit of normal; +1), albumin >3.5g/dL (0) versus albumin <3.5g/dL (+1), and number of metastatic sites of disease ≤2 (0) versus >2 (+1; ref. 7). Patients were subclassified into good (RMH score 0-1) or poor-prognosis groups (RMH

Table 1. Patients characteristics

Characteristic	*n* (%)
Gender	
Male	51 (84%)
Female	10 (6%)
Age (y)	
Median	55
Range	26-80
ECOG performance status	
0-1	58 (95%)
2-3	3 (5%)
No. prior chemotherapy for metastatic disease	
Median	2
Range	1-8
1-2	42 (69%)
≥3	19 (31%)
No. metastatic sites	
Median	3
Range	1-6
1-2	31 (51%)
≥3	30 (49%)
Metastatic sites	
Lymph nodes	31 (51%)
Liver	11 (18%)
Lung	43 (70%)
Bone	29 (48%)
Brain	8 (13%)
Baseline albumin (g/dL)	
Median	4
Range	3-4.9
<3.5	4 (7%)
≥3.5	57 (93%)
Baseline hemoglobin (g/dL)	
Median	12.6
Range	9-16.2
<10.5	8 (13%)
≥10.5	53 (87%)
Baseline LDH (U/dL)	
Median	480
Range	270-4,660
Normal LDH	17 (28%)
Elevated LDH	44 (72%)
Tumor histology	
HNSCC	38 (62%)
ACC	12 (20%)
Other	11 (18%)
RMH prognostic score	
Good (0-1)	48 (79%)
Poor (2-3)	13 (21%)

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Table 2. Phase I trials

Phase I	No. patients	Drug
Mixed (cytotoxic + targeted)	11	DVG, TTV, TAS-106/CBDCA, AZA/VPA/CBDCA, DBT, XL-147/CBDCA/paclitaxel, CBDCA/paclitaxel/temsirolimus
Multityrosine kinase inhibitor	7	R04612910, tipifarnib/sorafenib, BMS-690514, BAY73-4506
Microtubule inhibitors	6	ANG-1005, MPC6827, MST-997
mTOR inhibitor	6	BEV/temsirolimus
Proteasome inhibitor	6	NPI, bortezomib/BEV
Antiangiogenics	4	BEV/VPA, BEV/AZD2171, PX-478
Cytotoxics	3	PBI-05204, EZN-2208
Hypomethylating agents	3	Azacytidine/VPA, decitabine
MEK inhibitor	3	AZD8330
PI3K inhibitor	2	PX-866, XL-184
Cell cycle	2	R04584820
HDAC inhibitors	1	PX-101
HSP90 inhibitors	1	BIIB-028
IGF-IR	1	R0485696
Organic arsenic	1	ZIO-101
Proapoptotic	1	AMG-655
Farnesyl transferase inhibitor	1	FTS
IFN based	1	Immunologic
Src inhibitor	1	Dasatinib
Total	61	

Abbreviations: BEV, bevacizumab; DBT, Doxil, bevacizumab, temsirolimus; DVG, Doxil, Velcade, gemcitabine; HDAC, histone deacetylase; HSP90, heat shock proteins; IGF-IR, insulin-like growth factor-I receptor; TTV, topotecan, Torisel, Velcade; VPA, valproic acid; PI3K, phosphatidylinositol 3-kinase; MEK, mitogen-activated protein/extracellular signal-regulated kinase kinase.

score 2-3) after summing the value for each variable. The probabilities of overall survival (OS) and PFS were estimated using the method of Kaplan and Meier (11). OS and PFS were defined as date from start of therapy (last FDA-approved therapy or initial phase I trial) until date of death or progression, respectively. Patients who were alive or free from disease progression at the time this analysis was conducted were censored on that date. Log-rank test was used to compare OS or PFS among subgroups of patients (12). Univariate and multivariate Cox proportional hazards models were fit to assess the association between patient characteristics and clinical outcomes (13). A P value of <0.05 was considered significant for the purpose of all statistical analyses. All statistical analyses were conducted in SAS version 9.1 (SAS Institute, Inc.) and SPSS (version 17.0; SPSS).

Results

Patient characteristics

A total of 61 patients with head and neck cancers who participated in an M.D. Anderson phase I clinical trial were included in this retrospective review. There were 51 men (84%). The most common histology was head and neck squamous cell carcinoma (HNSCC; $n = 38$, 62%), followed by adenocystic carcinoma (ACC; $n = 12$, 20%) and other histologies ($n = 11$, 18%) including acinic carcinoma, adenocarcinoma, myoepithelial gland carcinoma, pleomorphic adenoma, ductal adenocarcinoma, and mucoepidermoid carcinoma. The median age was 55 years (range, 26-80 years). The baseline characteristics of these patients are summarized in Table 1.

Therapy before patient inclusion in phase I trials

Overall, patients had a median of two prior systemic therapies for metastatic disease before inclusion in phase I trials (range, 1-8). Fifty-nine patients received treatments based on FDA-approved drugs as their last chemotherapy before inclusion in phase I trials. The standard treatment for relapsed squamous head and neck cancer based on the National Comprehensive Cancer Network guidelines may include platinum-based combinations or single agents including platinums, anti–epidermal growth factor receptor therapies, taxanes, ifosfamide, or gemcitabine (14). In our retrospective review of FDA-approved treatments, 34% of these patients received platinum-based combinations as their last FDA-based therapy before phase I treatment, 42% received anti–epidermal growth factor receptor therapies, 7% received taxanes, 3% received other cytotoxics including ifosfamide or gemcitabine, and 14% received Alimta as part of an investigational protocol for HNSCC. Thus, the last systemic treatment for all patients before

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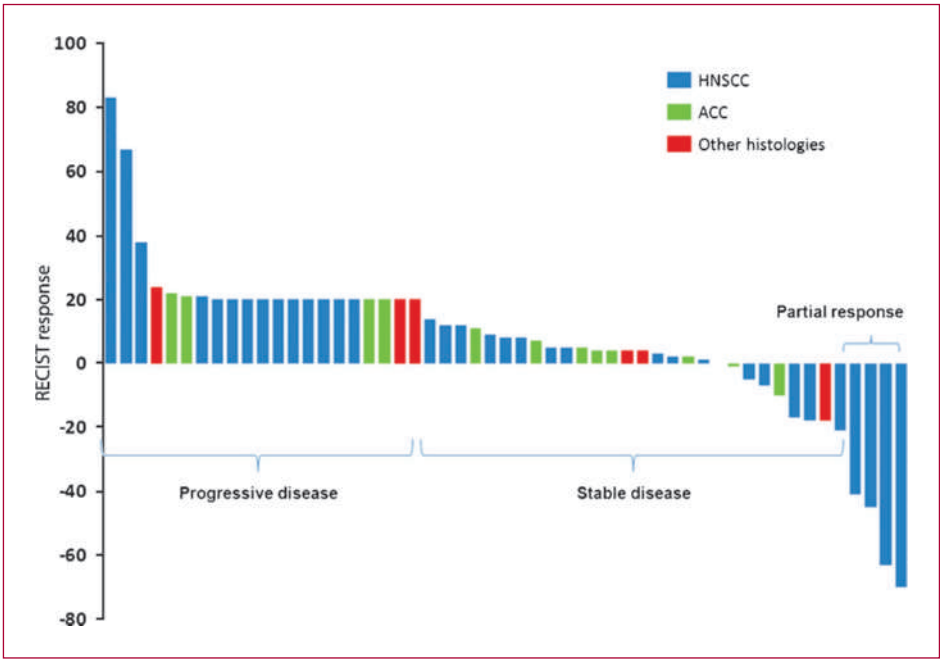

Fig. 1. RECIST response in 53 evaluable patients.

inclusion in phase I trials included a combination of drugs in which the backbone of therapy was an FDA-approved drug. Most importantly, in 86% of the patients, the treatment was based in drugs with a proven role in squamous cell cancer of the head and neck. For histologies other than HNSCC, there is no standard of care in the setting of metastatic disease, so the current recommendation by National Comprehensive Cancer Network guidelines is referral to a clinical trial. Details on last therapy before inclusion in phase I trials are summarized on Supplementary Table S1

Phase I trials

Of the 61 patients, 11 were included in phase I trials combining classic cytotoxics with targeted agents, 7 were included in trials with multityrosine kinase inhibitors, 6 were in phase I trials with mammalian target of rapamycin (mTOR) inhibitors, 6 were in trials with microtubule inhibitors, and 6 patients were included in trials with proteasome inhibitors. Overall, 28 patients (47%) were treated with a first-in-human drug. The phase I treatments of these 36 patients and the remaining 25 patients are summarized in Table 2.

Clinical outcomes

Among the 61 patients included in the analysis, 59 patients had received treatment based on FDA-approved drugs as their last therapy for metastatic disease before enrollment in phase I trials. Among these 59 patients, 34 (58%) had died at the time of analysis. The 90-day mortality rate was 21% and treatment-related mortality rate was 1.7% (1 of 59 patients). After a median follow-up of 50 weeks (range, 2.4-203 weeks), the median OS for the entire population was 30.8 weeks [95% confidence interval (CI), 14-47.6]. The median survival for patients with HNSCC was 27 weeks (95% CI, 18.6-45.4 weeks), and for patients with ACC, it was 93.1 weeks (95% CI, 42.8-203.0 weeks). Fifty-three patients were evaluable for response per RECIST criteria (Fig. 1). The remaining 6 patients were not evaluable because of suicide (n = 1), off study due to infection and declining ECOG performance status before restaging (n = 3), no measurable disease (n = 1), and new-onset pleural effusion (n = 1). Four patients (7%) had partial responses and 34 (58%) had stable disease. Sixteen patients (26%) had stable disease for >4 months.

We conducted univariate analysis to examine the effect on survival of variables including number of prior chemotherapies for metastatic disease, number of metastatic sites of disease, LDH baseline levels, and RMH prognostic score. The number of metastatic sites (1-2 versus ≥3), LDH levels (<ULN versus ≥ULN), and RMH prognostic score (good versus poor) were significant predictors of survival in the univariate analyses. Median OS in patients with ≤2 sites of metastatic disease was 69.7 weeks (95% CI, 27.0-203.0 weeks) versus 25.7 weeks (95% CI, 12.0-51.7; P = 0.03, log-rank test) in those with 3 or more sites of metastatic disease. Patients whose LDH levels were within normal limits (≤618 units/L) had a median OS of 61.7 weeks (95% CI, 29.7-203 weeks), whereas OS for patients with LDH above the ULN was 12 weeks (95% CI, 6.4-22.6 weeks; P = 0.0001, log-rank test). Patients with a good RMH prognosis score also had a longer survival in the univariate analyses (median, 51.7 weeks versus 9.6 weeks

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between good and poor RMH scores; $P < 0.0001$). Next, we analyzed whether increasing values of RMH prognostic score predicted a shorter survival. Twenty-four patients had a score of 0, 22 patients had a score of 1, 12 patients had a score of 2, and only 1 patient had a score of 3. Median OS was gradually longer in patients with lower RMH prognosis score, and this was statistically significant [score 0; median OS, 93.1 weeks (95% CI, 29.3-203 weeks); score, 1; median OS, 38.4 weeks (95% CI, 22.6-61.7 weeks); score, 2 or 3; median OS, 9.6 weeks (95% CI, 6.4-21.7 weeks); $P < 0.0001$, log-rank test; Fig. 2].

In the multivariate analysis, LDH level at baseline [hazard ratio (HR), 6.35 for elevated versus normal LDH] was the only significant predictor of survival ($P \leq 0.0001$).

PFS for patients enrolled on phase I trials was not inferior to PFS while on last FDA-approved therapy

To test whether the clinical outcomes of patients with metastatic head and neck tumors enrolled on phase I trials were inferior to their clinical outcomes with the last therapy they received based on FDA-approved drugs, we conducted a log-rank analysis that compared PFS in both settings. We found that PFS while on phase I treatment was not inferior to PFS with the last FDA-approved drug (median PFS, 12 versus 10.7 weeks; log-rank $P = 0.87$; Fig. 3). We conducted the same type of analysis in the subset of patients with HNSCC and similarly found that for these specific population of patients, PFS while on phase I treatment was not inferior to PFS with the last FDA-approved drug (median PFS, 9.7 versus 9.3; log-rank $P = 0.43$; Supplementary Fig. S1). Therefore, for patients with metastatic head and neck cancers that have progressed after two lines of systemic therapy for metastatic disease, referral for evaluation of eligibility for phase I trials might be considered.

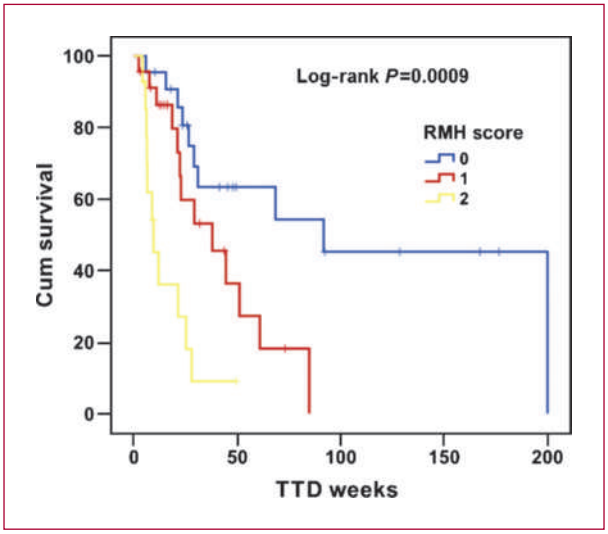

Fig. 2. Univariate survival analysis based on RMH prognostic score. Patients with good RMH prognosis score (defined by lower values of this score) had longer survival.

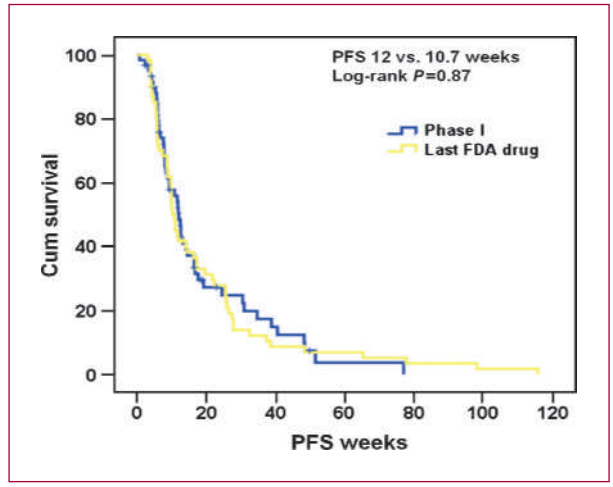

Fig. 3. The median PFS in phase I trials was not inferior to the median PFS on the last FDA-approved therapy.

Patients with stable disease or partial response while on phase I therapy had increased median OS

Next, we conducted survival analysis to examine whether RECIST response to phase I trials may predict survival of these patients. Patients with ACCs are frequently characterized by long periods of stable disease. To avoid confounding our results by including this subset of patients, we restricted the analysis to patients with HNSCCs. Of the 38 patients with HNSCCs, 36 had undergone restaging by RECIST criteria as previously explicated. We found that patients with stable disease or partial response per RECIST criteria had an increased median OS [stable disease or partial response: median OS, 44.42 weeks (95% CI, 26.0-62.8 weeks); progressive disease: median OS, 15.42 weeks (95% CI, 5.98-24.87 weeks); $P = 0.003$, log-rank test; Fig. 4].

Discussion

Whether or not there is clinical benefit for patients included in phase I trials continues to be a concern for many physicians, thus limiting referrals to and recruitment for such trials (15). Here, we show that the clinical outcomes of patients with advanced head and neck tumors that progressed on standard FDA-approved therapies were not inferior to the outcomes of the same patients on their last FDA-approved therapy. The median number of systemic therapies for metastatic disease that these patients had received before inclusion in phase I trials was two. In the absence of specific biomarkers of response, there was no difference for patients with refractory metastatic head and neck tumors being treated with standard versus experimental drugs.

The explosion of new technologies has led to the identification of unique genetic features in many tumor types (16, 17). A plethora of targeted therapies have entered clinical trials, although matching patients with targeted

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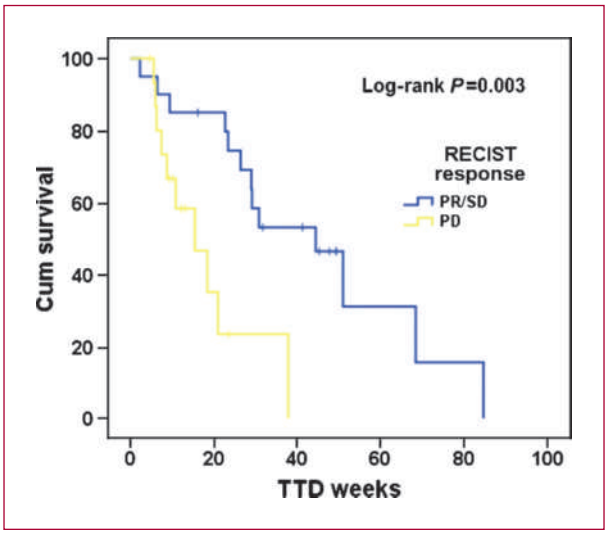

Fig. 4. Kaplan-Meier analysis based on RECIST response to phase I therapy. Patients with partial response (PR) or stable disease (SD) by RECIST criteria had a longer median OS compared with those who had progressive disease (PD) as their best response to phase I treatment.

therapies is complicated by the heterogeneity of various cancers. The genetic portrait of different tumor types has recently been elucidated. The finding that each cancer, on average, harbors >60 different mutations shows the complexity of this disease. There is a need to separate "mountains from hills" and identify driver as opposed to passenger mutations (18, 19). This would offer a myriad of therapeutic opportunities, possibly even in the setting of phase I trials (20). As an example of this targeted approach, a phase I trial with a B-Raf inhibitor showed a striking response rate of 60% in a subset of patients with metastatic melanoma, a disease for which no treatment had significantly increased survival (21). A similar strategy has proven to be successful in the treatment of patients with non–small cell lung cancer and ALK4 mutations (22). Our group recently presented data showing high response rates in patients with PIK3CA mutations enrolled on trials with phosphatidylinositol 3-kinase/Akt/mTOR inhibitors (23).

The phase I group at RMH recently developed a score that can be used to predict survival in patients with advanced cancer using baseline clinical and laboratory parameters including albumin, LDH, and number of metastatic sites of disease (7). In this study, we tested the predictive value of the RMH score in our patients. Although we found in univariate analyses that survival was longer for patients who had good RMH prognosis scores and that increasing values of RMH score gradually predicted for poorer survival, we were not able to validate this score in multivariate analyses. However, the relatively small number of patients in our study precludes carrying out a robust analysis. Our findings in multivariate analysis showed that the LDH value at baseline was the only significant predictor of survival for these patients.

In summary, the clinical outcomes for patients with head and neck tumors are not inferior to their outcomes with last standard FDA-approved treatment in a selected group of individuals with good performance status. The rate of stable disease for ≥4 months plus partial response was 33% in these individuals. Patients who achieved stable disease or a partial response had a superior OS to those with progressive disease. However, without a randomized study, it is unclear whether response influences survival or simply if responders were a group of patients who had better prognosis.

Future validation of prognostic scores to assist physicians in better selecting specific subgroups of patients who can benefit from novel therapies as well as the identification of rational therapeutic targets to target in the setting of phase I trials may further affect the outcomes of these patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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