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Original Article

Baseline Tumor Size as Prognostic Index in Patients With Advanced Solid Tumors Receiving Experimental Targeted Agents

Eleonora Nicolò[1,2,‡], Paolo Tarantino[1,2,3,4,‡], Oriana D'Ecclesiis[2], Gabriele Antonarelli[1,2], Luca Boscolo Bielo[1,2], Antonio Marra[1], Sara Gandini[2], Edoardo Crimini[1,2], Federica Giugliano[1,2], Paola Zagami[1,2], Chiara Corti[1,2], Dario Trapani[1], Stefania Morganti[1,2], Carmen Criscitiello[1,2], Marzia Locatelli[1], Carmen Belli[1], Angela Esposito[1], Ida Minchella[1], Massimo Cristofanilli[5], Sara M. Tolaney[3,4], Giuseppe Curigliano[*,1,2]

[1]Division of New Drugs and Early Drug Development, European Institute of Oncology, IRCCS, Milan, Italy
[2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[3]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA, USA
[4]Harvard Medical School, Boston, MA, USA
[5]Department of Medicine, Division of Hematology-Oncology, Weill Cornell Medicine, New York, NY, USA

[*]Corresponding author: Giuseppe Curigliano, MD PhD, Division of Early Drug development, Department of Oncology and Hemato-Oncology, University of Milano, European Institute of Oncology, IRCCS, 20141 Milano, Italy. Email: giuseppe.curigliano@ieo.it
[‡]Contributed equally.

Abstract

Background: Baseline tumor size (BTS) has been associated with outcomes in patients with cancer treated with immunotherapy. However, the prognostic impact of BTS on patients receiving targeted therapies (TTs) remains undetermined.

Methods: We reviewed data of patients with advanced solid tumors consecutively treated within early-phase clinical trials at our institution from 01/2014 to 04/2021. Treatments were categorized as immunotherapy-based or TT-based (biomarker-matched or not). BTS was calculated as the sum of RECIST1.1 baseline target lesions.

Results: A total of 444 patients were eligible; the median BTS was 69 mm (IQR 40-100). OS was significantly longer for patients with BTS lower versus higher than the median (16.6 vs. 8.2 months, $P < .001$), including among those receiving immunotherapy (12 vs. 7.5 months, $P = .005$). Among patients receiving TT, lower BTS was associated with longer PFS (4.7 vs. 3.1 months, $P = .002$) and OS (20.5 vs. 9.9 months, $P < .001$) as compared to high BTS. However, such association was only significant among patients receiving biomarker-matched TT, with longer PFS (6.2 vs. 3.3 months, $P < .001$) and OS (21.2 vs. 6.7 months, $P < .001$) in the low-BTS subgroup, despite a similar ORR (28% vs. 22%, $P = .57$). BTS was not prognostic among patients receiving unmatched TT, with similar PFS (3.7 vs. 4.4 months, $P = .30$), OS (19.3 vs. 11.8 months, $P = .20$), and ORR (33% vs. 28%, $P = .78$) in the 2 BTS groups. Multivariate analysis confirmed that BTS was independently associated with PFS ($P = .03$) and OS ($P < .001$) but not with ORR ($P = .11$).

Conclusions: Higher BTS is associated with worse survival outcomes among patients receiving biomarker-matched, but not biomarker-unmatched TT.

Key words: baseline tumor size; tumor burden; targeted therapy; biomarker; phase I trials; solid tumor.

Implications for Practice

Baseline tumor size (BTS) has been used as a surrogate marker of tumor burden and its prognostic value in patients with advanced solid tumors receiving immunotherapy is well established. Fewer data is available regarding its role in patients treated with targeted therapies (TTs). In this retrospective study, we found a significant association between BTS and outcomes among patients with advanced solid tumors receiving experimental TTs, but only when these agents were matched to a specific molecular biomarker. If validated, BTS could represent an accessible and promising biomarker for risk-adapted treatment decision-making in clinical practice. In addition, it could be a useful stratification factor in clinical trials testing novel anticancer drugs.

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Introduction

The extension of solid tumors at diagnosis, namely disease stage, has traditionally driven the choice of treatment (surgery, radiotherapy, and systemic therapy) of non-metastatic disease. In general, more intensive systemic treatments are preferred for larger tumors.[1-3] However, no such subdivision exists for tumors once they have spread to distant sites. With few exceptions, the intent of systemic therapy for metastatic solid tumors is palliative and is not based on the burden of disease.

In recent years, several studies have shown the relevant prognostic impact of baseline disease burden in patients with metastatic cancer. Most of the available evidence emerged with the use of immune-checkpoint inhibitors (ICIs) for the treatment of patients with advanced melanoma,[4] non-small-cell lung cancer (NSCLC),[5] and head and neck cancer.[6] For all these indications, ICIs showed more favorable treatment outcomes in patients with lower baseline disease burden, either assessed through computed tomography (CT) or through positron emission tomography (PET) scans. Additionally, our group has confirmed the prognostic role of CT-based baseline tumor burden among patients treated with next-generation immunotherapy agents within early-phase clinical trials, potentially highlighting the broad validity of this association among different tumor types.[7]

The prognostic role of baseline tumor burden among cancer patients treated with other treatment modalities remains instead undefined. Targeted therapies (TTs) are emerging as a highly effective treatment for multiple tumor types, with some showing efficacy even independently from the histological background.[8] Efforts are required to elucidate whether the prognostic value of tumor burden is specific to immunotherapy, or if it also applies to TT.

The main aim of the present retrospective study was to evaluate whether the baseline burden of disease measured by CT scan correlates with outcomes in patients with advanced solid tumors receiving experimental TT as part of early-phase clinical trials. Moreover, we aim to validate in a larger cohort our previous finding of the association between baseline tumor burden and outcome in cancer patients treated with novel immunotherapies.

Material and Methods

Study Population

We report a single-institution retrospective observational study. We identified all consecutive patients treated within early-phase clinical trials at the New Drugs and Early Drug Development for Innovative Therapies Division of the European Institute of Oncology (Milan, Italy), from January 2014 until April 2021. Data on baseline characteristics, type of therapy, response to treatment, and survival outcomes were collected from patient medical records. The study protocol was approved by the institutional review board and local ethics committee (approval number UID 3560) and was conducted in accordance with the Declaration of Helsinki.

Study Treatments

We included all patients with advanced solid tumors receiving at least one dose of experimental medications within an early-phase trial of immunotherapy or targeted agents. A detailed list of all experimental treatments' targets included, and their categorization is reported in Supplementary Table S1. Treatments were categorized as immunotherapy-based if any immune-oncology agent was included in the regimen, or TT-based if including a targeted agent, with or without chemotherapy. Thus, the regimen including both immunotherapy and TT were considered as immunotherapy-based. In this study, endocrine therapy-based treatments were included among TT. TTs were further divided into biomarker-matched if administered to patients based on the identification of a specific molecular biomarker, or biomarker-unmatched if not requiring any molecular feature.

Imaging Assessments

Baseline imaging assessments including CT scan of the chest, abdomen, and pelvis were performed within 28 days before treatment initiation, as per study protocol. Consistently with prior studies, in this study baseline tumor size (BTS) was used as a metric of baseline burden of cancer. BTS at the time of treatment initiation was calculated according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1,[9] ie, a maximum of 5 lesions and a maximum of 2 per organ. All image assessments were performed by radiologists from the European Institute of Oncology affiliated with the phase I facility. Patients could only be included in the study if having at least 1 RECIST-measurable lesion, at baseline. Patients were divided into 2 subgroups according to the median BTS value: greater than the median as the high group or lower and equal to the median as the low BTS group.

Statistical Analysis

Descriptive statistics were used to present patients and tumor characteristics. Data were presented as relative frequencies (percentage) or median and interquartile range (IQR) for continuous variables. BTS was analyzed as a categorical variable, considering the median and quartiles of the distribution. We investigated differences in terms of tumor objective response rate (ORR) and clinical benefit rates (CBRs) at 6 months using Mantel-Haenszel chi-square tests. Progression-free survival (PFS) was calculated from the first treatment cycle to disease progression or death (event), or last follow-up (censored). Overall survival (OS) was calculated from the first treatment cycle to death (event) or the last follow-up (censored). PFS and OS curves were estimated with the Kaplan-Meier method, and survival distributions were compared using the Log-Rank test. Factors found to be associated with PFS and OS in the univariate analyses were considered for the multivariate models. Multivariate Cox proportional hazard models were used to investigate the independent prognostic role of BTS, adjusting for other significant prognostic factors and confounders. Results are presented as hazard ratios (HRs) with 95% CIs. For all analyses, 2-tailed $P < .05$ was considered statistically significant. The statistical analyses were performed with R software, version 4.1.1.

Results

Patients Characteristics

Four hundred and forty-four patients were eligible and included in the analysis. The baseline clinical and pathological characteristics of the study population are reported in Table 1. The median age at the time of enrolment was 56 years (48-65 years), 328 (73.9%) patients were female, and the majority had a baseline Eastern Cooperative Oncology Group (ECOG)

Table 1. Baseline patients and disease characteristics by baseline tumor size

		Overall (*N* = 444)	BTS ≤ 69 mm (*N* = 211)	BTS > 69 mm (*N* = 210)	*P* value
Age, median (IQR)		56 (48-64.74)	54.5 (47.8-64.0)	56.3 (49.0-65)	.69
Sex, *n* (%)	Female	328 (73.9)	175 (82.9)	133 (63.3)	<.0001
	Male	116 (26.1)	36 (17.1)	77 (36.7)	
PS ECOG baseline, *n* (%)	0	280 (63.1)	145 (68.7)	117 (55.7)	.008
	1	163 (36.7)	66 (31.3)	93 (44.3)	
	2	1 (0.2)	-	-	
Primary tumor type, *n* (%)	Breast	216 (48.6)	130 (61.6)	71 (33.8)	<.001
	Head and Neck	17 (3.8)	11 (5.2)	6 (2.8)	
	Lung	41 (9.2)	15 (7.1)	25 (11.9)	
	Mesothelioma	12 (2.7)	5 (2.4)	7 (3.3)	
	Other	158 (35.5)	50 (23.7)	101 (48.1)	
Prior lines, median (IQR)		2 (1-3)	2 (1-3)	2 (1-3)	.05
Prior IO, *n* (%)	No	394 (88.7)	195 (92.4)	178 (84.8)	.02
	Yes	50 (11.3)	16 (7.6)	32 (15.2)	
	No	294 (66.2)	144 (68.2)	134 (63.8)	.39
Prior TT, *n* (%)	Yes	150 (33.8)	67 (31.7)	76 (36.2)	
	No	88 (19.8)	41 (19.4)	41 (19.5)	.99
Prior CT, *n* (%)	Yes	356 (80.2)	170 (80.6)	169 (80.5)	
	No	295 (66.4)	122 (57.8)	159 (75.7)	.0001
Prior ET, *n* (%)	Yes	149 (33.6)	89 (42.2)	51 (24.3)	
	TT	198 (44.4)	112 (53.1)	74 (35.2)	.0008
Experimental therapy, *n* (%)	IO	220 (49.3)	90 (42.6)	125 (59.5)	
	ADC	26 (5.8)	9 (4.3)	11 (5.2)	
Biomarker matched TT, *n* (%)	No	73 (37.4)	45 (40.2)	26 (35.1)	.59
	Yes	125 (62.6)	67 (59.8)	48 (64.9)	
Albumin, median (IQR)		4.1 (3.8-4.3)	4.2 (4.0-4.3)	4.0 (3.7-4.3)	.0003
LDH, median (IQR)		217 (176-315)	201 (166-246)	234 (189-385)	<.0001
NLR, median (IQR)		3.37 (2.33-5.21)	2.97 (2.03-4.9)	3.7 (2.7-5.6)	.0004
RMH score, *n* (%)	0-1	191 (70)	117 (81.8)	74 (57.8)	
	2-3	80 (30)	26 (18.2)	54 (42.2)	<.001

Abbreviations: BTS, baseline target sum; CT, chemotherapy; ET, endocrine therapy; IO, immunotherapy; LDH, lactate dehydrogenase; n, number; NLR, neutrophil/lymphocyte ratio; PS, performance status; TT, target therapy

performance status (PS) of 0 (63%). The most represented tumor types were breast (49%), lung (9%), melanoma (5%), gastric, colorectal, head/neck, and ovarian (4% each) carcinomas (Table 1; Supplementary Table S2). Median number of prior treatment lines for advanced disease was 2 (range: 1-3). Two hundred and twenty patients received an immunotherapy-based regimen (49%), 198 received a TT-based regimen (44%), 26 (6%) received an antibody drug-conjugate. TT-based regimens were biomarker-matched in 63% of patients treated with TT, with no significant difference between the two BTS subgroups. Median BTS was 69 mm (IQR 40-100); BTS by density plot and histogram is shown in Supplementary Fig. S1. Higher median BTS was observed in patients with ECOG PS 1 compared to ECOG PS 0 (*P* = .008). Albumin and lactate dehydrogenase (LDH) values at treatment initiation were available for 54.3% and 77% of the study population respectively. According to LDH, albumin and number of metastatic sites variables, patients were classified into a good prognosis group [Royal Marsden Hospital (RMH) prognostic score 0-1; *n* = 191] or a poor prognostic group (RMH score 2-3; *n* = 80). Higher BTS was significantly associated with lower albumin levels (*P* = .0003), higher LDH levels (*P* < .0001), higher neutrophil-to-lymphocyte ratio (NLR) (*P* = .0004), and poorer RMH prognostic score (*P* < .001) (Table 1). These factors were significantly associated with OS and PFS (Supplementary Table S3).

Impact of BTS on Outcomes in the Overall Population

The median follow-up was 11.7 months (range: 4.1-22.6 months). In the overall population, median OS (mOS) was 11.8 months, significantly longer for patients with low versus high BTS (16.6 vs. 8.2 months, *P* < .001). The 24-months OS was 40% for patients with low BTS compared to 18% for those with BTS > 69 mm (*P*-value log-rank <.0001). Similarly, PFS was significantly longer for patients with low versus high BTS (3.6 vs. 2 months, *P* = .0004). BTS was not significantly associated with disease progression at

6 weeks from treatment initiation (17.1% and 24.0% for BTS low and high respectively; $P = .10$). Figure 1 shows the Kaplan-Meier survival curves of PFS and OS in the overall population according to BTS. The association of BTS with OS remained statistically significant when considering only those patients receiving immunotherapy ($P = .005$) or those receiving targeted therapy ($P < .001$; Fig. 2). Even when considering BTS quartiles rather than the median, in the overall population we found an inverse association between mOS and BTS: 15.9 months, 16.6 months, 8.4 months, and 8.1 months with increasing quartiles ($P < .001$). A similar association was observed for mPFS: 3.9 months, 3.6 months, 2.2 months, and 1.9 months with increasing quartiles of BTS ($P = .003$). The association of BTS quartiles with OS and PFS remained statistically significant when evaluating patients receiving immunotherapy and targeted therapy as separate groups (Supplementary Fig. S2).

Among eligible patients, 415 were evaluable for response. The ORR was numerically higher among patients with low BTS (25% vs. 17%) however this difference was not statistically significant ($P = .06$). The CBR was significantly higher in the BTS-low subgroup (58%) compared to patients with high BTS (39%) ($P = .0001$; Supplementary Table S4). The same association with ORR ($P = .06$) and CBR ($P < .001$) was observed when considering BTS quartiles. In the overall population, factors associated with outcomes in the univariate model were tested in the multivariate analysis that confirmed that high BTS was independently associated with shorter OS (HR: 1.77, $P < .001$) and shorter PFS (HR: 1.27, $P = .03$), but not with ORR ($P = .11$; Table 2). When included in the model the RMH score, the association of BTS with OS remained significant ($P = .02$), whereas the significant association with PFS was lost (Supplementary Table S5).

Impact of BTS on Outcomes in Patients Receiving TT

Among patients receiving experimental TT, mOS was 16.5 months (11.37-20.02 months) and those with BTS > 69 mm had significantly shorter OS compared to the patients with lower BTS (mOS: 20.5 vs. 9.9 months, $P < .001$; Fig. 2A). Similarly, median PFS was significantly lower in patients with higher BTS compared to the BTS-low subgroup (4.7 vs. 3.1 months, $P = .002$; Supplementary Fig. S3). However, when patients were divided into 2 subgroups based on the type of targeted therapy (biomarker-matched and biomarker-unmatched) BTS was only found to be prognostic among patients receiving biomarker-matched TT. In this subgroup, mOS was 16.5 months and appeared significantly longer for patients with BTS ≤ 69 mm (21.2 months) compared to those with higher BTS (6.7 months, $P < .001$). Similarly, among these patients, BTS was significantly associated with PFS, with a mPFS of 6.2 versus 3.3 months in the BTS-low versus BTS-high respectively ($P = .009$). On the contrary, among patients receiving unmatched TT, outcomes did not significantly differ

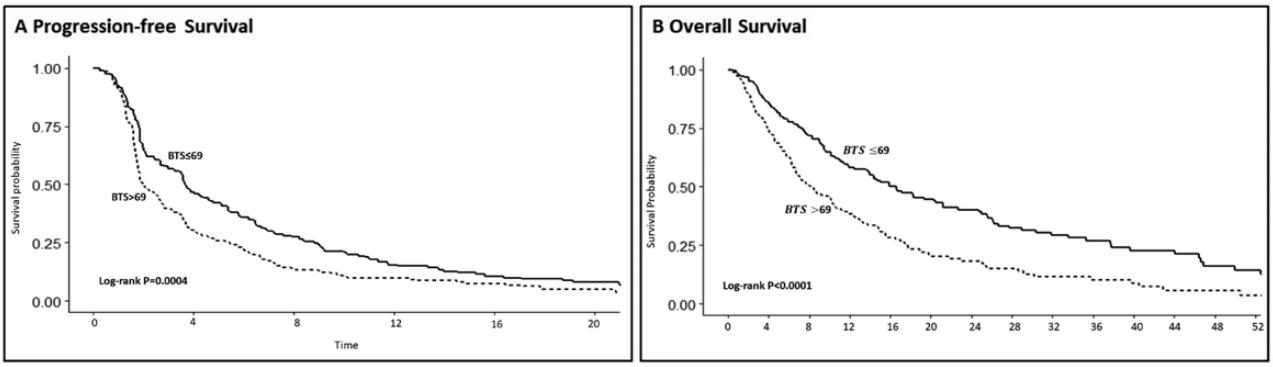

Figure 1. Kaplan-Meier analysis of progression-free survival ($N = 417$) and overall survival ($N = 416$) by baseline tumor size (BTS) in the overall population.

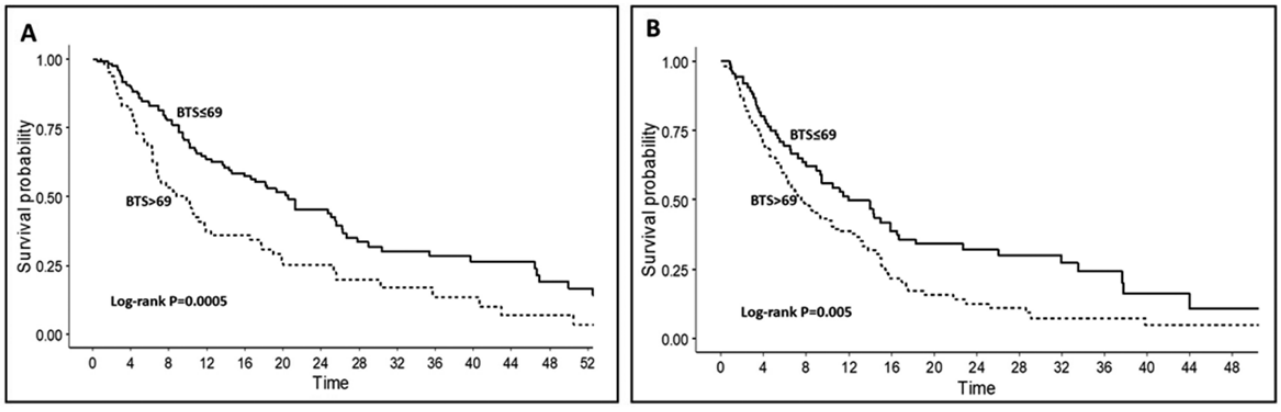

Figure 2. Kaplan-Meier analysis of overall survival by baseline tumor size (BTS) in patient receiving targeted therapy (**A**, $N = 203$) or immunotherapy (**B**, $N = 213$).

Table 2. Multivariate cox regression model for overall survival, progression-free survival, objective response rate, and clinical benefit rate

	HR (95% CI)	*P* value
Overall survival		
Tumor site		
Breast vs. other	1.15 (0.87-1.52)	.31
Experimental therapy		
TT vs. IO	0.74 (0.56-0.97)	.03
Baseline tumor size		
>69 vs. ≤69 mm	1.77 (1.38-2.27)	<.0001
PS ECOG baseline		
1 vs. 0	1.68 (1.31-2.14)	<.0001
Progression-free survival		
Tumor site		
Breast vs. other	1.93 (1.51-2.47)	<.0001
Experimental therapy		
TT vs. IO	0.58 (0.45-0.73)	<.0001
Baseline tumor size		
>69 vs. ≤69 mm	1.27 (1.02-1.60)	.034
Liver metastasis		
Yes vs. no	1.47 (1.17-1.84)	.0008
Soft tissue		
Yes vs. no	1.52 (1.15-2.01)	.003
NLR		
>3.37 vs. ≤3.37	1.42 (1.15-1.76)	.001
Prior lines		
>2 vs. ≤2	1.26 (1.01-1.58)	.04
	OR (95% CI)	***P* value**
Objective response rate		
Tumor site		
Breast vs. other	0.38 (0.21-0.69)	.0018
Experimental therapy		
TT vs. IO	4.56 (2.56-8.37)	<.0001
Baseline tumor size	0.64 (0.37-1.11)	.11
>69 vs. ≤69 mm		
Prior lines		
>2 vs. ≤2	0.39 (0.21-0.70)	.002
Clinical benefit rate		
Tumor site	0.33 (0.18-0.57)	.0001
Breast vs. other		
Experimental therapy		
TT vs. IO	6.69 (3.92-11.82)	<.0001
Baseline tumor size		
>69 vs. ≤69 mm	0.52 (0.32-0.84)	.008
Liver metastasis	0.45 (0.28-0.72)	.001
Yes vs. no		
NLR	0.60 (0.38-0.95)	.03
>3.37 vs. ≤3.37		
Prior lines		
>2 vs. ≤2	0.58 (0.36-0.93)	.02

Abbreviations: IO, immunotherapy; NLR, neutrophil/lymphocytes ratio; PS: performance status; TT, target therapy.

between the 2 BTS subgroups with similar mOS (19.3 vs. 11.8 months, $P = .20$) and mPFS (3.7 vs. 4.4 months, $P = .30$). Fig. 3 shows the Kaplan-Meier survival curves of OS and PFS by BTS in patients receiving biomarker-matched or unmatched TT. Among patients receiving TT, significant differences among survival curves were also observed by quartile of BTS for both OS ($P = .006$) and PFS ($P = .002$; Supplementary Fig. S2A) however, in a similar manner, this association was significant only for patients treated with biomarker-matched TT (Supplementary Table S6).

When the response rate was evaluated according to BTS in patients receiving TT-based regimens, both ORR and CBR were not found significantly associated with BTS, regardless of biomarker matching (ORR for biomarker-matched, low vs. high BTS: 28% vs. 22%, $P = .57$; ORR for biomarker-unmatched, low vs. high BTS: 33% vs. 28%, $P = .78$; Table 3).

A subgroup analysis restricted to patients with metastatic breast cancer treated with TT (N=141) showed a shorter OS in the BTS-high population as compared to the BTS-low (12.6 vs. 19.3 months, $P = .07$) and a significantly lower PFS (2.8 vs. 3.9 months, $P = .02$). Of note, when considering the type of TT received, the association of BTS with PFS remained significant only among patients receiving biomarker-matched TT (4.7 vs. 2.5 months, $P < .001$) (Supplementary Table S7). Similar to the overall population, in patients with breast cancer ORR and CBR were not significantly associated with BTS regardless of the type of TT.

Discussion

Our results provide preliminary insights into the prognostic value of CT-assessed baseline disease burden among patients with solid tumors treated with experimental TT. We found a statistically significant association between BTS and treatment outcomes among patients receiving TT in early-phase clinical trials. Of note, a different association between outcomes and BTS was observed when TTs were further divided into biomarker-matched or unmatched based on the selection of patients upon the identification of molecular biomarkers: only among patients receiving biomarker-matched TT BTS was significantly associated with OS and PFS, with longer survival observed among those in the BTS-low subgroup. BTS was not found to be significantly associated with response rate among patients receiving TT, regardless of biomarker selection. Moreover, when considering the whole population enrolled in early-phase clinical trials at our Institution, regardless of treatment received, we found that BTS was an independent predictor of OS and PFS. This study also supported the significant association between BTS and treatment outcome in patients with solid tumors treated with next-generation immunoncology agents, with an expanded population compared to what we had included in the prior study.[7]

In recent years, the development and clinical implementation of multiple targeted drugs have changed the treatment scenario for multiple solid tumors, leading to a dramatic improvement in patients' prognosis.[10] However, clinicians still lack the ability to fully predict which patients will most likely achieve this long-term benefit. In advanced cancers, multiple clinical or biological factors have been associated with prognosis and are used to guide oncological treatment such as measures of PS [eg, Karnofsky (KPS) or ECOG],[11]

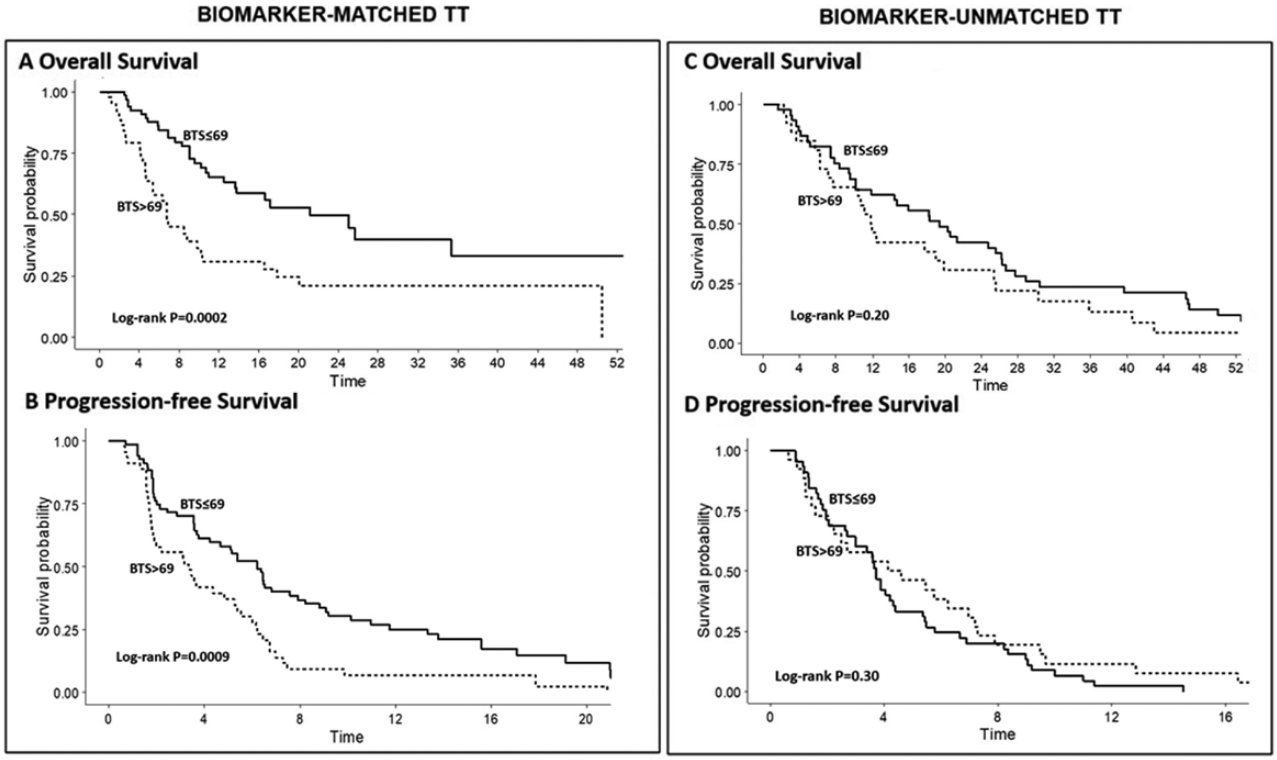

Figure 3. Kaplan-Meier analysis of overall survival and progression-free survival according to baseline tumor size (BTS) in patients receiving biomarker-matched (**A**, *N* = 112 and **B**, *N* = 113) or unmatched (**C**, *N* = 71 and **D**, N = 71) targeted therapy (TT).

Table 3. Objective response rate (ORR) and clinical benefit rate (CBR) by median baseline tumor sum (BTS) in patients receiving TT

Biomarker-matched TT						
			Total (*n* = 113)	**BTS ≤ 69 mm (*n* = 67)**	**BTS>69 mm (*n* = 46)**	***P* value**
ORR	No	*N*	84	48	36	.57
		%	74.3	71.6	78.2	
	Yes	*N*	29	19	10	
		%	25.7	28.3	21.8	
CBR	No	*N*	43	22	21	.24
		%	38.0	32.8	45.6	
	Yes	*N*	70	45	25	
		%	62.0	67.2	54.4	
Biomarker-unmatched TT						
			Total (*n* = 70)	**BTS ≤69 mm (*n* = 45)**	**BTS>69 mm (*n* = 25)**	***P* value**
ORR	No	*N*	48	30	18	.78
		%	68.6	66.7	72.0	
	Yes	*N*	22	15	7	
		%	31.4	33.3	28.0	
CBR	No	*N*	22	13	9	.61
		%	31.4	28.9	36.0	
	Yes	*N*	48	32	16	
		%	68.6	71.1	64.0	

certain types of circulating white blood cells and their respective ratio,[12] or serum biomarkers, such as LDH.[13] The RMH prognostic score predicts survival in patients enrolled in early clinical trials and it includes albumin, LDH, and number of metastatic sites.[14] Regarding the latter, tumor burden has been suggested as a useful prognostic factor in patients

with metastatic disease; however, there is a relative lack of data on both the definition of tumor burden and its impact on patients' outcomes with different therapies. Although available evidence clearly demonstrates that tumor burden provides relevant prognostic information for patients treated with ICIs,[15] little data is available regarding its impact on patients who underwent treatment with targeted therapies. Some retrospective data are available in patients with renal cell carcinoma treated with TT (ie, tyrosine kinase and mTOR inhibitors) that showed an association between high tumor burden and worse outcomes.[16-18] To our knowledge, ours is the first study aimed at evaluating the prognostic value of the baseline burden of disease among patients with different solid tumors treated with experimental TT. We demonstrated an association between BTS and outcome only among patients receiving biomarker-matched TT. These findings, apparently in contrast to those available in renal carcinoma, require further validation as this type of cancer is greatly underrepresented in our population. Moreover, the importance of the mechanistic target of rapamycin (mTOR) and angiogenesis in the biology of renal cell carcinoma may be associated with the different outcomes with unmatched-TT.[19,20]

One of the most interesting findings of our analysis was that the PFS and OS improvement observed in the low-BTS subgroup was not associated with an increase in ORR when compared to patients with BTS over the median. An explanation for this phenomenon could be found in intratumor heterogeneity[21]: despite the similar activity of TT in terms of response rate, higher tumor volume could be associated with higher heterogeneity that may promote tumor adaptation and treatment failure through a selection of preexisting drug-resistant clones.[22] For those patients with a high burden of disease who can tolerate an escalation of treatment, a more intensive approach such as combination treatment, could be considered to overcome the occurrence of resistance. Another potential implication of our findings is in the conduct of early-phase clinical trials testing TT, as BTS could be useful to improve patients' selection. The enrolled population may be enriched not only based on molecular biomarker selection but also on imaging biomarkers such as BTS. Finally, the association between baseline tumor size and outcomes also raises the question of whether locoregional treatments aimed at reducing tumor burden could increase the benefit of systemic therapy and thus improve survival. So far, conflicting evidence has accumulated on the role of metastases-directed treatment in addition to systemic therapy in different tumor types. In oligometastatic disease, while a role of local ablative therapy approaches has been established in patients with metastatic colorectal cancer,[23] no impact on survival has been demonstrated in patients with metastatic breast cancer.[24]

In our study, the baseline burden of disease was assessed through CT scan and BTS was defined as per RECIST 1.1 criteria.[9] However, not all metastatic lesions are suitable for CT-based measurement, and these are recognized in the RECIST guidelines as "non-target" lesions, including bone lesions without identifiable soft-tissue components, metastatic effusions, or lesions < 10 mm in diameter. Moreover, the RECIST-based definition of tumor burden fails to differentiate the presence of multiple small metastases from a single large metastatic lesion, 2 clinical settings in which tumor biology is probably different. In addition, RECIST assessment does not consider the site of metastasis which could strongly affect the prognosis based on the organ involved as well as be associated with different responses to treatment. Finally, the selection of the 5 target lesions may also be subjective reflecting not only their size but also how well the lesions are delineated on CT scan allowing reproducible repeated measurement. Thus, doubts may arise regarding CT-based assessment of tumor burden since this could not be sufficient to dissect the complexity of metastatic disease. Other methods have been proposed to improve the definition of tumor burden such as 2-Deoxy-2-[18F]fluoro-D-glucose ([18F]FDG)-PET and liquid biopsy. Among the parameters obtained by FDG-PET/CT, tumor burden can be defined through the total metabolic tumor volume (tMTV), as the sum of all FDG-avid lesions.[25] This might represent a better marker for tumor burden than BTS allowing a whole-body examination and inclusion of lesions normally excluded from CT-based BTS analysis such as bone lesions. A recently published study demonstrated a significant association between tMTV and OS among patients with NSCLC receiving pembrolizumab while no difference was found in the group of patients treated with epidermal growth factor receptor (EGFR) inhibitors for EGFR-mutated NSCLC (n = 40).[26] Further studies are required to fully elucidate the role of PET scan in the definition of tumor burden and its impact on patients treated with TT. However, a systematic evaluation of the correlation between tMTV and prognosis is limited by the less consistent use of PET scan in clinical practice and the absence of PET assessments in the majority of clinical trials. Another attractive research area for the definition of tumor burden is liquid biopsy. Evidence supporting a role of circulating tumor cells (CTCs)[27-29] and circulating tumor DNA (ctDNA)[30] as a surrogate marker for tumor burden is currently growing. However, especially for CTCs difficulty in the isolation process and the requirement of specific expertise have limited their incorporation into clinical practice. Therefore, also considering the limitations of CT-based assessment, measuring the size of tumors with radiological imaging remains the simplest way to estimate tumor burden and possibly predict outcomes in routine clinical practice at most cancer centers worldwide. Indeed, contrast-enhanced CT imaging is currently performed for most patients with advanced cancer and may be used not only in tumor diagnosis and staging but also as a prognostic tool.

A strength of our study is that, by evaluating patients included in clinical trials, there is homogeneity regarding the timing of the CT scan relative to treatment initiation, given the typical time window of up to 4 weeks allowed in clinical trials. In addition, all imaging assessments were performed by radiologists from the European Institute of Oncology affiliated with the phase I facility. There are some relevant limitations of this work to be pointed out. First, the retrospective and single institution nature of our analysis may represent a source of bias. Second, the population treated with TT is relatively small, especially in the biomarker-unmatched subgroup. Moreover, the cutoff of 69 mm for defining patients with high and low BTS was not pre-specified but was adjusted according to the median in our population. Finally, the population included in this analysis is highly heterogeneous in terms of tumor type, with a predominance of patients with breast cancer, as well as in terms of treatment received. All these limitations make the results of this work hypothesis generating rather than conclusive, requiring validation in an independent cohort.

Several aspects should be assessed and clarified by future research. We used the median BTS value of our population

to distinguish between high and low baseline tumor burden however, considering the continuous relationship between BTS and risk of death, further studies should be designed to establish a universal definition of high tumor burden with validated cutoff for BTS, which might be different for different tumor types. Furthermore, future studies should address the question of whether the value of BTS is different among patients with the same tumor burden but a different distribution of metastases such as specific organ involvement or the presence of single large metastasis versus multiple smaller metastases. Finally, whether the role of BTS would be confirmed, future research should investigate the possibility to use BTS to escalate or de-escalate treatment in patients with advanced solid tumors receiving TT.

Conclusion

In summary, in this retrospective study, we found a significant association between BTS and outcomes among patients with advanced solid tumors receiving experimental TT in early-phase clinical trials only when treatment was based on target selection. Although independent validation of this finding is necessary, we hypothesize that BTS could represent an accessible and promising independent prognostic factor in clinical practice to select those patients with poorer prognosis that could benefit from treatment intensification. Moreover, BTS could be taken into account, among other baseline factors, to stratify patients in future clinical trials involving TT.

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Conflict of Interest

Paolo Tarantino has served as consultant or advisor for AstraZeneca, Daiichi Sankyo, Gilead, and Lilly. Carmen Criscitiello reports consultancy/advisory role/speaker bureau for AstraZeneca, Daiichi Sankyo, MSD, Gilead, Lilly, Roche, Pfizer, Novartis, and Seagen, all outside the submitted work. Massimo Cristofanilli reports personal fees from Lilly, Sermonix, Foundation Medicine, Guardant Health, Celcuity, Iylon, and Ellipses and grants and personal fees from Pfizer and Menarini. Sara M. Tolaney reports consulting or advisory role for Novartis, Pfizer, Merck, Lilly, Nektar, NanoString Technologies, AstraZeneca, Puma Biotechnology, Genentech/Roche, Eisai, Sanofi, Bristol Myers Squibb, Seattle Genetics, Odonate Therapeutics, OncoPep, Kyowa Hakko Kirin, Samsung Bioepis, CytomX Therapeutics, Daiichi Sankyo, Athenex, Gilead, Mersana, Certara, Chugai Pharma, Ellipses Pharma, Infinity, 4D Pharma, OncoSec Medical Inc., BeyondSpring Pharmaceuticals, OncXerna, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, and ARC Therapeutics; Institutional Research Funding from Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol Myers Squibb, Eisai, AstraZeneca, NanoString Technologies, Cyclacel, Nektar, Gilead, Odonate Therapeutics, Sanofi, and Seattle Genetics (all competing interests outside the submitted work). Giuseppe Curigliano served as consultant or advisor for Roche, Lilly, and Bristol-Myers Squibb, served on the speaker's bureau for Roche, Pfizer, and Lilly, received travel funding from Pfizer and Roche, and received honoraria from Roche, Pfizer, Lilly, Novartis, and Seagen, all outside the submitted work. The other authors indicated no financial relationships.

Author Contributions

All authors contributed to the conception/design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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