ORIGINAL RESEARCH

Predictive value of positron emission tomography for the prognosis of molecularly targeted therapy in solid tumors

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Objective: This study aimed at comprehensively exploring the value applying positron emission tomography (PET) to predict the effect of molecularly targeted therapy in solid tumors.

Materials and methods: A systematic search was performed for potentially relevant studies from the time of inception to February 2017. The primary endpoints were progression-free survival (PFS), overall survival (OS), and time to progression (TTP). The results were analyzed by Review Manager version 5.3 (RevMan 5.3) statistical software. Subgroup analyses were implemented based on the type of molecularly targeted agents (monoclonal antibodies arm and small molecular targeted agents arm), mechanism (erlotinib/gefitinib arm and bevacizumab arm), radioactive tracers, type of tumor, and reevaluated PET timing.

Results: Twenty-six studies incorporating 865 individuals were eligible. Compared with PET nonresponse group, PET response group displayed a decrease in maximal standard uptake value (SUVmax), which was associated with a significantly prolonged PFS (HR =0.41, 95% CI [0.29, 0.59]; $P<0.00001$), OS (HR =0.52, 95% CI [0.40, 0.67]; $P<0.00001$), and TTP (HR =0.30, 95% CI [0.14, 0.66]; $P=0.003$). Similar results were obtained in the subgroup analyses of PFS in erlotinib/gefitinib arm and small molecular targeted agents arm; and OS in lung cancer arm, erlotinib/gefitinib arm, bevacizumab arm, small molecular targeted agents arm, monoclonal antibodies arm, 18F-fluorodeoxythymidine (18F-FLT) arm, 18F-fluorodeoxyglucose (18F-FDG) arm, and early PET timing arm.

Conclusion: Our study demonstrated that PET was a favorable approach to predict the prognosis of molecularly targeted therapy for solid tumors. PET assessment within 2 weeks could be useful to predict clinical outcome.

Keywords: positron emission tomography, PET, molecularly targeted therapy, monoclonal antibody, malignancy, solid tumor

Introduction

It is well known that early prediction of the treatment response is critical for patients with malignancies to optimize effective therapeutic regimen, avoid adverse effects, and save cost.

Classical imaging tools, such as computed tomography (CT) and magnetic resonance imaging (MRI), are widely used for response assessment. Nevertheless, the limitations of these morphologic imaging techniques can hardly be neglected, for they barely distinguishes posttreatment fibrosis, scar, and necrosis from residual or recurrent disease[1] and only provides information on tumor anatomy by assessing volume change. Moreover, tumor shrinkage usually scarcely occurs until after several cycles of therapy,[2] which hinders an early estimating response.

Recently, molecularly targeted therapy, with its high specificity, efficacy, and fewer toxicities in managing malignant tumor, has been rapidly put into a routine clinical practice. They are designed to block pathological cellular pathways related to cancer cell survival, proliferation, and metastasis,[3] and to decrease vascular permeability, microvascular density, and cell density.[4] However, response monitoring in malignant tumor treated with molecularly targeted therapy is challenging. Individuals frequently benefit from targeted agents without volumetric change.[5–8] Thus, with the evolution of treatment regimens and availability of molecularly targeted therapies, a novel imaging approach for supervising therapeutic efficacy focusing more on the biochemistry of the tumor is imperative.

Fortunately, positron emission tomography (PET) has been increasingly noted for its metabolic tumor response assessment, especially in targeted therapy. It was exerting a fascination on predicting long-term outcome via monitoring the metabolism of tissues even in the absence of tumor shrinkage,[9–11] and was potentially providing an early assessment of the response of targeted therapy[3] but was inconsistent in various tumors and evaluating time points. Therefore, the goal of this study was to investigate whether the early tumor uptake change in PET was associated with clinical outcomes, and to identify whether PET could be a candidate for measuring response in malignancies treated with molecularly targeted agents.

Materials and methods
Literature search
Researches were identified by a systematic electronic literature search for abstracts of relevant studies in the published literature. MEDLINE/PubMed, Google Scholar, EMBASE, and Cochrane Library were scrutinized and updated from July 1, 2016 to February 9, 2017. The following basic search terms were used: "positron emission tomography," "PET," "targeted therapies," "bevacizumab," "cetuximab," "Erbitux," "trastuzumab," "Herceptin," "erlotinib," "Tarceva," "gefitinib," "Iressa," "sorafenib," "Nexavar," "axitinib," "lapatinib," "rituximab," "tyrosine kinase inhibitor," "antiangiogenic treatment," "solid tumor," "lung cancer," "breast cancer," "gliomas," "gastrointestinal stromal tumor," "colon cancer," "renal cell carcinoma," and "biliary tract cancer." Full-text articles were reviewed if abstracts did not provide sufficient information. Moreover, the reference lists of relevant articles were traced for additional studies. Reviews, letters to the editor, case reports, conference abstracts, and editorials comments were excluded. The search was performed without any language restriction.

Selection of studies
Two investigators independently performed an initial screening of titles and abstracts, and then further examined the full-text articles to recruit relevant studies. Disagreement on whether an article should be included was resolved by a third reviewer.

Detailed inclusion criteria
Inclusion criteria were as follows: 1) prospective or retrospective studies exploring the correlation of maximal standard uptake value (SUVmax) with progression-free survival (PFS), overall survival (OS), and/or time to progression (TTP); 2) evaluating over 10 cases involving molecularly targeted agents; 3) individuals had been histologically or cytologically confirmed as having malignant solid tumors; 4) utilizing PET to monitor therapy response of pretherapy and posttreatment; 5) supervising response according to quantitative changes on SUVmax; and 6) HRs with 95% CIs of survival data were accessible.

Data extraction
Data extraction was conducted conforming to the PRISMA guidance (S1 PRISMA Checklist).[12] Two authors independently extracted information from all the eligible studies. Disagreement between the two reviewers was resolved by a third reviewer. All of the eligible studies contained the following data: first author's name, published year, median ages, number of patients, number of males, study design, type of tumor, molecularly targeted agents, reevaluated PET timing, and survival endpoints. PFS, OS, and/or TTP data were served as the endpoints to evaluate the prognostic significance of PET and expressed by HRs. HRs with 95% CIs were calculated from survival curves based on Tierney's and Parmar's methods if they were presented indirectly.[13,14]

Quality assessment
Two reviewers independently evaluated the quality items and discrepancies were solved by conferring with a third reviewer. We deemed the description of PET to be qualified if the study elaborated the scanner type and the timing of scanning after injection.

Statistical methods
Statistical analyses were calculated by Review Manager version 5.3 (RevMan 5.3) statistical software. Survival data from each study were evaluated based on the Kaplan–Meier curves. The impact of SUVmax on PFS, OS, and TTP was measured using HRs with 95% CIs, which were extracted from papers

or from the survival curves via the methods by Parmar et al,[14] and Tierney et al[13] when HRs were not provided directly. Survival rates represented on the graphical survival curves were calculated by Engauge Digitizer version 2.5. An HR <1 denoted the survival benefit from a response PET scan, while an HR >1 implied worse survival outcomes. It was considered statistically significant when P-value was less than 0.05. Cutoff values of the change on SUVmax were determined by the definition in each individual study, and PET response and nonresponse groups were defined according to the alteration in cutoff value of SUVmax. Subgroup analyses were carried out based on the variety of molecularly targeted agents, mechanism, the reevaluated PET timing, types of malignancies, and radioactive tracers. Statistical heterogeneity was estimated via the chi-square and the I-square tests.[15] The significant heterogeneity existed if $P<0.1$ or $I^2>50\%$, and no heterogeneity existed when $P>0.1$ and $I^2<50\%$. A fixed effect model was applied to calculate the pooled HRs when no heterogeneity was observed, otherwise, a random effect model was employed. Publication bias was exhibited via funnel plot.

Results

Study selection

Initially, 2,920 potentially relevant articles were thoroughly searched from all databases. Of them, 313 were filtered due to duplication. After screening the titles and abstracts, 2,527 were excluded for deviating from the subject. Then, the full text of remaining 80 papers was intensively scrutinized, and 55 were removed for the following reasons: SUVmax was unavailable (n=11), targeted therapy based on regimen was not administered in every individual (n=7), evaluating less than 10 patients (n=18), unable to calculate the log HR and its variance (n=13), and unfit design (n=6). Ultimately, a total of 25 articles (including 26 studies)[2,3,16–38] were eligible for this analysis. The detailed study selection process is described in Figure 1.

Study characteristics

Totally, 865 participants in the 25 articles (including 26 studies) published from the time of inception to February 9, 2017 were eligible. The sample size varied from 12 to 86 subjects. Of these articles, 12 were on non-small cell lung cancer (NSCLC) (49.48% of patients),[2,3,16,18,19,21,22,24,26,27,35,38] two on malignant glioma (5.90% of patients),[23,34] two on metastatic colorectal cancer (CRC) (7.63% of patients),[31,36] two on gastrointestinal stromal tumor (GIST) (7.28% of patients),[29,30] two on metastatic renal cell carcinoma (RCC) (9.60% of patients),[25,37] and five on other solid tumors
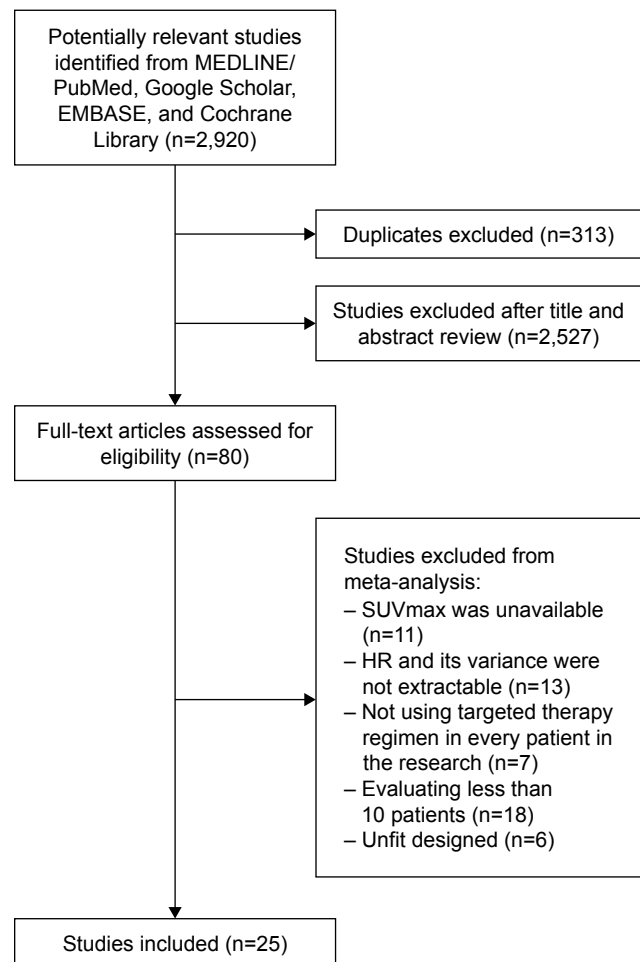
Figure 1 Flowchart on selection including trials in the meta-analysis.
Abbreviation: SUVmax, maximal standard uptake value.

(metastatic gastric adenocarcinoma, metastatic breast cancer, metastatic melanoma, biliary tract cancer, and mixed kinds of tumors; 20.12% of patients).[17,20,28,32,33] Meanwhile, all of these articles coped with molecularly targeted therapy: six with erlotinib,[3,16,21,22,24,27] six with bevacizumab,[23,26,28,31,34,36] four with gefitinib,[2,19,35,38] three with imatinib,[17,29,32] two with sunitinib,[25,30] one with cetuximab,[33] and three with mixed kinds of molecularly targeted agents.[18,20,37] PET-CT/PET was performed pretherapy and posttreatment. SUVmax was measured in all articles, which normalized values by body weight. PFS, OS, and TTP were defined as the endpoints to assess the prognostic significance of the changing SUVmax. Owing to the absence of consensus on metabolic response criteria, the participants were assigned to PET response or PET nonresponse group based on the change of SUVmax in each article. Of all the eligible studies, 17 provided an extractable HR value for PFS,[3,16,18,20,21,23–26,28,30–32,35,36,38] 19 for OS,[2,3,16,17,19,21–28,31,33–37] and five for TTP.[2,17,27,29,33] The principal characteristics and further details are summarized in Table 1.

Table 1 The principal characteristics and further details of eligible articles

Study	Study design	Radioactive tracers	Tumor	Stage	Molecular targeted drug	Median age (range)	Time	Endpoint	Total cases	Male (%)	Evaluable cases	Responder	Non-responder
Benz et al[27]	Prospectively, cohort study	FDG	NSCLC	IIIb–IV	Erlotinib	64 (42–86)	Baseline, 2 weeks	TTP, OS	22	6 (27.2)	22	6	16
Chen et al[34]	Prospectively, cohort study	FLT	Malignant gliomas	III–IV	Bevacizumab	58 (26–78)	Baseline, 1–2 weeks	OS	21	11 (52.4)	19	9	10
Choi et al[29]	Prospectively, cohort study	FDG	GIST	/	Imatinib	/ (28–86)	Baseline, 3 months	TTP	40	19 (47.5)	40	33	7
de Jong et al[26]	Prospectively, Phase II trial	FDG	NSCLC	IV	Bevacizumab		Baseline, 22–24 days	PFS, OS	60	30 (50.0)	60	/	/
de Langen et al[18]	Prospectively, Phase II trial	FDG	NSCLC	IIIb–IV	Bevacizumab and erlotinib	/	Baseline, 3 weeks	PFS	47	/	40	7	33
Engelmann et al[31]	Prospectively, cohort study	FDG	mCRC	/	Bevacizumab	66 (42–81)	Baseline, 20 days	PFS, OS	33	13 (39.3)	27	14	13
Di Fabio et al[33]	Prospectively, Phase II trial	FDG	Metastatic gastric adenocarcinoma	/	Cetuximab	64.5 (39–74)	Baseline, 6 weeks	TTP, OS	22	16 (72.7)	20	12	8
Farnebo et al[37]	Prospectively, cohort study	FDG	mRCC	/	Sunitinib (n=18), sorafenib (n=19), pazopanib (n=2)		Baseline, 14 days	PFS, OS	39	/	32	8	24
Hachemi et al[24]	Prospectively, cohort study	FDG	NSCLC	IIIa–IV	Erlotinib	60 (/)	Baseline, 9±3 days	PFS, OS	12	6 (50.0)	12	4	8
Ho et al[16]	Retrospective, cohort study	FDG	Lung adenocarcinoma	IIIb–IV	Erlotinib	57 (38–81)	Baseline, 14 days	PFS	23	7 (30.4)	23	11	12
Kanazu et al[35]	Cohort study	FDG	NSCLC	IIIb–IV	Gefitinib	61 (34–84)	Baseline, 3 days	PFS, OS	19	4 (21.0)	19	7	12
Kayani et al[25]	Prospectively, Phase II trial	FDG	mRCC	/	Sunitinib	61 (44–78)	Baseline, 4 weeks	PFS, OS	44	33 (75.0)	42	24	18
Lastoria et al[36]	Prospectively, Phase II trial	FDG	mCRC	/	Bevacizumab	58 (30–71)	Baseline, 14 days	PFS, OS	33	21 (63.4)	33	12	21
Lin et al[20] (group 1)	Prospectively, Phase II trial	FDG	MBC	I–IV	Lapatinib and trastuzumab	52 (32–83)	Baseline, 1 week	PFS, OS	41	0	39	28	11
Lin et al[20] (group 2)	Prospectively, Phase II trial	FDG	MBC	I–IV	Lapatinib and trastuzumab	52 (32–83)	Baseline, 1 week	PFS OS	45	0	43	21	22
Mileshkin et al[3]	Prospectively, cohort study	FDG	NSCLC	/	Erlotinib	61 (47–78)	Baseline, 14 days	PFS OS	51	30 (58.8)	51	13	38
O'Brien et al[22]	Prospectively, Phase II trial	FDG	NSCLC	IIIb–IV	Erlotinib	63 (42–82)	Baseline, 6 weeks	OS	47	18 (38.3)	38	15	23
Prior et al[30]	Prospectively, cohort study	FDG	GIST	/	Sunitinib	53 (24–76)	Baseline, 4 weeks	PFS	23	16 (69.6)	23	12	11
Rong et al[19]	Cohort study	FDG	Lung adenocarcinoma	IIIb–IV	Gefitinib	62 (34–81)	Baseline, 6 months	OS	46	17 (37.0)	46	13	33

Study	Study design	Tracer	Tumor	Stage	Agent	Age	PET timing	Endpoint					
Sahani et al[28]	Prospectively, cohort study	FDG	BTC	/	Bevacizumab	58.3 (/)	Baseline, 8 weeks	PFS OS	28	11 (39.2)	28	13	15
Schwarzenberg et al[23]	Prospectively, cohort study	FLT	Malignant glioma	IIIb–IV	Bevacizumab	58 (26–78)	Baseline, 2 weeks	PFS OS	30	18 (60.0)	30	17	13
Sohn et al[2]	Prospectively, cohort study	FLT	Lung adenocarcinoma	IV	Gefitinib	58 (40–76)	Baseline, 7 days	TTP OS	28	5 (17.8)	28	14	14
Stroobants et al[32]	Prospectively, Phase I/II trial	FDG	Soft tissue sarcoma	/	Imatinib	55 (38–70)	Baseline, 8 days	PFS	21	12 (57.1)	21	13	8
Takahashi et al[38]	Cohort study	FDG	Lung adenocarcinoma	IIIa–IV	Gefitinib	69 (58–83)	Baseline, 2 days	PFS OS	20	5 (25.0)	19	11	8
Tiseo et al[21]	Prospectively, cohort study	FDG	NSCLC	IV	Erlotinib	65 (38–79)	Baseline, 2 days	PFS OS	53	35 (66.0)	53	45	8
Zukotynski et al[17]	Prospectively, Phase II trial	FDG	Metastatic melanoma	/	Imatinib	65.5 (47–81)	Baseline, 4 weeks	TTP OS	17	4 (23.5)	17	10	7

Note: "/" indicates not mentioned.
Abbreviations: BTC, biliary tract cancer; FDG, fluorodeoxyglucose; FLT, fluorodeoxythymidine; GIST, gastrointestinal stromal tumor; MBC, metastatic breast cancer; NSCLC, non-small-cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; TTP, time to progression; mCRC, metastatic colorectal cancer; mRCC, metastatic renal cell carcinoma.

Data analysis

Predictive value of ΔSUVmax for PFS

A total of 16 articles including 17 studies focused on predictive value of ΔSUVmax for PFS. In pooled analysis, PFS was significantly prolonged in the responding group (HR =0.41, 95% CI [0.29–0.59]) by random model due to heterogeneity between the studies (I^2=54%, P=0.004) (Figure 2A). The funnel plot indicated that there was no significant publication bias for included studies on PFS (Figure 2D). Subgroup analyses based on the tumors, targeted agents, mechanism, radioactive tracers, and reevaluated PET timing were performed owing to the apparent heterogeneity. We implemented subgroup analyses based on the type of molecularly targeted agents (monoclonal antibodies arm and small molecular targeted agents arm), mechanism (erlotinib/gefitinib arm and bevacizumab arm), radioactive tracers (18F-fluorodeoxythymidine [18F-FLT] arm and 18F-fluorodeoxyglucose [18F-FDG] arm), type of tumor (NSCLC arm), and reevaluated PET timing (early assessment and late assessment arms). Repeating PET within 2 weeks was defined as early assessment arm; otherwise, it was defined as late assessment arm.

With respect to PFS, response group exhibited a significant longer survival in both erlotinib/gefitinib arm (Figure 3A) (HR =0.24, 95% CI [0.15–0.39], P<0.00001)[3,16,21,24,35,38] and small molecular targeted agents arm as compared to PET non-response group (Figure 3B) (HR =0.34, 95% CI [0.23–0.50], P<0.00001)[3,16,21,24,25,30,32,35,38] without heterogeneity.

In regard to PFS of bevacizumab arm (Figure 3C),[23,26,28,31,36] monoclonal antibodies arm (Figure 3D),[18,23,26,28,31,36] NSCLC arm (Figure 3E),[3,16,18,21,24,26,35,38] 18F-FDG arm (Figure 3F),[3,16,18,20,21,24–26,28,30–32,35,36,38] early assessment arm (Figure 3G),[3,16,20,21,23,24,32,35,36,38] and late assessment arm (Figure 3H),[18,25,26,28,30,31] the outcome demonstrated that response group predicted a significantly longer PFS compared to nonresponse group with obvious heterogeneity.

Predictive value of ΔSUVmax for OS

Nineteen eligible studies incorporating 600 individuals[2,3,16,17,19,21–28,31,33–37] were compared to OS of PET response group with that of PET nonresponse group. A fixed effect model was utilized owing to no heterogeneity (P=0.42, I^2=3%). Compared to PET nonresponse group, PET response group displayed a prolonged pooled OS (HR =0.52; 95% CI [0.40–0.67]; P<0.00001) (Figure 2B). The shape of the funnel plots appeared to be generally symmetric, and indicated no publication bias (Figure 2E). Then further subgroup analyses showed that response group acquired a significant longer OS without heterogeneity in NSCLC arm (Figure 4A) (HR =0.52,

95% CI [0.38–0.72], $P<0.0001$),[2,3,16,18,19,21,22,24,26,35] erlotinib/gefitinib arm (Figure 4B) (HR =0.39, 95% CI [0.27–0.58], $P<0.00001$),[2,3,16,19,21,22,24,27,35] bevacizumab arm (Figure 4C) (HR =0.65, 95% CI [0.43–0.99], $P=0.04$),[23,26,28,31,34,36] monoclonal antibodies arm (Figure 4D) (HR =0.65, 95% CI [0.43–0.98], $P=0.04$),[23,26,28,31,33,34,36] small molecular targeted agents arm (Figure 4E) (HR =0.46, 95% CI [0.34–0.63], $P<0.00001$),[2,3,16,17,19,21,22,24,25,27,35] 18F-FDG arm (Figure 4H) (HR =0.53, 95% CI [0.41–0.69], $P<0.00001$),[3,16,17,19,21,22,24–28,31,33,35–37] 18F-FLT arm (Figure 4I) (HR =0.43, 95% CI [0.19–0.96], $P=0.04$),[2,23,34] and in early assessment arm (Figure 4F) (HR =0.38, 95% CI [0.27–0.53], $P<0.00001$).[2,3,16,21,]

A

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI
de Jong 2016	0.04688359	0.29220406	9.1	1.05 (0.59, 1.86)
de Langen 2011	−0.96758403	0.37731533	7.9	0.38 (0.18, 0.80)
Engelmann 2014	−0.91629073	0.49149969	6.4	0.40 (0.15, 1.05)
Hachemi 2014	−1.30933332	0.6865416	4.4	0.27 (0.07, 1.04)
Ho 2016	−1.07880966	0.61857212	5.0	0.34 (0.10, 1.14)
Kanazu 2014	−2.40794561	0.78266656	3.7	0.09 (0.02, 0.42)
Kayani 2011	−0.13926207	0.40929219	7.4	0.87 (0.39, 1.94)
Lastoria 2013	−0.91629073	0.43894478	7.0	0.40 (0.17, 0.95)
Lin 2015 group 1	−1.23787436	0.41446566	7.3	0.29 (0.13, 0.65)
Lin 2015 group 2	0.42526774	0.3860444	7.7	1.53 (0.72, 3.26)
Mileshkin 2011	−1.27296568	0.39015184	7.7	0.28 (0.13, 0.60)
Prior 2009	−0.89159812	0.6698942	4.6	0.41 (0.11, 1.52)
Sahani 2015	−1.66073121	0.67684744	4.5	0.19 (0.05, 0.72)
Schwarzenberg 2012	−0.63487827	0.46308418	6.7	0.53 (0.21, 1.31)
Stroobants 2003	−0.96758403	1.02134954	2.5	0.38 (0.05, 2.81)
Takahashi 2012	−3.21887582	1.21044187	1.9	0.04 (0.00, 0.43)
Tiseo 2014	−1.2039728	0.50294709	6.2	0.30 (0.11, 0.80)
Total (95% CI)			**100**	**0.41 (0.29, 0.59)**

Heterogeneity: $\tau^2=0.28$; $\chi^2=35.05$, $df=16$ ($P=0.004$); $I^2=54\%$
Test for overall effect: $Z=4.83$ ($P<0.00001$)

B

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Benz 2011	0.00995033	0.94816807	1.8	1.01 (0.16, 6.48)
Chen 2007	−0.65392647	1.0169222	1.6	0.52 (0.07, 3.82)
de Jong 2016	0.02469261	0.29764033	18.4	1.03 (0.57, 1.84)
Engelmann 2014	−0.77652879	0.59809931	4.6	0.46 (0.14, 1.49)
Fabio 2007	−0.61618614	1.44756839	0.8	0.54 (0.03, 9.22)
Farnebo 2014	−0.54472718	0.40661575	9.9	0.58 (0.26, 1.29)
Hachemi 2014	−1.07880966	0.67322891	3.6	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	6.7	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	5.8	0.36 (0.13, 1.02)
Kayani 2011	−0.22314355	0.43214166	8.7	0.80 (0.34, 1.87)
Lastoria 2013	−2.52572864	1.0528404	1.5	0.08 (0.01, 0.63)
Mileshkin 2011	−0.82098055	0.38233988	11.2	0.44 (0.21, 0.93)
O'Brien 2012	−0.41551544	0.58617648	4.7	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	0.7	0.37 (0.02, 7.14)
Sahani 2015	−0.46203546	0.51177789	6.2	0.63 (0.23, 1.72)
Schwarzenberg 2012	−1.42711636	0.70729304	3.3	0.24 (0.06, 0.96)
Sohn 2008	−0.51082562	0.58739416	4.7	0.60 (0.19, 1.90)
Tiseo 2014	−1.96611286	0.59161082	4.7	0.14 (0.04, 0.45)
Zukotynski 2014	−0.89159812	1.18294725	1.2	0.41 (0.04, 4.17)
Total (95% CI)			**100**	**0.52 (0.41, 0.67)**

Heterogeneity: $\chi^2=18.57$, $df=18$ ($P=0.42$); $I^2=3\%$
Test for overall effect: $Z=5.09$ ($P<0.00001$)

Figure 2 (*Continued*)

C

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Benz 2011	−1.56064775	0.99106998	16.5	0.21 (0.03, 1.46)
Choi 2007	−2.20727491	1.38947382	8.4	0.11 (0.01, 1.68)
Fabio 2007	−0.38566248	0.91989587	19.2	0.68 (0.11, 4.13)
Sohn 2008	−1.2039728	0.61170798	43.3	0.30 (0.09, 0.99)
Zukotynski 2014	−1.34707365	1.13232704	12.6	0.26 (0.03, 2.39)
Total (95% CI)			**100**	**0.30 (0.14, 0.66)**

Heterogeneity: χ^2=1.46, df=4 (P=0.83); I^2=0%
Test for overall effect: Z=3.00 (P=0.003)

Figure 2 (**A**) PFS of the study; (**B**) OS of the study; (**C**) TTP of the study; (**D**) funnel plot of PFS for included studies; (**E**) funnel plot of OS for included studies; (**F**) funnel plot of TTP for included studies.
Note: Lin 2015 (group 1) and Lin 2015 (group 2) were two studies included in one article.
Abbreviations: OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; SE, standard error; TTP, time to progression.

[23,24,27,34–37] However, late assessment arm displayed a longer survival in response group despite no statistical significance (Figure 4G) (HR =0.77, 95% CI [0.53–1.11], P=0.16).[17,19,22,25,26,28,31,33]

Predictive value of ΔSUVmax for TTP

Five studies comprising 127 individuals[2,17,27,29,33] explored the correlation between the decrease of ΔSUVmax and TTP. A fixed effect model was employed because of no heterogeneity

(I^2=83%, P=0). The result indicated that less decline of ΔSUVmax was associated with a significant shorter TTP (HR =0.30, 95 % CI [0.14–0.66]; P=0.03) (Figure 2C). The funnel plot indicated that no remarkable publication bias existed, suggesting that the obtained results were reliable (Figure 2F).

Discussion

To our best knowledge, this is the first meta-analysis to systematically estimate the value of PET in solid tumor treated

with molecularly targeted therapy. Previous studies had proved PET to be competent to assess survival in diffuse large B-cell lymphoma after rituximab based regimen effectively.[9] However, the prognostic value of PET in evaluating molecularly targeted therapy in solid tumor remained unclear.

Based on data from 25 articles, our study demonstrated that the decline of PET uptake administered with molecularly targeted therapy was related to a longer PFS, OS, and TTP, despite obvious heterogeneity in PFS. Further subgroup analyses displayed that in PET response group, a significant longer PFS was observed in erlotinib/gefitinib arm and small molecular targeted agents arm; and a longer OS in NSCLC arm, erlotinib/gefitinib arm, bevacizumab arm, small molecular targeted agents arm, monoclonal antibodies arm, 18F-FDG arm, 18F-FLT arm, and early assessment arm with no heterogeneity. These evidences supported that PET was a favorable approach to determine response of solid tumor treated with molecularly targeted therapy, especially with small molecular targeted agents, and a promising tool for the early detection of response.

When measuring response to anticancer treatment, a reliable and standardized methodology is essential in determining whether the ongoing therapy is beneficial. Anatomic tumor response metrics comprising WHO criteria (1979),

Response Evaluation Criteria in Solid Tumors (RECIST) (2000), and RECIST 1.1 (2009)[39,40] were widely applied, but were incompetent to distinguish necrosis, inflammation, and cavitation from residual or recurrent tumor lesions. Meanwhile, necrosis and cavitation without an alteration in size are frequently observed in angiogenesis inhibitors and anti-vascular therapies.[41] Therefore, these anatomic criteria are insufficient for the evaluation of response to molecularly targeted therapies. In 1999, the European Organization for Research and Treatment of Cancer proposed a set of criteria to judge PET response based on metabolism.[42] However, a workshop of the National Cancer Institute stated that there was neither one best criterion for assessing 18F-FDG PET, nor one unified standard for determining the significance of 18F-FDG PET.[41] Subsequently, Positron Emission tomography Response Criteria In Solid Tumors assessed by changes in peak standard uptake value-lbm (SULpeak) was formulated but not widely applied. Summarily, the role of PET in assessing response of molecularly targeted therapy in solid tumor remains to be explored. Thereby, we proceeded this analysis to elaborate this issue.

The reason for conducting the reevaluated PET timing subgroup analysis was that the optimal time point to judge PET response remains to be determined. For morphologic imaging techniques, such as CT, which was based on volume,

A

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI	Hazard ratio IV, fixed, 95% CI
Erlotinib/gefitinib					
Hachemi 2014	−1.30933332	0.6865416	4.8	0.27 (0.07, 1.04)	
Ho 2016	−1.07880966	0.61857212	5.9	0.34 (0.10, 1.14)	
Kanazu 2014	−2.40794561	0.78266656	3.7	0.09 (0.02, 0.42)	
Mileshkin 2011	−1.27296568	0.39015184	14.8	0.28 (0.13, 0.60)	
Takahashi 2012	−3.21887582	1.21044187	1.5	0.04 (0.00, 0.43)	
Tiseo 2014	−1.2039728	0.50294709	8.9	0.30 (0.11, 0.80)	
Subtotal (95% CI)			**39.7**	**0.24 (0.15, 0.39)**	

Heterogeneity: χ^2=4.46, df=5 (P=0.49); I^2=0%
Test for overall effect: Z=5.93 (P<0.00001)

B

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI	Hazard ratio IV, fixed, 95% CI
Small molecular targeted agents					
Hachemi 2014	−1.30933332	0.6865416	4.8	0.27 (0.07, 1.04)	
Ho 2016	−1.07880966	0.61857212	5.9	0.34 (0.10, 1.14)	
Kanazu 2014	−2.40794561	0.78266656	3.7	0.09 (0.02, 0.42)	
Kayani 2011	−0.13926207	0.40929219	13.5	0.87 (0.39, 1.94)	
Mileshkin 2011	−1.27296568	0.39015184	14.8	0.28 (0.13, 0.60)	
Prior 2009	−0.89159812	0.6698942	5.0	0.41 (0.11, 1.52)	
Stroobants 2003	−0.96758403	1.02134954	2.2	0.38 (0.05, 2.81)	
Takahashi 2012	−3.21887582	1.21044187	1.5	0.04 (0.00, 0.43)	
Tiseo 2014	−1.2039728	0.50294709	8.9	0.30 (0.11, 0.80)	
Subtotal (95% CI)			**60.3**	**0.34 (0.23, 0.50)**	

Heterogeneity: χ^2=11.79, df=8 (P=0.16); I^2=32%
Test for overall effect: Z=5.53 (P<0.00001)

| **Total (95% CI)** | | | **100** | **0.30 (0.22, 0.40)** | |

Heterogeneity: χ^2=17.50, df=14 (P=0.23); I^2=20%
Test for overall effect: Z=8.03 (P<0.00001)
Test for subgroup differences: χ^2=1.26, df=1 (P=0.26); I^2=20.4%

0.01 0.1 1 10 100
PET-response PET-non-response

Figure 3 (*Continued*)

C

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
Bevacizumab					
de Jong 2016	0.04688359	0.29220406	15.1	1.05 (0.59, 1.86)	
Engelmann 2014	−0.91629073	0.49149969	9.1	0.40 (0.15, 1.05)	
Lastoria 2013	−0.91629073	0.43894478	10.3	0.40 (0.17, 0.95)	
Sahani 2015	−1.66073121	0.67684744	5.8	0.19 (0.05, 0.72)	
Schwarzenberg 2012	−0.63487827	0.46308418	9.7	0.53 (0.21, 1.31)	
Subtotal (95% CI)			**50**	**0.51 (0.29, 0.89)**	

Heterogeneity: τ^2=0.20; χ^2=8.13, df=4 (P=0.09); I^2=51%
Test for overall effect: Z=2.37 (P=0.02)

D

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
Monoclonal antibodies					
de jong 2016	0.04688359	0.29220406	15.1	1.05 (0.59, 1.86)	
Engelmann 2014	−0.91629073	0.49149969	9.1	0.40 (0.15, 1.05)	
Lastoria 2013	−0.91629073	0.43894478	10.3	0.40 (0.17, 0.95)	
Sahani 2015	−1.66073121	0.67684744	5.8	0.19 (0.05, 0.72)	
Schwarzenberg 2012	−0.63487827	0.46308418	9.7	0.53 (0.21, 1.31)	
Subtotal (95% CI)			**50**	**0.51 (0.29, 0.89)**	

Heterogeneity: τ^2=0.20; χ^2=8.13, df=4 (P=0.09); I^2=51%
Test for overall effect: Z=2.37 (P=0.02)

| **Total (95% CI)** | | | **100** | **0.52 (0.36, 0.75)** | |

Heterogeneity: τ^2=0.15; χ^2=16.26, df=9 (P=0.06); I^2=45%
Test for overall effect: Z=3.50 (P=0.0005)
Test for subgroup differences: χ^2=0.00, df=1 (P=1.00); I^2=0%

E

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
NSCLC					
de Jong 2016	0.04688359	0.29220406	18.1	1.05 (0.59, 1.86)	
de Langen 2011	−0.96758403	0.37731533	16.3	0.38 (0.18, 0.80)	
Hachemi 2014	−1.30933332	0.6865416	10.4	0.27 (0.07, 1.04)	
Ho 2016	−1.07880966	0.61857212	11.5	0.34 (0.10, 1.14)	
Kanazu 2014	−2.40794561	0.78266656	9.0	0.09 (0.02, 0.42)	
Mileshkin 2011	−1.27296568	0.39015184	16.1	0.28 (0.13, 0.60)	
Takahashi 2012	−3.21887582	1.21044187	4.9	0.04 (0.00, 0.43)	
Tiseo 2014	−1.2039728	0.50294709	13.7	0.30 (0.11, 0.80)	
Subtotal (95% CI)			**100.0**	**0.32 (0.17, 0.57)**	

Heterogeneity: τ^2=0.43; χ^2=19.56, df=7 (P=0.007); I^2=64%
Test for overall effect: Z=3.77 (P=0.0002)

| **Total (95% CI)** | | | **100** | **0.32 (0.17, 0.57)** | |

Heterogeneity: τ^2=0.43; χ^2=19.56, df=7 (P=0.007); I^2=64%
Test for overall effect: Z=3.77 (P=0.0002)
Test for subgroup difference: not applicable

F

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
FDG-PET					
de Jong 2016	0.04688359	0.29220406	9.5	1.05 (0.59, 1.86)	
de Langen 2011	−0.96758403	0.37731533	8.3	0.38 (0.18, 0.80)	
Engelmann 2014	−0.91629073	0.49149969	6.8	0.40 (0.15, 1.05)	
Hachemi 2014	−1.30933332	0.6865416	4.8	0.27 (0.07, 1.04)	
Ho 2016	−1.07880966	0.61857212	5.4	0.34 (0.10, 1.14)	
Kanazu 2014	−2.40794561	0.78266656	4.1	0.09 (0.02, 0.42)	
Kayani 2011	−0.13926207	0.40929219	7.9	0.87 (0.39, 1.94)	
Lastoria 2013	−0.91629073	0.43894478	7.5	0.40 (0.17, 0.95)	
Lin 2015 group 1	−1.23787436	0.41446566	7.8	0.29 (0.13, 0.65)	
Lin 2015 group 2	0.42526774	0.3860444	8.2	1.53 (0.72, 3.26)	
Mileshkin 2011	−1.27296568	0.39015184	8.1	0.28 (0.13, 0.60)	
Prior 2009	−0.89159812	0.6698942	5.0	0.41 (0.11, 1.52)	
Sahani 2015	−1.66073121	0.67684744	4.9	0.19 (0.05, 0.72)	
Stroobants 2003	−0.96758403	1.02134954	2.8	0.38 (0.05, 2.81)	
Takahashi 2012	−3.21887582	1.21044187	2.1	0.04 (0.00, 0.43)	
Tiseo 2014	−1.2039728	0.50294709	6.7	0.30 (0.11, 0.80)	
Total (95% CI)			**100**	**0.40 (0.28, 0.59)**	

Heterogeneity: τ^2=0.32; χ^2=35.01, df=15 (P=0.002); I^2=57%
Test for overall effect: Z=4.65 (P<0.00001)

Figure 3 (*Continued*)

G

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
≤2 weeks					
Hachemi 2014	−1.30933332	0.6865416	4.4	0.27 (0.07, 1.04)	
Ho 2016	−1.07880966	0.61857212	5.0	0.34 (0.10, 1.14)	
Kanazu 2014	−2.40794561	0.78266656	3.7	0.09 (0.02, 0.42)	
Lastoria 2013	−0.91629073	0.43894478	7.0	0.40 (0.17, 0.95)	
Lin 2015 group 1	−1.23787436	0.41446566	7.3	0.29 (0.13, 0.65)	
Lin 2015 group 2	0.42526774	0.3860444	7.7	1.53 (0.72, 3.26)	
Mileshkin 2011	−1.27296568	0.39015184	7.7	0.28 (0.13, 0.60)	
Schwarzenberg 2012	−0.63487827	0.46308418	6.7	0.53 (0.21, 1.31)	
Stroobants 2003	−0.96758403	1.02134954	2.5	0.38 (0.05, 2.81)	
Takahashi 2012	−3.21887582	1.21044187	1.9	0.04 (0.00, 0.43)	
Tiseo 2014	−1.2039728	0.50294709	6.2	0.30 (0.11, 0.80)	
Subtotal (95% CI)			**60.2**	**0.35 (0.22, 0.57)**	

Heterogeneity: $\tau^2=0.33$; $\chi^2=21.86$, $df=10$ ($P=0.02$); $I^2=54\%$
Test for overall effect: $Z=4.27$ ($P<0.0001$)

H

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Hazard ratio IV, random, 95% CI
>2 weeks					
de Jong 2016	0.04688359	0.29220406	9.1	1.05 (0.59, 1.86)	
de Langen 2011	−0.96758403	0.37731533	7.9	0.38 (0.18, 0.80)	
Engelmann 2014	−0.91629073	0.49149969	6.4	0.40 (0.15, 1.05)	
Kayani 2011	−0.13926207	0.40929219	7.4	0.87 (0.39, 1.94)	
Prior 2009	−0.89159812	0.6698942	4.6	0.41 (0.11, 1.52)	
Sahani 2015	−1.66073121	0.67684744	4.5	0.19 (0.05, 0.72)	
Subtotal (95% CI)			**39.8**	**0.54 (0.32, 0.89)**	

Heterogeneity: $\tau^2=0.19$; $\chi^2=9.81$, $df=5$ ($P=0.08$); $I^2=49\%$
Test for overall effect: $Z=2.40$ ($P=0.02$)

Total (95% CI) — Weight 100 — **0.41 (0.29, 0.59)**

Heterogeneity: $\tau^2=0.28$; $\chi^2=35.05$, $df=16$ ($P=0.004$); $I^2=54\%$
Test for overall effect: $Z=4.83$ ($P<0.00001$)
Test for subgroup difference: $\chi^2=1.45$, $df=1$ ($P=0.23$); $I^2=30.9\%$

PET-response | PET-non-response
0.01 0.1 1 10 100

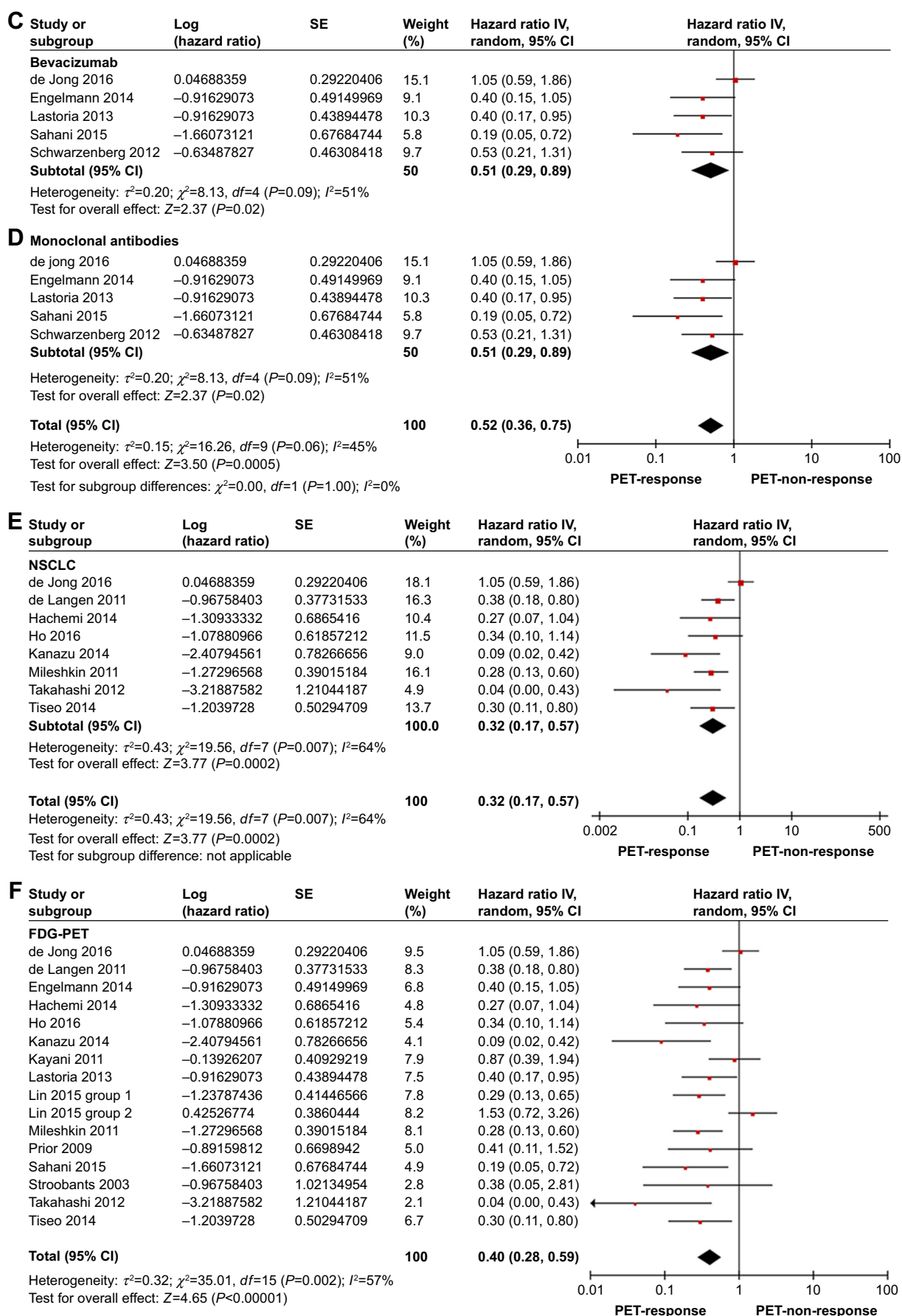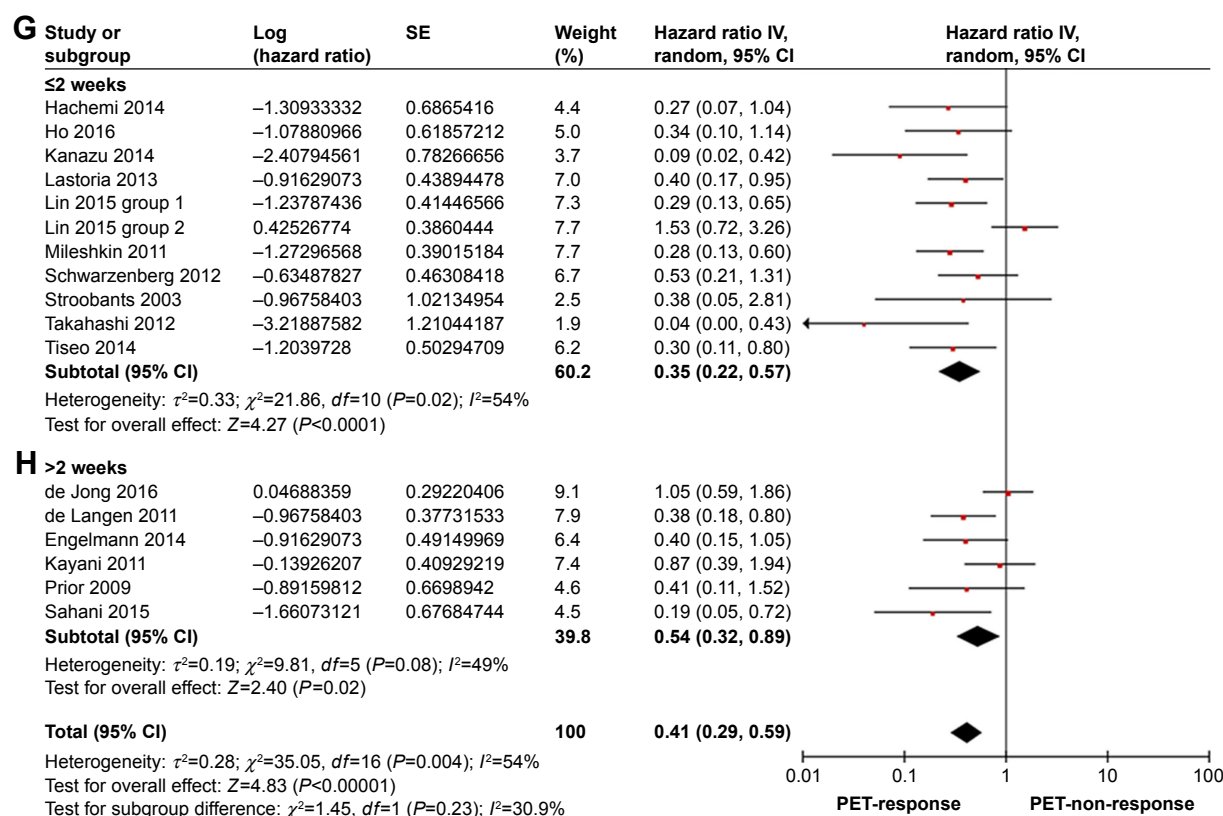**Figure 3** Subgroup analyses on the incidence of PFS in patients treated with (**A**) erlotinib/gefitinib; (**B**) small molecular targeted agents; (**C**) bevacizumab; (**D**) monoclonal antibodies; (**E**) NSCLC; (**F**) FDG-PET; (**G**) ≤2 weeks; and (**H**) >2 weeks.
Note: Lin 2015 (group 1) and Lin 2015 (group 2) were two studies included in one article.
Abbreviations: FDG, fluorodeoxyglucose; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; PFS, progression-free survival; SE, standard error.

the first evaluating response was generally performed not earlier than 4 weeks following the initial treatment since little change occurred at early stage. Accordingly, clinician was frequently in a dilemma to determine the early treatment response and modify treatment strategy opportunely. However, in regard to PET, several investigations manifested that early PET assessment had been established as a prognostic biomarker for the response to targeted therapy in various tumors. Some studies advocated that early PET evaluation (on day 2–14) was competent to predict survival in NSCLC treated with erlotinib/gefitinib.[2,3,16,18,19,21,22,24,26,27,35,38,43,44] Concordant results were also acquired in soft tissue sarcoma,[32] malignant glioma,[23,34] breast cancer,[20] CRC,[31,36] and RCC.[25,37] In our study, early assessment was defined as reevaluating PET within 2 weeks, and it indicated that early assessment proved to be a valuable predictor of long-term outcome. The inherent mechanism that lay behind it was the decline of 18F-FDG uptake 24–48 hours before inhibition of proliferation and induction of apoptosis in gefitinib-sensitive tumors,[45] but such phenomenon was not observed in response to conventional cytotoxic chemotherapy.[46] This study revealed the potential of applying PET screening during the early change in tumor activity, thereby facilitating an early adjustment of therapeutic strategy and to maximize therapeutic effect, minimize side effect, and save cost.

Furthermore, our results demonstrated that 18F-FLT and 18F-FDG possessed comparable advantage in assessing response in malignancies treated with molecularly targeted therapy. Currently, 18F-FDG PET has enjoyed widespread popularity for imaging extracranial tumors and 18F-FLT PET in gliomas,[47] but it fails to distinguish proliferation from inflammation, for both of them possess active glycometabolism. Moreover, 18F-FDG uptake is influenced not only by tumor glucose metabolism but also by inflammation,[48] hypoxia,[49] and fasting time or serum glucose level[50] as well. Interestingly, 18F-FLT, a PET tracer to mirror tumor cell proliferation, was a preferred tracer than 18F-FDG in identifying therapeutic effects. The mechanism behind it was possibly, in contrast to 18F-FDG (a glucose analog) and 18F-FLT (a thymidine analog), retained in proliferating tissues through the activity of thymidine kinase-1.[51] Briefly, 18F-FDG accumulates in tissues with high glycolytic

activity, but 18F-FLT aggregates in proliferating cells, the latter exhibiting a proliferation specificity[52,53] and being a potentially preferable candidate for evaluating response to targeted therapy.[54] Further studies are recommended since only three eligible articles about 18F-FLT were recruited.

Limitations

The limitations of this study included: first, the sample size was relatively small and some recruited articles were retrospective, although the eligible studies contained

25 comprising 865 participants; second, the cutoff changing level of SUVmax in eligible studies lacked uniform response criteria. This meta-analysis will be updated if further eligible studies are identified.

Conclusion

Our study demonstrated that PET was a favorable approach to predict the prognosis of molecularly targeted therapy for solid tumors. PET assessment within 2 weeks could be useful to predict clinical outcome.
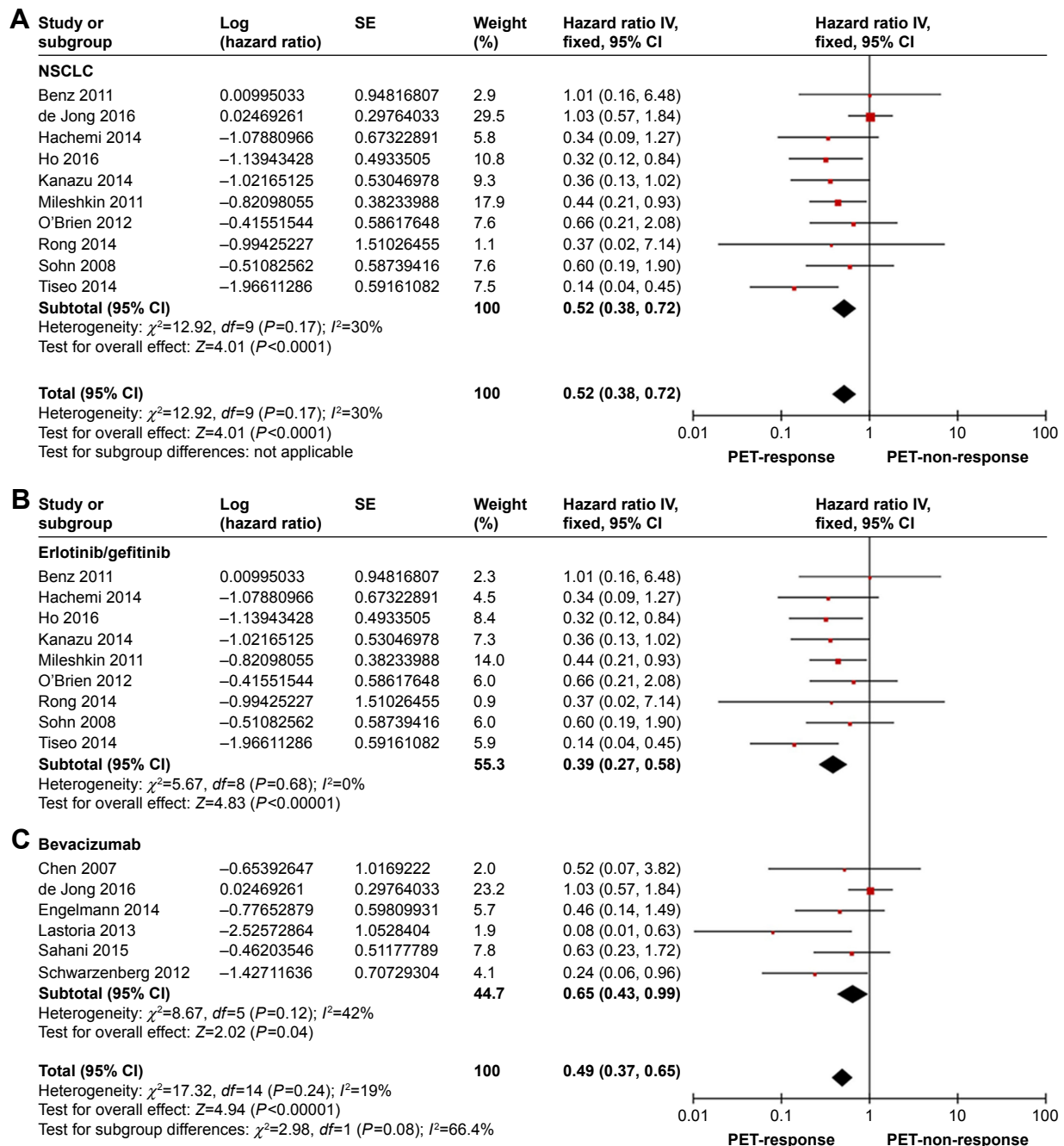

A

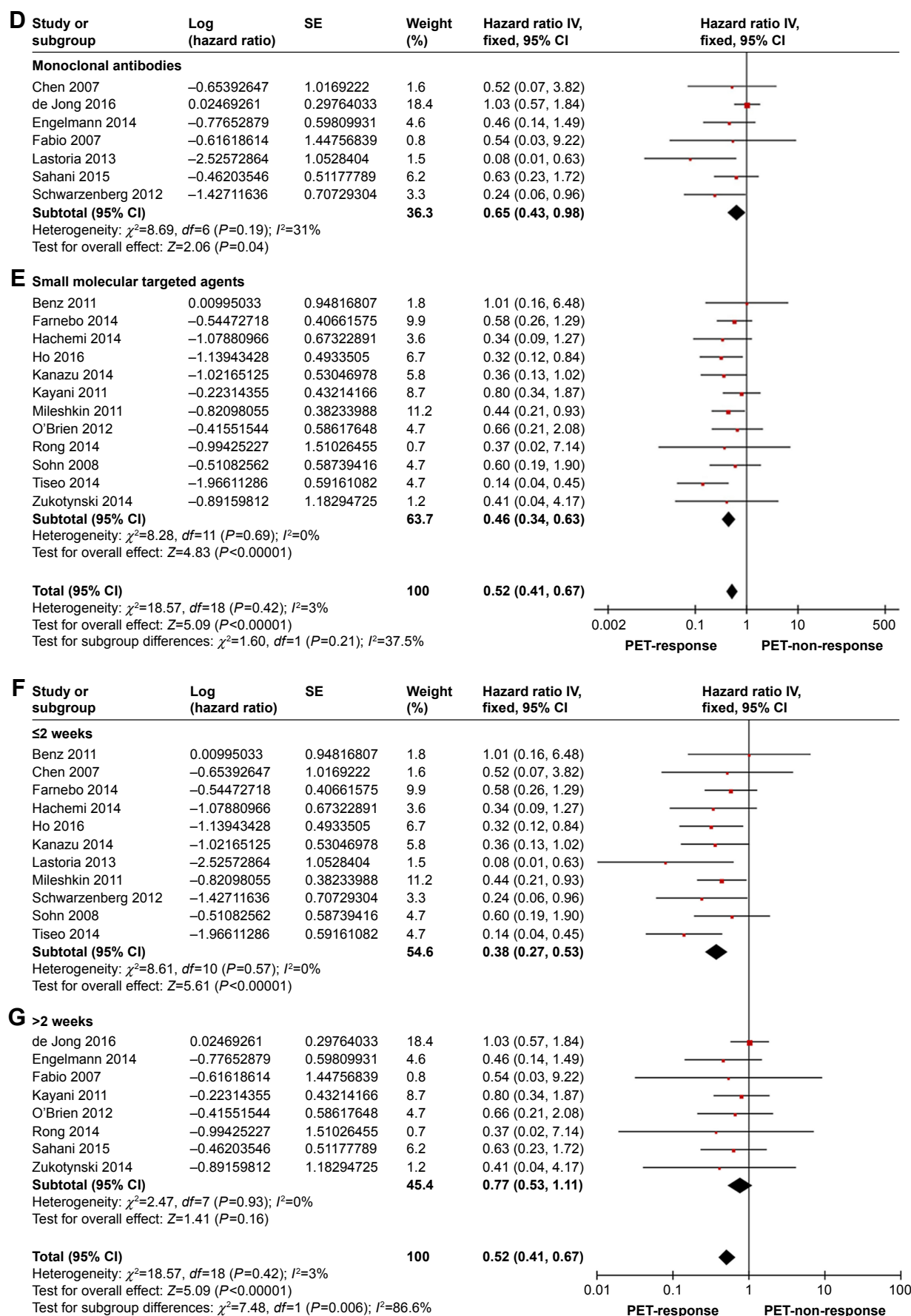| Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
NSCLC				
Benz 2011	0.00995033	0.94816807	2.9	1.01 (0.16, 6.48)
de Jong 2016	0.02469261	0.29764033	29.5	1.03 (0.57, 1.84)
Hachemi 2014	−1.07880966	0.67322891	5.8	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	10.8	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	9.3	0.36 (0.13, 1.02)
Mileshkin 2011	−0.82098055	0.38233988	17.9	0.44 (0.21, 0.93)
O'Brien 2012	−0.41551544	0.58617648	7.6	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	1.1	0.37 (0.02, 7.14)
Sohn 2008	−0.51082562	0.58739416	7.6	0.60 (0.19, 1.90)
Tiseo 2014	−1.96611286	0.59161082	7.5	0.14 (0.04, 0.45)
Subtotal (95% CI)			**100**	**0.52 (0.38, 0.72)**
Heterogeneity: χ^2=12.92, df=9 (P=0.17); I^2=30%				
Test for overall effect: Z=4.01 (P<0.0001)				
Total (95% CI)			**100**	**0.52 (0.38, 0.72)**
Heterogeneity: χ^2=12.92, df=9 (P=0.17); I^2=30%				
Test for overall effect: Z=4.01 (P<0.0001)				
Test for subgroup differences: not applicable				

B

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Erlotinib/gefitinib				
Benz 2011	0.00995033	0.94816807	2.3	1.01 (0.16, 6.48)
Hachemi 2014	−1.07880966	0.67322891	4.5	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	8.4	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	7.3	0.36 (0.13, 1.02)
Mileshkin 2011	−0.82098055	0.38233988	14.0	0.44 (0.21, 0.93)
O'Brien 2012	−0.41551544	0.58617648	6.0	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	0.9	0.37 (0.02, 7.14)
Sohn 2008	−0.51082562	0.58739416	6.0	0.60 (0.19, 1.90)
Tiseo 2014	−1.96611286	0.59161082	5.9	0.14 (0.04, 0.45)
Subtotal (95% CI)			**55.3**	**0.39 (0.27, 0.58)**
Heterogeneity: χ^2=5.67, df=8 (P=0.68); I^2=0%				
Test for overall effect: Z=4.83 (P<0.00001)				

C

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Bevacizumab				
Chen 2007	−0.65392647	1.0169222	2.0	0.52 (0.07, 3.82)
de Jong 2016	0.02469261	0.29764033	23.2	1.03 (0.57, 1.84)
Engelmann 2014	−0.77652879	0.59809931	5.7	0.46 (0.14, 1.49)
Lastoria 2013	−2.52572864	1.0528404	1.9	0.08 (0.01, 0.63)
Sahani 2015	−0.46203546	0.51177789	7.8	0.63 (0.23, 1.72)
Schwarzenberg 2012	−1.42711636	0.70729304	4.1	0.24 (0.06, 0.96)
Subtotal (95% CI)			**44.7**	**0.65 (0.43, 0.99)**
Heterogeneity: χ^2=8.67, df=5 (P=0.12); I^2=42%				
Test for overall effect: Z=2.02 (P=0.04)				
Total (95% CI)			**100**	**0.49 (0.37, 0.65)**
Heterogeneity: χ^2=17.32, df=14 (P=0.24); I^2=19%				
Test for overall effect: Z=4.94 (P<0.00001)				
Test for subgroup differences: χ^2=2.98, df=1 (P=0.08); I^2=66.4%				

Figure 4 (*Continued*)

D

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Monoclonal antibodies				
Chen 2007	−0.65392647	1.0169222	1.6	0.52 (0.07, 3.82)
de Jong 2016	0.02469261	0.29764033	18.4	1.03 (0.57, 1.84)
Engelmann 2014	−0.77652879	0.59809931	4.6	0.46 (0.14, 1.49)
Fabio 2007	−0.61618614	1.44756839	0.8	0.54 (0.03, 9.22)
Lastoria 2013	−2.52572864	1.0528404	1.5	0.08 (0.01, 0.63)
Sahani 2015	−0.46203546	0.51177789	6.2	0.63 (0.23, 1.72)
Schwarzenberg 2012	−1.42711636	0.70729304	3.3	0.24 (0.06, 0.96)
Subtotal (95% CI)			**36.3**	**0.65 (0.43, 0.98)**

Heterogeneity: χ^2=8.69, df=6 (P=0.19); I^2=31%
Test for overall effect: Z=2.06 (P=0.04)

E Small molecular targeted agents

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
Benz 2011	0.00995033	0.94816807	1.8	1.01 (0.16, 6.48)
Farnebo 2014	−0.54472718	0.40661575	9.9	0.58 (0.26, 1.29)
Hachemi 2014	−1.07880966	0.67322891	3.6	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	6.7	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	5.8	0.36 (0.13, 1.02)
Kayani 2011	−0.22314355	0.43214166	8.7	0.80 (0.34, 1.87)
Mileshkin 2011	−0.82098055	0.38233988	11.2	0.44 (0.21, 0.93)
O'Brien 2012	−0.41551544	0.58617648	4.7	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	0.7	0.37 (0.02, 7.14)
Sohn 2008	−0.51082562	0.58739416	4.7	0.60 (0.19, 1.90)
Tiseo 2014	−1.96611286	0.59161082	4.7	0.14 (0.04, 0.45)
Zukotynski 2014	−0.89159812	1.18294725	1.2	0.41 (0.04, 4.17)
Subtotal (95% CI)			**63.7**	**0.46 (0.34, 0.63)**

Heterogeneity: χ^2=8.28, df=11 (P=0.69); I^2=0%
Test for overall effect: Z=4.83 (P<0.00001)

Total (95% CI)			**100**	**0.52 (0.41, 0.67)**

Heterogeneity: χ^2=18.57, df=18 (P=0.42); I^2=3%
Test for overall effect: Z=5.09 (P<0.00001)
Test for subgroup differences: χ^2=1.60, df=1 (P=0.21); I^2=37.5%

Hazard ratio IV, fixed, 95% CI
0.002 0.1 1 10 500
PET-response   PET-non-response

F

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
≤2 weeks				
Benz 2011	0.00995033	0.94816807	1.8	1.01 (0.16, 6.48)
Chen 2007	−0.65392647	1.0169222	1.6	0.52 (0.07, 3.82)
Farnebo 2014	−0.54472718	0.40661575	9.9	0.58 (0.26, 1.29)
Hachemi 2014	−1.07880966	0.67322891	3.6	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	6.7	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	5.8	0.36 (0.13, 1.02)
Lastoria 2013	−2.52572864	1.0528404	1.5	0.08 (0.01, 0.63)
Mileshkin 2011	−0.82098055	0.38233988	11.2	0.44 (0.21, 0.93)
Schwarzenberg 2012	−1.42711636	0.70729304	3.3	0.24 (0.06, 0.96)
Sohn 2008	−0.51082562	0.58739416	4.7	0.60 (0.19, 1.90)
Tiseo 2014	−1.96611286	0.59161082	4.7	0.14 (0.04, 0.45)
Subtotal (95% CI)			**54.6**	**0.38 (0.27, 0.53)**

Heterogeneity: χ^2=8.61, df=10 (P=0.57); I^2=0%
Test for overall effect: Z=5.61 (P<0.00001)

G >2 weeks

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
de Jong 2016	0.02469261	0.29764033	18.4	1.03 (0.57, 1.84)
Engelmann 2014	−0.77652879	0.59809931	4.6	0.46 (0.14, 1.49)
Fabio 2007	−0.61618614	1.44756839	0.8	0.54 (0.03, 9.22)
Kayani 2011	−0.22314355	0.43214166	8.7	0.80 (0.34, 1.87)
O'Brien 2012	−0.41551544	0.58617648	4.7	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	0.7	0.37 (0.02, 7.14)
Sahani 2015	−0.46203546	0.51177789	6.2	0.63 (0.23, 1.72)
Zukotynski 2014	−0.89159812	1.18294725	1.2	0.41 (0.04, 4.17)
Subtotal (95% CI)			**45.4**	**0.77 (0.53, 1.11)**

Heterogeneity: χ^2=2.47, df=7 (P=0.93); I^2=0%
Test for overall effect: Z=1.41 (P=0.16)

Total (95% CI)			**100**	**0.52 (0.41, 0.67)**

Heterogeneity: χ^2=18.57, df=18 (P=0.42); I^2=3%
Test for overall effect: Z=5.09 (P<0.00001)
Test for subgroup differences: χ^2=7.48, df=1 (P=0.006); I^2=86.6%

Hazard ratio IV, fixed, 95% CI
0.01 0.1 1 10 100
PET-response   PET-non-response

Figure 4 (*Continued*)

H Study or subgroup | Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, fixed, 95% CI | Hazard ratio IV, fixed, 95% CI

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
FDG				
Benz 2011	0.00995033	0.94816807	1.8	1.01 (0.16, 6.48)
de Jong 2016	0.02469261	0.29764033	18.4	1.03 (0.57, 1.84)
Engelmann 2014	−0.77652879	0.59809931	4.6	0.46 (0.14, 1.49)
Fabio 2007	−0.61618614	1.44756839	0.8	0.54 (0.03, 9.22)
Farnebo 2014	−0.54472718	0.40661575	9.9	0.58 (0.26, 1.29)
Hachemi 2014	−1.07880966	0.67322891	3.6	0.34 (0.09, 1.27)
Ho 2016	−1.13943428	0.4933505	6.7	0.32 (0.12, 0.84)
Kanazu 2014	−1.02165125	0.53046978	5.8	0.36 (0.13, 1.02)
Kayani 2011	−0.22314355	0.43214166	8.7	0.80 (0.34, 1.87)
Lastoria 2013	−2.52572864	1.0528404	1.5	0.08 (0.01, 0.63)
Mileshkin 2011	−0.82098055	0.38233988	11.2	0.44 (0.21, 0.93)
O'Brien 2012	−0.41551544	0.58617648	4.7	0.66 (0.21, 2.08)
Rong 2014	−0.99425227	1.51026455	0.7	0.37 (0.02, 7.14)
Sahani 2015	−0.46203546	0.51177789	6.2	0.63 (0.23, 1.72)
Tiseo 2014	−1.96611286	0.59161082	4.7	0.14 (0.04, 0.45)
Zukotynski 2014	−0.89159812	1.18294725	1.2	0.41 (0.04, 4.17)
Subtotal (95% CI)			**90.4**	**0.53 (0.41, 0.69)**

Heterogeneity: χ^2=17.28, df=15 (P=0.30); I^2=13%
Test for overall effect: Z=4.69 (P<0.00001)

Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI
I **FLT**				
Chen 2007	−0.65392647	1.0169222	1.6	0.52 (0.07, 3.82)
Schwarzenberg 2012	−1.42711636	0.70729304	3.3	0.24 (0.06, 0.96)
Sohn 2008	−0.51082562	0.58739416	4.7	0.60 (0.19, 1.90)
Subtotal (95% CI)			**9.6**	**0.43 (0.19, 0.96)**

Heterogeneity: χ^2=1.04, df=2 (P=0.60); I^2=0%
Test for overall effect: Z=2.05 (P=0.04)

Total (95% CI)			**100**	**0.52 (0.41, 0.67)**

Heterogeneity: χ^2=18.57, df=18 (P=0.42); I^2=3%
Test for overall effect: Z=5.09 (P<0.00001)
Test for subgroup differences: χ^2=0.25, df=1 (P=0.62); I^2=0%

0.01 0.1 1 10 100
PET-response   PET-non-response

Figure 4 Subgroup analyses on the incidence of OS in patients treated with: (**A**) NSCLC; (**B**) erlotinib/gefitinib; (**C**) bevacizumab; (**D**) monoclonal antibodies; (**E**) small molecular targeted agents; (**F**) ≤2 weeks; (**G**) >2 weeks; (**H**) FDG-PET; and (**I**) FLT-PET.
Abbreviations: FLT, fluorodeoxythymidine; FDG, fluorodeoxyglucose; NSCLC, non-small-cell lung cancer; OS, overall survival; PET, positron emission tomography; SE, standard error.

Disclosure

The authors report no conflicts of interest in this work.

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