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Review

Relationship between Progression-free Survival and Overall Survival in Randomized Clinical Trials of Targeted and Biologic Agents in Oncology

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Abstract

Introduction: With a gap in a full understanding of the mechanisms by which survival is extended for patients with cancer who are treated with novel biologic and targeted agents, there is the risk that discordant progression-free and overall survival outcomes are observed due to poor clinical trial design or biases in the interpretation of data. This study was designed to examine the role of study quality and design on the outcomes observed with biologic and targeted agents.

Methods: A review of studies in clinicaltrials.gov supplemented with a literature review in OVID Medline was conducted to identify all randomized trials of a biologic/targeted agent versus a non-biologic/targeted comparator in oncology that report both median overall and progression-free survival outcomes. Details of the study, design, population, drugs, and outcomes were extracted. Study quality was evaluated using the PEDro scale. Data were summarized using SPSS 22.0.0.0.

Results: A total of 192 unique studies of 206 pairwise comparisons between a biologic/targeted and comparator were identified. The average absolute magnitude of post-progression survival (difference between OS and PFS) was 9.7 months for biologic/targeted therapy and 9.8 for the comparator. A total of 64 comparisons (31.1%) showed an increase in OS and decrease in PFS, or vice versa, and 25 (12.1%) showed a magnitude of more than 4 months difference between the delta of OS and delta of PFS between the biologic/targeted and comparator arms. Average study quality was high overall (7.7/10), and was comparable for studies with directional differences (7.2/10) as well as for those with the greatest magnitude in post-progression survival (7.4/10).

Conclusion: This review and analysis specifically examined small PFS benefit with large OS benefit as well as small OS benefit with large PFS benefit, including differences in direction of PFS and OS outcomes. No evidence was identified that these are the result of poor study design, but may rather be due to the mechanism of action, specific disease, and population under study. Further work is needed to understand the mechanism of action of novel biologic/targeted agents to better understand their interaction with the tumor microenvironment.

Key words: biologic therapy, overall survival, post-progression survival, disease progression, oncology

Introduction

A requirement of new drug approvals in oncology by the U.S. Food and Drug Administration (FDA) and other regulatory bodies is that the drug shows direct clinical benefit or indirect clinical benefit through a surrogate endpoint [1]. Progression-free survival (PFS), the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical benefit for drug approvals, depending on the disease and response observed, while overall survival (OS), the duration of patient survival from the time of treatment initiation, is a universally-accepted direct measure of clinical benefit.

While improvements in OS clearly demonstrate clinical benefits that are meaningful to patients, PFS, depending on the magnitude, may have high value as

well. By design, PFS and OS will be related, as OS is comprised of PFS plus post-progression survival. However, the relationship between PFS and OS is not always straightforward. In some diseases, such as advanced colorectal and ovarian cancers, there is a strong correlation between the two outcomes, while in others, like sarcoma, advanced breast cancer, prostate cancer and NSCLC, the relationship is less clear [2, 3]. The relationship between PFS and OS becomes more complex in the context of biologic and targeted therapies [3, 4]. Some of the recent novel targeted and immunologic agents have demonstrated relatively low PFS improvements, but dramatic improvements in OS (long periods of post-progression survival) [5, 6].

The development of novel targeted or biologic therapies (e.g. therapies that target specific mechanisms in a cancer cell, such as immune checkpoint inhibitors, or those that are derived from living organisms, such as antibodies and vaccines) has been of major interest in the field of oncology. As our understanding of the mechanisms of carcinogenesis has evolved, there has been a growth in the development of treatments targeting the tumor microenvironment and immune response. The pathway for checkpoint inhibition supporting the observed outcomes with PD-1 and PDL-1 inhibitors is relatively well characterized [7]; however, the exact mechanism by which some novel agents affect long-term survival, such those that act on platelet-derived growth factor receptor-alpha (PDGFRα) inhibition, remains elusive [8].

With the development of targeted biologic therapies, consideration must be given to the assessment of disease response using RECIST Criteria [9]. This is particularly challenging, given the various phenotypes and kinetics of tumor responses with targeted therapies. The development of novel imaging techniques to assess the micro-structural properties, as opposed to size-based parameters, as well as the reconsideration of timing assessment criteria, will be paramount in the assessment of these treatment-related changes. Tumor response criteria should take into account the mechanism of action of treatment, biological pathways expressed as well as tumor type and pathogenicity. Although tumor response rate, as measured through RECIST, will remain important, the meaningful benefit has thus far been with prolonged overall survival [4]. The combination of a strong clinical background and thorough understanding of the mechanism of action at work is crucial to the interpretation of the increased survival rates seen with novel targeted therapies.

With a gap in a full understanding of the mechanisms by which survival is extended, there is the risk that discordant response and survival outcomes are observed due to poor clinical trial design or biases in the interpretation of data. For example, design, conduct, analysis and publication flaws have been identified that can bias research findings [10, 11]. Design flaws may include: failure to conceal allocation, resulting in the subjective selection of patients perceived to be most appropriate for the treatment assignment; non-blinded designs, while may be the only solution in oncology if agents are being compared that have different infusion schedules, treatment schedules or toxicity profiles; study personnel may evaluate or remove participants from treatment differentially between arms if there is knowledge of which treatment is being administered; and imbalance in randomized groups that may be in part due to failure to stratify on key prognostic factors. Biases in the analysis and publication of trial results can be due to selective reporting of outcomes, analyses that are not conducted as intent-to-treat (e.g. exclusion of some randomized participants), and gaps in reported data (e.g. point estimates without measures of variability) [12]. In some ways, PFS is an outcome with some limitations, as it can only be measured at the time of a scheduled imaging scan or other assessment (e.g. leading to periodic intervals at which events are measured regardless of when it actually occurred), whereas OS can be measured to the exact day of the event.

As the number and complexity of new targeted and biologic agents grow, it becomes more complex to interpret and rely on the scientific evidence when the typical patterns of survival and response are not observed, as had been more common with cytotoxic agents. To address this issue, this study was designed to explore the relationship between PFS and OS observed in randomized trials of biologic and targeted agents. The primary purpose of this study was to evaluate the results of clinical trials reporting PFS and OS outcomes to examine situations in which these outcomes may differ (one increases, the other decreases) or where there may be large periods of post-progression survival differences. Observed differences of direction and magnitude were further evaluated in the context of study quality to identify the risk of study design flaws that may influence measured survival outcomes.

Methods

A clinical trial review was conducted within the U.S. National Library of Medicine's clinical trials registry (clinicaltrials.gov) supplemented by a search of the published literature. The clinicaltrials.gov search was conducted using i2E (Linguamatics Inc), a natural language processing text mining software.

The i2E query for clinicaltrials.gov included the terms Phase 2 or 3, biologic or targeted agents, cancer terms, and survival data without restriction on the year of the study or results. This was supplemented with a literature search in Ovid using the MEDLINE and pre-MEDLINE databases using similar terms as the i2E search for publications since 2014 (to capture any data that may not yet have been entered into clinicaltrials.gov). The search strategies were executed in April 2018 (complete search strategies are shown in the Supplemental Materials).

Eligible studies were limited to randomized trials that had a biologic or targeted agent in at least one, but not all, treatment arms. The minimum data reporting requirements included median PFS and OS. All cancer types and populations were eligible for inclusion; however, each trial was required to study a specific tumor type, so that trials of multiple tumor types were excluded. Eligible studies were published in English and enrolled adult cancer patients. Two independent reviewers evaluated all potential studies for eligibility. The final set of eligible studies underwent extensive data extraction to obtain study details according to PICO (population, intervention, control, outcome) criteria. Population variables included sample size, demographics and disease site. Intervention and control variables included the agents and regimens used, dose, duration and line of therapy. Outcomes included PFS, OS and tumor response. Additional variable collected included study quality using the Physiotherapy Evidence Database (PEDro) scale. This scale reports study quality across 11 items, with a total quality score ranging from 0-10 (the first item is related to external generalizability and is not included in the total score); scores above 6 generally represent good study quality, and scores below that level are poor study quality. In addition to the PEDro scale, imbalances in post-study therapies were recorded, as these may influence subsequent OS outcomes in oncology.

Studies were summarized descriptively. The difference in median months of OS and PFS (delta OS and delta PFS) was calculated between biologic/targeted and comparator (non-biologic and non-targeted) therapy. For trials with multiple treatment arms, these were calculated for each biologic/targeted therapy versus the comparator. Negative differences indicate that the comparator performed better than the biologic/targeted therapy, whereas positive differences indicate that the biologic/targeted therapy performed better.

Post-progression survival (PPS) is the time the patient is alive following disease progression (OS = PFS + PPS). To evaluate PPS, median PFS was subtracted from the median OS for each treatment arm, and the difference in PPS for the comparator from that of the biologic/targeted therapy was summarized (delta PPS = $PPS_{biologic} - PPS_{comparator}$). The difference in OS and PFS were also calculated (delta OS = $OS_{biologic} - OS_{comparator}$; delta PFS = $PFS_{biologic} - PFS_{comparator}$, respectively). To explore the difference in PPS between arms, the Delta PPS was calculated (deltaOS – delta PFS). Studies with differential outcomes (e.g. Delta PFS > 0 months and delta OS ≤ 0 months, or delta PFS ≤ 0 months and delta OS > 0 months) were summarized. Biologic/targeted therapies with large delta OS but small delta PFS as well as those with large delta PFS but small delta OS were also summarized. Absolute ratios between delta PFS and delta OS were explored as the primary outcome of this study but not pursued as an endpoint, as large ratios may result from small numerical differences (e.g. 3 days of PFS benefit and 1 months of OS benefit result in a 30:1 ratio, whereas a 2 month PFS and a 10 month OS benefit is only a 5:1 ratio). Due to the lack of direct clinical relevance of ratios, these were ultimately not included in this study.

SPSS 22.0.0.0. (IBM Corporation) and Excel 2016 (Microsoft, Inc.) were used to conduct analyses and to generate the summary figures.

Results

After applying eligibility criteria and excluding duplicates, a total of 24 clinicaltrials.gov records and 168 publications (representing 192 unique studies and 206 pairwise comparisons between biologic/targeted versus comparator) met eligibility criteria and were included in this analysis (the full list of included publications is provided in the Supplemental Materials). The number of eligible publications of trials comparing chemotherapy agents by year of publication are summarized in Figure 1. The most common tumor sites included lung (n=60, 31.3%), breast (n=24, 12.5%), colorectal (n=18, 9.4%), gastric/esophageal (n=17, 8.9%), pancreatic (n=13, 6.8%), gynecologic (n=8, 4.2%) and glioblastoma (n=8, 4.2%). Most eligible studies investigated first-line therapy (n=87, 45.3%); 53 (27.6%) were second-line trials, 9 (4.7%) investigated maintenance therapy, 2 (1.0%) studied neoadjuvant or adjuvant therapy and the remaining were not limited to a single line of therapy.

Differences in PFS and OS

There were 206 pairwise comparisons between biologic/targeted and comparator therapy across all included studies due to the inclusion of multiple-arm trials. The distribution of delta in OS and PFS of these comparisons is presented in in Figure 2 (excluding dual publications of the same study), sorted by

magnitude in OS improvement. Values close to zero indicate similar magnitude of improvement between the biologic/targeted and comparator (non-biologic/targeted) therapy. Higher values indicate greater improvement associated with the biologic/targeted therapy, and lower values indicate greater improvement associated with the comparator therapy. Overall survival associated with the biologic/targeted therapy ranged from 9.8 months lower than the comparator to a gain of 25.4 months versus the comparator. PFS associated with the biologic/targeted therapy ranged from 8.2 months lower than the comparator to 14.9 months more than the comparator. Biologic/targeted therapies improved both OS and PFS an average of 1.2 months (SD: 3.8 and 2.5, respectively) versus non-biologic/targeted therapy.

The absolute magnitude of PPS for patients treated with biologic/targeted therapy was an average of 9.7 months (standard deviation, SD=7.4), and the absolute magnitude of PPS for the non-biologic/targeted comparator was 9.8 months (SD=7.6). Figure 3 presents the delta PPS across all comparisons included in this study.

Direction of survival outcomes

The direction of OS and PFS findings was not consistent across all studies. While there were 33 (16.0%) comparisons in which both OS and PFS were lower for patients treated in the biologic/targeted arm than the comparator, and 104 (50.5%) in which OS and PFS were both higher with the biologic/targeted therapy; 39 (18.9%) showed improvement in PFS but none in OS, and 25 (12.1%) showed improvement in OS but none in PFS. The studies demonstrating differential results between PFS and OS are summarized in Tables 1 and 2. Among the comparisons that demonstrated inconsistent results between PFS and OS, the magnitude of inconsistency was relatively low. Among the 39 showing improvement in PFS but not OS, the average PFS benefit was 1.5 months (standard deviation [SD] =

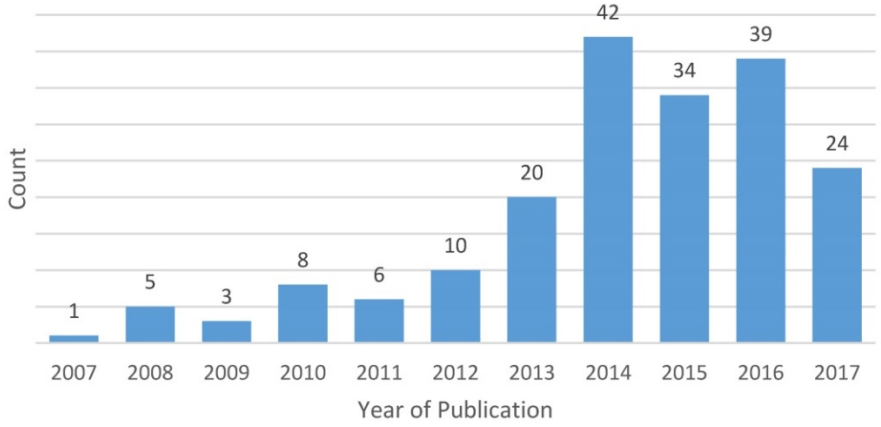

Figure 1. Year of publication of eligible studies (n=192)

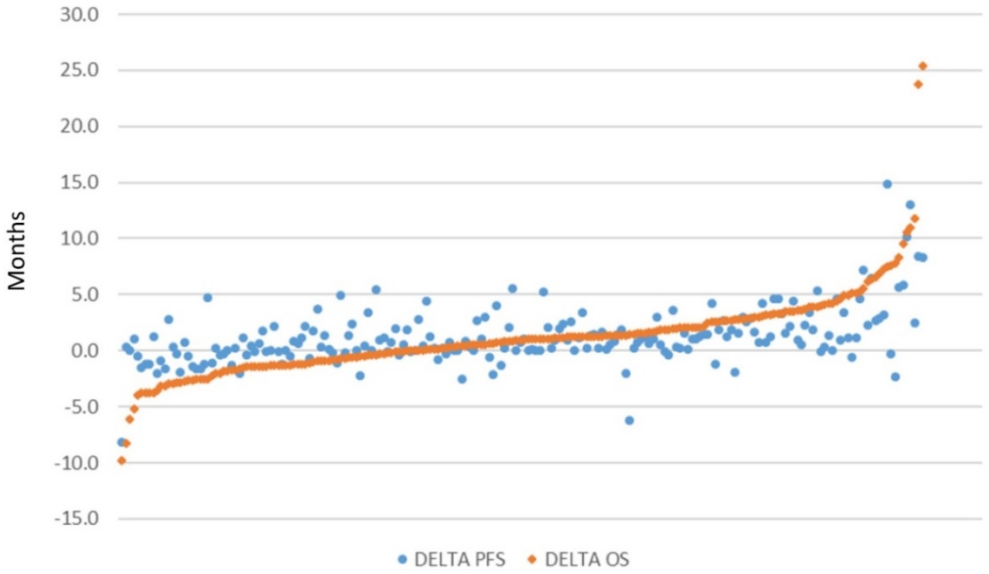

Figure 2. Scatterplot of difference in median months of overall survival (OS) and median progression-free survival (PFS), respectively, between treatment arms (n=206)

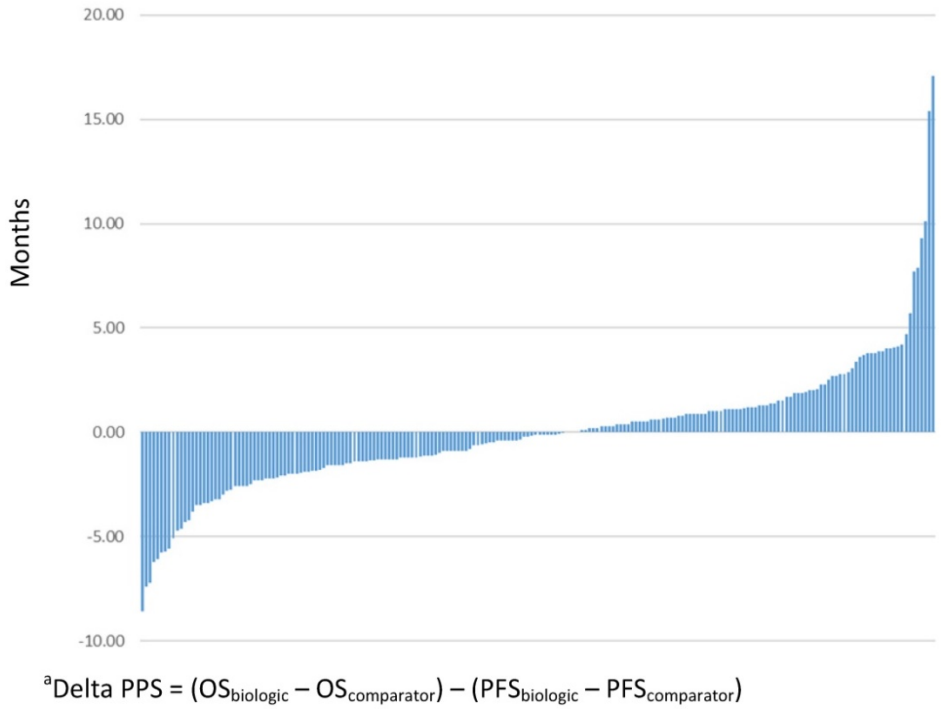

Figure 3. Delta post-progression survival (PPS) between biologic/targeted and non-biologic/targeted comparator[a] (N=206)

1.4), and the average decline in OS was -1.4 months (SD=1.6). Among the 25 comparisons with improvements in OS but not PFS, the average benefit in OS was 2.0 months (SD = 2.2), and the average decline in PFS was -0.9 months (SD=1.4).

Magnitude of survival difference

Comparisons with at least a 4-month difference in delta PPS (n=25) are presented in Table 3. Of these, 16 showed OS benefits biologic/targeted therapy, and 9 showed no benefit in OS for the patients treated with biologic/targeted therapy. Studies of biologic/targeted therapies that improved OS investigated regimens that included pembrolizumab, nivolumab, gefitinib and erlotinib in NSCLC, trastuzumab in breast cancer, lapatinib in breast cancer and SCCHN, rituximab and bortezomib in mantle cell lymphoma, bevacizumab in glioblastoma, vandetanib in SCLC, and olaratumab in soft tissue sarcoma, and MK-2206, a novel AKT inhibitor. Other than MK-2206, which is still in development, and vendetanib, which was associated with increased toxicity [13], each of these other agents had FDA approval and/or NCCN guideline placement for use in these diseases. In February 2019, olaratumab was removed from NCCN clinical practice guidelines following the results of a phase III clinical trial, which found no difference in the primary endpoint of overall survival between study arms [14].

Study quality

The average PeDRO score of included studies was 7.7 (SD: 1.8). Quality scores ranged from 3 to 10. Only 24 (12.6%) were considered low-quality studies, and 15 of these (62.5%) were not published (e.g. clinicaltrials.gov record only). Studies with differential PFS and OS outcomes had an average score of 7.2 (SD: 1.7). Studies with the largest differences in OS-PFS between biologic/targeted and comparator arms had an average quality score of 7.4 (SD: 1.7). Most studies (127, 66.5%) did not report post-study therapies received. However, among the 64 (33.5%) that did report these data, 41 (64.1%) showed differences in subsequent treatments received, and 23 (35.9%) reported similarities in post-study therapies. Of those 23 with similar post-study therapies, three (13.0%) showed differential OS/PFS direction of benefit,[15-17] and 2 (8.7%) showed large magnitude in the difference between OS and PFS outcomes.[5, 15] Of studies with imbalanced post-study therapies, 19 (46.3%) found directional differences in OS/PFS and 10 (24.3%) showed large differences in OS/PFS, and 12 (29.3%) found a no benefit in OS with the biologic/targeted therapy. Among all studies with a benefit in OS, only 49 (36.8%) reported post study therapies; of those, 29 (59.2%) reported imbalance. Among all studies with no benefit in OS, 15 (20.5%) reported post-study therapies; of those, 12 (80%) had imbalance in post-study therapies. The average study quality of studies reporting benefits in OS was 7.8/10 (SD=1.8) and for those with no OS benefit the average study quality was 7.4/10 (SD=1.7).

Table 1. Comparisons showing improvement (>0 months) in progression-free survival (PFS) and no improvement (≤0 months) in overall survival (n=39)

Reference	Disease site	Line of therapy	Treatment comparison	N	Median OS (months)	Median PFS (months)	Study Quality
Beer et al. 2017[18]	Prostate	1	ipilumumab	400	28.7	5.6	9
			placebo	202	29.7	3.8	
Belani et al. 2014[19]	NSCLC	1	axitinib + pemetrexed + cisplatin	58	14.7	7.9	8
			pemetrexed + cisplatin	57	15.9	7.1	
Blumenschein et al. 2015[20]	NSCLC	2	trametinib	86	8.1	2.7	6
			docetaxel	43	9.9	2.6	
Burtness et al. 2016 [21]	Pancreatic	1	irinotecan + docetaxel + cetuximab	45	5.3	4.5	7
			irinotecan + docetaxel	46	6.5	3.9	
Chauffert et al. 2014[22]	Glioblastoma	Neoadjuvant/ adjuvant	bevacizumb + irinotecan	60	11.1	7.1	7
			temozolomide	60	11.1	5.2	
Doebele et al. 2015[23]	NSCLC	1	ramucirumab + gemcitabine + cisplatin	71	9.8	5.6	6
			gemcitabine + cisplatin	69	11.8	5.4	
Evans et al. 2017[24]	Pancreatic	1	dasatinib + gemcitabine	100	12.33	5.49	9
			placebo + gemcitabine	102	12.93	5.46	
Gilbert et al. 2014[25]	Glioblastoma	1	bevacizumab	320	15.7	10.7	9
			placebo	317	16.1	7.3	
Gridelli et al. 2014[26]	NSCLC	1	vandetanib + gemcitabine	61	8.6	6.0	9
			placebo + gemcitabine	63	10.0	5.6	
Hegewisch-Becker, et al. 2015[15]	Colorectal	Maintenance	fluoropyrimidine + bevacizumab	158	20.2	6.3	7
			no maintenance	158	23.1	3.5	
Hegewisch-Becker et al. 2015[15]	Colorectal	Maintenance	bevacizumab	156	21.9	4.6	7
			no maintenance	158	23.1	3.5	
Herrlinger et al. 2016[27]	Glioblastoma	1	bevacizumb + irinotecan	122	16.6	9.7	7
			temozolomide	60	17.5	6.0	
Kim et al. 2013[28]	NSCLC	2	cetuximab + pemetrexed	301	6.9	2.9	7
			pemetrexed	304	7.8	2.8	
Leone et al. 2016[29]	Biliary tract	1	gemcitabine + oxaliplatin + panitumumab	45	9.9	5.3	7
			gemcitabine + oxaliplatin	44	10.2	4.4	
Li et al. 2014[30]	NSCLC	2	erlotinib	61	11.7	4.1	6
			pemetrexed	62	13.4	3.9	
Malka et al. 2014[31]	Biliary tract	1	gemcitabine + oxaliplatin + cetuximab	76	11.0	6.1	6
			gemcitabine + oxaliplatin	74	12.4	5.5	
Martin et al. 2015[32]	Breast	1	letrozole or fulvestrant + bevacizumab	191	52.1	19.3	6
			letrozole or fulvestrant	189	52.8	14.4	
Masi et al. 2015[33]	Colorectal	2	FOLFIRI or FOLFOX6 + bevacizumab	92	14.1	6.8	7
			FOLFIRI or FOLFOX6	92	15.5	5.0	
McDermott et al. 2008[34]	Melanoma	1	sorafenib + dacarbazine	51	10.5	4.9	9
			placebo + dacarbazine	50	11.8	2.7	
Middleton et al. 2017[35]	Pancreatic	1	vandetanib + gemcitabine	72	8.8	8.0	9
			placebo + gemcitabine	70	9.0	6.1	
Miller et al. 2012[36]	NSCLC	2+	atafanib	390	10.8	3.3	9
			placebo	195	12.0	1.1	
Moore et al. 2016[37]	Colorectal	2	ramucirumab + modified FOLFOX6	52	9.6	4.9	5
			modified FOLFOX6	54	12.3	4.2	
NCT00110019[38]	Melanoma	1	paclitaxel + carboplatin + sorafenib	410	11.1	4.9	8
			paclitaxel + carboplatin + placebo	413	11.3	4.2	
NCT00393939[39]	Breast	1	sunitinib + docetaxel	296	26.0	8.6	5
			docetaxel	297	28.9	8.3	
NCT00403403[40]	SCLC	1	cisplatin or carboplatin + etoposide + bevacizumab	52	9.4	5.5	7
			cisplatin or carboplatin + etoposide + placebo	50	10.9	4.4	
NCT00459043[41]	SCCHN	Multiple	vandetanib + docetaxel	15	5.6	2.1	3
			docetaxel	15	6.2	0.7	
NCT00777179[42]	NSCLC	Maintenance	vandetanib	75	15.6	2.7	7
			placebo	42	20.8	1.7	
NCT01234337[43]	Breast	1+	sorafenib + capecitabine	266	18.9	5.5	10
			placebo + capecitabine	271	20.3	5.4	
Oza et al. 2015[44]	Ovarian	1	carboplatin + paclitaxel + bevacizumab	764	58.0	19.9	8
			carboplatin + paclitaxel	764	58.6	17.5	
Paz-Ares et al. 2012[45]	NSCLC	1	gemcitabine + cisplatin + sorafenib	452	12.4	6.0	10
			gemcitabine + cisplatin + placebo	452	12.5	5.5	
Ramlau et al. 2012[46]	NSCLC	2	aflibercept + docetaxel	456	10.1	5.2	10
			placebo + docetaxel	457	10.4	4.1	
Schuler et al. 2016[47]	NSCLC	2+	afatinib + paclitaxel	134	12.2	5.6	6
			chemotherapy	68	12.2	2.8	
Shaw et al. 2013[48]	NSCLC	2	crizotinib	173	20.3	7.7	8
			pemetrexed or docetaxel	174	22.8	3.0	
Shen et al. 2015[49]	Gastric	1	capecitabine + cisplatin + bevacizumab	102	10.5	6.3	10

Reference	Disease site	Line of therapy	Treatment comparison	N	Median OS (months)	Median PFS (months)	Study Quality
			capecitabine + cisplatin + placebo	100	11.4	6.0	
Tabernero et al. 2013[17]	Colorectal	1	modified FOLFOX6 + sorafenib	97	17.6	9.1	9
			modified FOLFOX6 + placebo	101	18.1	8.7	
Vergote et al. 2014[50]	Ovarian	Maintenance	erlotinib	420	50.8	12.7	7
			no treatment	415	59.1	12.4	
Vincent et al. 2017[51]	Colorectal	1	erlotinib + capecitabine	42	12.4	9.2	7
			capecitabine	40	16.2	7.9	
Wirth et al. 2016[52]	SCCHN	1	docetaxel + cisplatin + panitumumab	56	12.9	6.9	5
			docetaxel + cisplatin	57	13.8	5.5	
Wu et al. 2014[53]	NSCLC	1	afatinib	242	23.1	11.0	7
			gemcitabine + cisplatin	122	23.5	5.6	

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; SCCHN=squamous cell carcinoma of the head and neck; FOLFIRI=fluorouracil + irinotecan; FOLFOX=fluorouracil + oxaliplatin

Table 2. Comparisons showing improvement (>0 months) in overall survival and no improvement (≤0 months) in progression-free survival (n=25)

Reference	Disease site	Line of therapy	Treatment comparison	N	Median OS (months)	Median PFS (months)	Study Quality
Allen et al. 2014[54]	SCLC	2	topotecan + ziv-aflibercept	55	4.6	1.4	8
			topotecan	51	4.2	1.4	
Belani et al. 2016[55]	SCLC	1	cisplatin + etoposide + vismodegib	52	9.8	4.4	6
			cisplatin + etoposide	48	8.8	4.4	
Bokemeyer et al. 2009[56]	Colorectal	1	FOLFOX4 + cetuximab	170	18.3	7.2	7
			FOLFOX4	168	18.0	7.2	
Borghaei et al. 2015[57]	NSCLC	2	nivolumab	292	12.2	2.3	6
			docetaxel	290	9.4	4.2	
Buikhuisen et al. 2016[58]	Mesothelioma	1	axitinib	14	18.9	5.8	4
			no treatment	11	18.5	8.3	
Govindan et al. 2017[59, 60]	NSCLC	1	chemotherapy + ipilimumab	479	10.9*	5.6	8
			chemotherapy + placebo	477	10.7*	5.6	
Han et al. 2017[61]	NSCLC	1	gefitinib	41	25.8	5.7	7
			pemetrexed + carboplatin	40	24.3	11.9	
Herbst et al. 2016[62]	NSCLC	2+	pembrolizumab 2 mg/kg	345	10.4	3.9	7
			docetaxel	343	8.5	4.0	
Herbst et al. 2016[62]	NSCLC	2+	pembrolizumab 10 mg/kg	346	12.7	4.0	7
			docetaxel	343	8.5	4.0	
Jonasch et al. 2017[63]	Renal cell	2+	MK-2206	29	23.5	3.7	5
			everolimus	14	15.7	6.0	
Kawaguchi et al. 2014[16]	NSCLC	2+	erlotinib	150	14.8	2.0	7
			docetaxel	151	12.2	3.2	
Lee et al. 2013[64]	NSCLC	2	erlotinib	82	22.8	3.8	7
			pemetrexed	80	17.7	4.4	
Lee et al. 2014[65]	NSCLC	2+	erlotinib	40	3.4	1.6	9
			placebo	40	2.9	1.6	
NCT00069095[66]	Colorectal	1	(FOLFOX4 or XELOX) + bevacizumab	699	18.9	8.0	7
			(FOLFOX4 or XELOX) + placebo	701	18.1	9.4	
NCT00448279[67]	Breast	2	chemotherapy + trastuzumab	29	26.7	9.4	4
			chemotherapy	29	19.1	9.7	
NCT00597116[68]	Mesothelioma	2	vandetanib	14	7.8	1.8	3
			vinorelbine	11	6.4	3.8	
NCT00887159[69]	SCLC	1	cisplatin + etoposide + vismodegib	56	9.8	4.4	5
			cisplatin + etoposide	56	8.8	4.4	
NCT01585987[70]	Gastric	2	ipilimumab	57	12.7	2.7	5
			best supportive care	57	12.1	4.9	
Pirker et al. 2009[71]	NSCLC	1	cetuximab + cisplatin + vinorelbine	557	11.3	4.8	7
			cisplatin + vinorelbine	568	10.1	4.8	
Powles et al. 2017[72]	Bladder	Maintenance	lapatinib	116	12.6	4.5	9
			placebo	116	12.0	5.1	
Propper et al. 2014[73]	Pancreatic	2	erlotinib	104	4.0	1.4	9
			placebo	103	3.1	1.4	
Sanborn et al. 2017[13]	SCLC	1	platinum + etoposide + vandetanib	34	13.2	5.6	8
			platinum + etoposide + placebo	33	9.2	5.7	
Scagliotti et al. 2010[74]	NSCLC	1	carboplatin + paclitaxel + sorafenib	464	10.7	4.6	10
			carboplatin + paclitaxel + placebo	462	10.6	5.4	
Vilgrain et al. 2017[75]	Hepatocellular	1	sorafenib	222	9.9	3.7	8
			radiotherapy	237	8.0	4.1	
Yoon et al. 2016[76]	Esophagogastric	1	modified FOLFOX6 + ramucirumab	84	11.7	6.4	10
			modified FOLFOX6 + placebo	84	11.5	6.7	

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; FOLFOX=fluorouracil + oxaliplatin; XELOX= capecitabine + oxaliplatin
*Survival data for the full cohort were not published, these data are available in the clinicaltrials.gov record

Table 3. Comparisons with the greatest differences (positive or negative) in post-progression survival (n=25)

Reference	Disease site	Line of therapy	Comparison (n)	Median OS (months)	Median PFS (months)	Delta PPS between arms	Study quality
Comparisons showing a benefit in OS with the biologic/targeted therapy							
Rule et al. 2016[77]	Mantle cell lymphoma	1	fludarabine + cyclophosphamide + rituximab (n=186)	44.5	29.8	-7.4	6
			fludarabine + cyclophosphamide (n=184)	37	14.9		
Wu et al. 2015[77]	NSCLC	1	erlotinib (n=110)	26.3	11.0	-4.7	8
			gemcitabine + cisplatin (n=107)	25.5	5.5		
Chinot et al. 2014[78]	Glioblastoma	1	temozolomide + bevacizumab (n=458)	16.8	10.6	-4.3	10
			temozolomide + placebo (n=463)	16.7	6.2		
Schwartzberg et al. 2010[79]	Breast	1	lapatinib + letrozole (n=111)	33.3	8.2	-4.2	10
			placebo + letrozole (n=108)	32.3	3.0		
Krop et al. 2017[80]	Breast	3+	trastuzumab (n=404)	22.7	6.2	4.0	8
			physician choice (n=198)	15.8	3.3		
Sanborn et al. 2017[13]	SCLC	1	platinum + etoposide + vandetanib (n=34)	13.2	5.6	4.1	8
			platinum + etoposide + placebo (n=33)	9.2	5.7		
Guan et al. 2013[81]	Breast	1	lapatinib + paclitaxel (n=222)	27.8	9.7	4.1	10
			placebo + paclitaxel (n=222)	20.5	6.5		
Herbst et al. 2016[62]	NSCLC	2+	Pembrolizumab 10mg/kg (n=346)	12.7	4	4.2	7
			docetaxel (n=343)	8.5	4		
Borghaei et al. 2015[57]	NSCLC	2	nivolumab (n=292)	12.2	2.3	4.7	6
			docetaxel (n=290)	9.4	4.2		
Lee et al. 2013[64]	NSCLC	2	erlotinib (n=82)	22.8	3.8	5.7	7
			pemetrexed (n=80)	17.7	4.4		
Han et al. 2017[61]	NSCLC	1	gefitinib (n=41)	25.8	5.7	7.7	7
			pemetrexed + carboplatin (n=40)	24.3	11.9		
NCT00448279[67]	Breast	2	chemotherapy + trastuzumab (n=29)	26.7	9.4	7.9	4
			chemotherapy (n=29)	19.1	9.7		
Tap et al. 2016[5]	Sarcoma	1+	olaratumab + doxorubicin (n=66)	26.5	6.6	9.3	7
			doxorubicin (n=67)	14.7	4.1		
Jonasch et al. 2017[63]	Renal cell	2+	MK-2206 (n=29)	23.5	3.7	10.1	5
			everolimus (n=14)	15.7	6.0		
Furtado et al. 2015[82]	Mantle cell lymphoma	2	cyclophosphamide + doxorubicin + vincristine + bortezomib (n=23)	35.6	16.5	15.4	5
			cyclophosphamide + doxorubicin + vincristine (n=23)	11.8	8.1		
Harrington et al. 2013[83]	SCCHN	1	lapatinib + cisplatin (n=34)	48.4	20.4	17.1	10
			placebo + cisplatin (n=33)	23.0	12.1		
Comparisons showing no benefit in OS with the biologic/targeted therapy							
Vergote, et al. 2014[50]	Ovarian	Maintenance	erlotinib (n=420)	50.8	12.7	-8.6	7
			no treatment (n=415)	59.1	12.4		
Shaw et al. 2013[48]	NSCLC	2	crizotinib (n=173)	20.3	7.7	-7.2	8
			pemetrexed or docetaxel (n=174)	22.8	3.0		
NCT00777179[42]	NSCLC	Maintenance	vandetanib (n=75)	15.6	2.7	-6.2	7
			placebo (n=42)	20.8	1.7		
Mok et al. 2017[84]	NSCLC	2	gefitinib + chemotherapy (n=133)	13.4	5.4	-6.1	10
			placebo + chemotherapy (n=132)	19.5	5.4		
Wu et al. 2014[53]	NSCLC	1	afatinib (n=242)	23.1	11.0	-5.8	7
			gemcitabine + cislatin (n=122)	23.5	5.6		
Hegewisch-Becker et al. 2015[15]	Colorectal	Maintenance	fluoropyrimidine + bevacizumab (n=158)	20.2	6.3	-5.7	7
			no maintenance (n=158)	23.1	3.5		
Martin et al. 2015[32]	Breast	1	letrozole or fulvestrant + bevacizumab (n=191)	52.1	19.3	-5.6	6
			letrozole or fulvestrant (n=189)	52.8	14.4		
Vincent et al. 2017[51]	Colorectal	1	erlotinib + capecitabine (n=42)	12.4	9.2	-5.1	7
			capecitabine (n=40)	16.2	7.9		
Herrlinger et al. 2016[27]	Glioblastoma	1	bevacizumb + irinotecan (n=122)	16.6	9.7	-4.6	7
			temozolomide (n=60)	17.5	6.0		

Conclusions

There does not appear to be a difference in the magnitude of OS versus PFS benefits among biologic/targeted therapies versus their comparators. However, approximately 10% of comparisons showed a substantial (≥ 4 month) difference in OS/PFS benefits versus non-biologic/targeted comparators. Among those, slightly over half (n=16, 64%) showed a benefit in OS versus the comparator, suggesting that the phenomenon of long OS and short PFS or vice versa may not be simply an artifact or a reflection of suboptimal trial design, but could possibly be due to their specific mechanism of action.

Study quality did not appear to have any role in the findings of large differential between OS and PFS or in the direction of study results, but rather publication status. The low study quality of unpublished studies could be either due to the inability to publish studies of this quality, or due to the lack of sufficient information in the

clincaltrials.gov record to provide information to populate the study score across all variables. Similarly, studies reporting no gains in OS outcomes were if anything potentially more likely to have imbalance in post-study therapies (80% of reporting studies) than those with positive OS findings (imbalance in post-study therapies was 21.8% of reporting studies); however, any interpretation of the role of post-study treatment imbalances is very limited due to the low number of studies reporting these data.

In summary, this analysis has evaluated the observation of small PFS benefit with large OS benefit as well as small OS benefit with large PFS benefit, and no systematic evidence was identified that this was a result of poor study design, post-study treatment or specific to any other factor evaluated in this review. The biologic and targeted agents identified with these differentials are generally FDA approved and NCCN-recommended therapies for the diseases in which they are evaluated. The observed OS and PFS benefits of these agents are likely due to the unique mechanism of action of these drugs, which should be better understood as the use of these novel agents increases and further scientific evidence is generated.

Supplementary Material

Supplementary search strategies and table.
http://www.jcancer.org/v10p3717s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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