Correlation between overall survival and surrogate endpoint in clinical trials for anticancer drugs considering tumor shrinkage

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Abstract

Overall survival (OS) is the most reliable endpoint to assess clinical benefit of cancer patients. However, OS assessment generally requires a large sample size and long-term survival follow-up of patients. Although intermediate endpoints such as progression-free survival (PFS) and objective response rate (ORR) are broadly employed to assess drug efficacy and clinical benefit of patients earlier, none of them has been validated as a surrogate endpoint for OS. Endpoints originated from the concept of tumor shrinkage dynamics, such as early tumor shrinkage (ETS) and depth of response (DpR), were reported to be strongly associated with OS in patients with colorectal cancer (CRC) and non-small cell lung cancer (NSCLC). In addition, a combinatory endpoint of ETS and DpR with PFS showed a stronger correlation with OS compared to the correlations between OS and either ETS or DpR. Based on these findings, we conducted a research to investigate the impact of advantage in tumor response on the correlation between treatment effects on PFS and OS in clinical trials with CRC patients (Research 1) and NSCLC patients (Research 2).

Based on an electronic search, we identified randomized controlled trials of first-line therapy for CRC and NSCLC. The impact of advantage in ORR on the correlation between treatment effects on PFS and OS was evaluated based on Spearman correlation coefficients (r_s).

In Research 1, forty-seven trials with a total of 24,018 patients were identified. The hazard ratio (HR) for PFS showed a relatively higher correlation with HR for OS (r_s=0.63) when the trials were limited to those that demonstrated a larger difference in ORR, compared to the case for trials that demonstrated a smaller difference (r_s=0.32). This tendency was also observed in the subgroup analysis stratified by the types of treatment agents (targeted or non-targeted).

In Research 2, sixty trials with a total of 29,134 patients were identified. The HR for PFS showed a relatively higher correlation with HR for OS (r_s=0.75) when the trials were limited to those demonstrated a larger advantage in ORR, compared to the case for trials that demonstrated a smaller advantage (r_s=0.66). This tendency was also observed in the subgroup analysis stratified by the types of treatment agents (non-targeted, anti-angiogenic, and immunotherapy) except for the group of EGFR-targeted agents.

The magnitude of advantage in tumor response was suggested to contribute to a better prediction of OS benefit based on PFS in either patients with CRC or with NSCLC. The accuracy of OS estimation in these patients is expected to be improved by considering the degree of tumor shrinkage in conjunction with PFS.

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Abbreviations

AD_{ORR}	Absolute difference in objective response rate
ALK	Anaplastic lymphoma kinase
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CRC	Colorectal cancer
DpR	Depth of response
EGFR	Epidermal growth factor receptor
ETS	Early tumor shrinkage
HR	Hazard ratio
HR_{OS}	Hazard ratio for overall survival
HR_{PFS}	Hazard ratio for progression-free survival
IPD	Individual patient data
KRAS	Kirsten rat sarcoma
NSCLC	Non-small cell lung cancer
mAD_{ORR}	Median of absolute difference in objective response rate
mCRC	Metastatic colorectal cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-frees survival
PPS	Post-progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAS	Rat sarcoma
TTP	Time to progression
TTR	Time to response

1. Introduction

Malignant neoplasm is one of the intractable diseases and is now widely recognized as a threat to global development. The numbers of incidence and death due to the disease have been increasing, and this trend is likely to continue globally [1]. The prognosis of cancer patients especially at the advanced stage (i.e. disease is metastasized to distant organs from the primary lesion) is considerably poor. Five-year survival rates in patients with advanced colorectal cancer and in patients with advanced non-small cell lung cancer are reported to be around 10-20% and less than 10%, respectively [2,3].

Given the high unmet medical needs in cancer patients, researchers have been actively investigating a new treatment that could benefit the patients. However, clinical development success rates for investigational cancer drugs have been relatively low compared to drugs in other therapeutic areas [4]. In addition, development expenditure on new treatment agents in oncology area is reported to be the highest among all therapeutic areas [5]. To deliver a new effective treatment to cancer patients more efficiently with an affordable price, these represent significant challenges.

In oncology clinical trials, various endpoints are employed depending on factors such as purpose of the study, treatment setting, and expected survival time of cancer patients. Overall survival (OS) is considered the most reliable endpoint which represents clinical benefit for cancer patients. [6] However, the evaluation of OS generally requires a large sample size and a long follow-up period, and can also significantly be affected by subsequent therapies. Therefore, as the survival in cancer patients extends, it becomes more difficult to predict and evaluate the efficacy of drugs on survival. In fact, it is not rare to see phase 3 trials failing to demonstrate a prolonged OS despite the expectations based on the results from early phase studies. [7]

Intermediate endpoints such as progression-free survival (PFS) and objective response rate (ORR) are often employed to assess drug efficacy and clinical benefit of cancer patients earlier than OS assessment. Although it is ideal that OS can be predicted based on these intermediate endpoints from the perspective of both patient management and clinical development of cancer drugs, none of the intermediate endpoints has been validated as surrogate endpoint for OS. Considering that survival in cancer patients is presumed to be prolonged by emerging cancer drugs and treatment modalities, it is

critical to establish a reliable surrogate endpoint for OS.

We conducted trial-level meta-analyses with data reported in clinical trials for the treatment of cancer patients to investigate what makes the current intermediate endpoints more reliable surrogate for OS.

Here we report our research on colorectal cancer (Research 1) followed by the research on non-small cell lung cancer (Research 2) and overall discussion as well as the conclusion based on the insights suggested through our research.

2. Research on Colorectal Cancer (Research 1)

2.1. Background

Colorectal cancer (CRC) is one of the most common cancers in the world, and its global burden is estimated to persist rising until 2035 and likely beyond. [8] On the other hand, the survival of patients with metastatic colorectal cancer (mCRC) has been prolonged with the emerging new treatment agents. In particular, the median survival time in patients with rat sarcoma (RAS) gene wild type mCRC was reported to be over 30 months. [9,10] This situation encouraged researchers to explore surrogate endpoints for OS. However, none of the intermediate endpoints have been validated as surrogate to date. [11]

Early tumor shrinkage (ETS), a categorical parameter defined as 10-30% tumor shrinkage from baseline at 6-8 weeks after randomization [12], and depth of response (DpR), defined as the percentage of tumor shrinkage observed at the lowest point (nadir) compared with baseline [13], were revealed to be strongly associated with OS in patients with mCRC in several first-line clinical trials. [10,12,14-16] These insights suggest the importance of tumor shrinkage dynamics to be accounted in predicting the survival benefit of mCRC patients. These parameters, however, are still not commonly collected in a prospective manner in clinical trials, and possibly because of the limited number of trials reporting ETS or DpR, the surrogacy of ETS or DpR for OS is not clear. [17]

Nakayama et al. [18] retrospectively analyzed individual data of patients with mCRC treated with oxaliplatin-based chemotherapy with bevacizumab as first-line treatment to investigate the correlation between OS and the two-dimensional response, a parameter obtained by combining the degree of tumor shrinkage and its time course. In their research, they found that the two-dimensional response showed a better correlation with OS compared to either ETS or DpR alone. These results suggest that it is important to consider both tumor shrinkage and time-based parameters compositely, not independently, for the prediction of OS. Among the established endpoints in oncology field, PFS and ORR are the most commonly and prospectively evaluated intermediate endpoints. However, most of the researches investigating surrogate endpoints to date have evaluated individual correlations between PFS and OS, or ORR and OS. There is

no research which investigated surrogate endpoints for OS considering both PFS, a time-based parameter, and ORR, a parameter of tumor shrinkage.

In the present study, we carried out a trial-level meta-analysis with published data of clinical trials of first-line therapy for patients with mCRC, with the aim to investigate the relationship between treatment effects in ORR and PFS for a better prediction of OS improvement.

2.2. Methods

Literature search and selection criteria

Articles on mCRC trials published until December 31st, 2018 were identified through a systematic search in the National Library of Medicine medical literature database via PubMed gateway using the keywords 'colorectal cancer' and 'randomized controlled trial' and 'overall survival' and 'progression free survival'. Inclusion criterion was first-line randomized controlled trials reporting hazard ratios for both OS and PFS, and ORR. Exclusion criteria were adjuvant/neoadjuvant therapy, trials with surgical intervention or radiotherapy, small sample size (<100 patients per trial), sequential or maintenance therapy, meta-analysis, subgroup analysis, and trials allowing in-protocol crossover. Data from trials with EGFR inhibitors were limited to those investigating treatments in patients with Kirsten rat sarcoma (KRAS) wild type genetic feature. Only articles published in English were reviewed following the PRISMA guidelines for the reporting of systematic reviews and meta-analyses. [19]

Data extraction

We collected the following information from trials that met the eligibility criteria: trial phase, treatment regimen, year of trial execution, number of patients, primary endpoint, median OS (months), median PFS (months), hazard ratios for OS and PFS, and ORR (%). Two investigators (YY and MK) independently abstracted the data from the publications. In this research, we selected PFS as a time-based parameter for the assessment of correlation with OS, as it is the most common parameter among time to event type endpoints. One of the trials reviewed in this research reported not PFS but

only time to progression (TTP). In contrast to PFS, TTP focuses in only disease progression as the event of interest and disregards death from any causes. Because both endpoints, TTP and PFS, are unaffected by subsequent therapies, they were used exchangeably for this analysis and were referred to as PFS as previously reported in similar meta-analyses of colorectal cancer trials. [20] For the tumor shrinkage-based parameter, we selected ORR on the basis of its popularity and past reports demonstrating strong correlation with ETS. [17] ORR is considered the most common tumor response endpoint that reflects tumor shrinkage dynamics in patients. Also, as it is suggested that post-progression survival (PPS) is one of the factors which affect the correlation between PFS and OS [21,22], we calculated PPS of each trial arm by subtracting the median PFS from the median OS, to ensure that it does not complicate our results.

Statistical analysis

The surrogacy of intermediate endpoints for OS (i.e., prediction of OS) is dependent on the correlation between the treatment effect on the surrogate endpoint and its effect on OS, with a strong correlation indicating a better precision of the prediction. [23] In this analysis, nonparametric Spearman rank correlation coefficient (r_s) was used as a measure of correlation between the treatment effect on the surrogate endpoint and OS. Linear regression analysis weighted by study sample size was performed to determine the proportion of variability explained (R^2). [24] Hazard ratios (HRs) were used to summarize the treatment effects for PFS (HR_{PFS}) and OS (HR_{OS}). Absolute differences in the objective response rate (AD_{ORR}) between the treatment arms were used to summarize the treatment effect for response rate. To investigate the impact of the degree of AD_{ORR} on prediction of OS based on PFS, we evaluated the correlation between HR_{PFS} and HR_{OS} in the studies stratified by the median of AD_{ORR} (mAD_{ORR}). Also, as a sensitivity analysis, similar analyses were carried out by the type of treatment agent (targeted, defined as studies that include molecule(s)-targeted drugs as monotherapy or in combination with other drug(s), or non-targeted, defined as studies that only include comparable chemotherapy regimens using cytotoxic drugs).

All statistical analyses were performed using R software version 3.5.0

(http://www.r-project.org). P-values<0.05 were considered statistically significant.

2.3. Results

Trials included in the analysis

In total, 294 publications were identified through PubMed search. After reviewing titles, abstracts, and full texts, 47 articles [9,25-70] were selected for our analyses with 9 publications retrieved from citations in the reviewed articles. (Fig. 1, Supplementary Table 7) Of those excluded, there were subgroup analysis reports (n=71), lack of information for the results (n=35), small sample size (n=25), and trials for second-line or later (n=25). As 4 trials had 3 arms (one control arm + two experimental arms) in their studies, we performed our analyses with the data from 51 comparisons representing 24,018 participants in total. (Table 1)

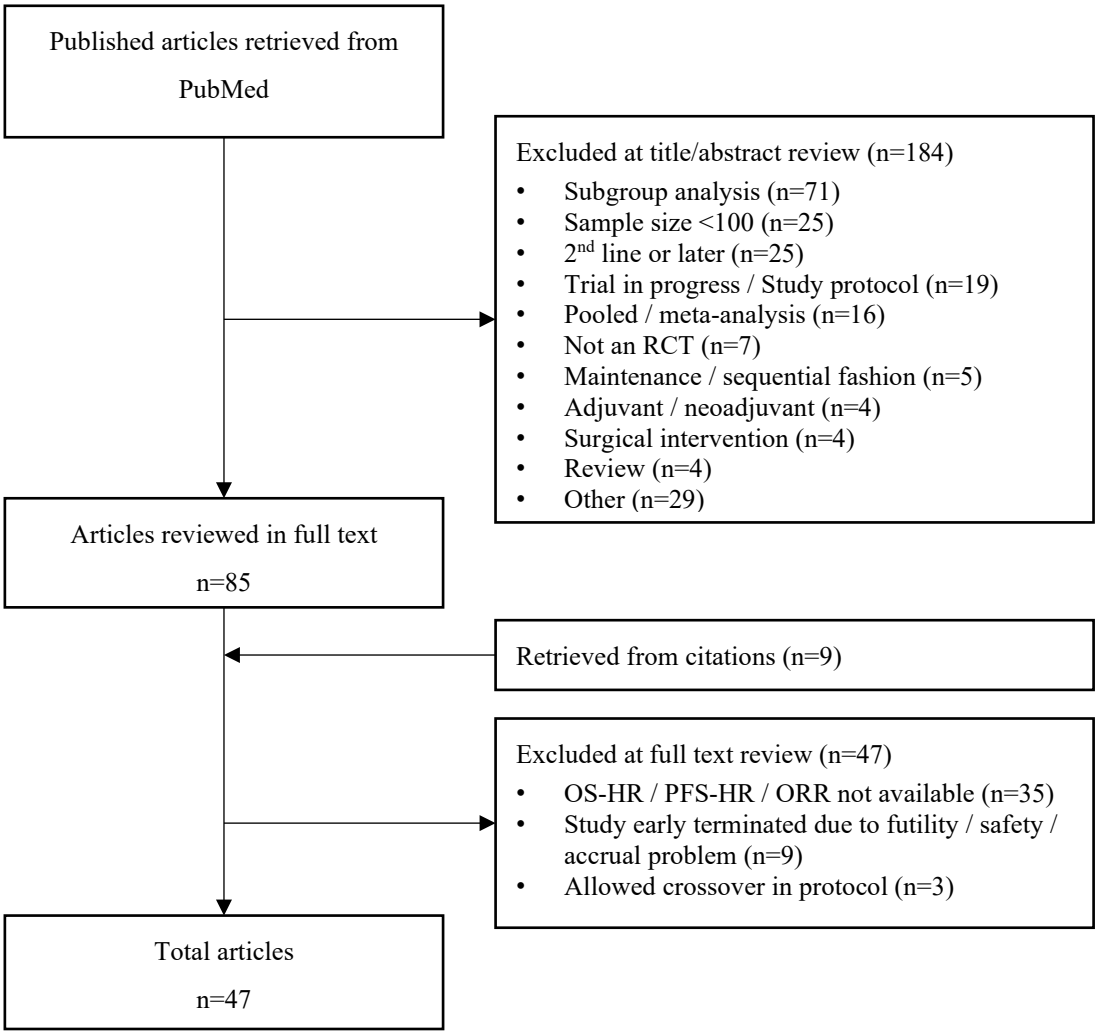


Figure 1 PRISMA diagram / literature search

Table 1 Descriptive summary of median hazard ratios (PFS, OS), response rates (ORR), and post-progression survival (months) with trial demographics

		Absolute difference in ORR	
	ALL	< median	median ≤
No. trials/comparisons	47/51	23/24	25/27
No. patients	24,018	13,378	10,640
Non-targeted agents [n, (%)]	22 (43)	11 (46)	11 (41)
Targeted agents [n, (%)]	29 (57)	13 (54)	16 (59)
Anti-EGFR containing [n, (%)]	13 (25)	5 (21)	8 (30)
Anti-angiogenic containing [n, (%)]	20 (39)	12 (50)	8 (30)
OS HR [median (min - max)]	0.93 (0.62 - 1.15)	0.96 (0.62 - 1.15)	0.88 (0.62 - 1.13)
PFS HR [median (min - max)]	0.87 (0.44 - 1.22)	0.98 (0.81 - 1.22)	0.78 (0.44 - 1.1)
ORR difference [median (min - max)]	7.0 (0.0 - 27.8)	2.0 (0.0 - 6.0)	10.0 (7.0 - 27.8)
PPS-ctr (months) [median (min - max)]	10.6 (3.55 - 19.4)	10.8 (3.55 - 19.4)	10.2 (5.4 - 16.1)
PPS-exp (months) [median (min - max)]	10.9 (3.6 - 23.3)	10.9 (3.6 - 23.3)	10.8 (6.0 - 17.7)

Note: PPS is calculated by subtracting median PFS (months) from median OS (months) within each control (ctr) and experimental (exp) arm.

EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PPS, post progression survival

Correlation between PFS, ORR, and OS

First, we evaluated correlations between treatment effects in PFS, ORR, and OS each other in the data set of all the included trials to see how these were associated to each other. The correlation coefficient of HR_{PFS} and HR_{OS} was r_s=0.57, AD_{ORR} and HR_{OS} was r_s=-0.30, and AD_{ORR} and HR_{PFS} was r_s=-0.46. Although PFS showed a moderate correlation with OS, ORR barely correlated with either OS or PFS. (Table 2)

Table 2 Correlation between treatment effects in each endpoint (PFS, ORR, and OS)

No. of comparisons	Endpoints	r_s	95% CI	p-value	Adjusted R^2
51	HR_{PFS} vs HR_{OS}	0.57	0.35, 0.73	<0.001	0.36
	AD_{ORR} vs HR_{OS}	-0.30	-0.53, -0.02	0.035	0.07
	AD_{ORR} vs HR_{PFS}	-0.46	-0.65, -0.21	<0.001	0.23

AD_{ORR}, absolute difference in objective response rate; HR_{OS}, hazard ratio for overall survival; HR_{PFS}, hazard ratio for progression-free survival; r_s, Spearman rank correlation coefficient

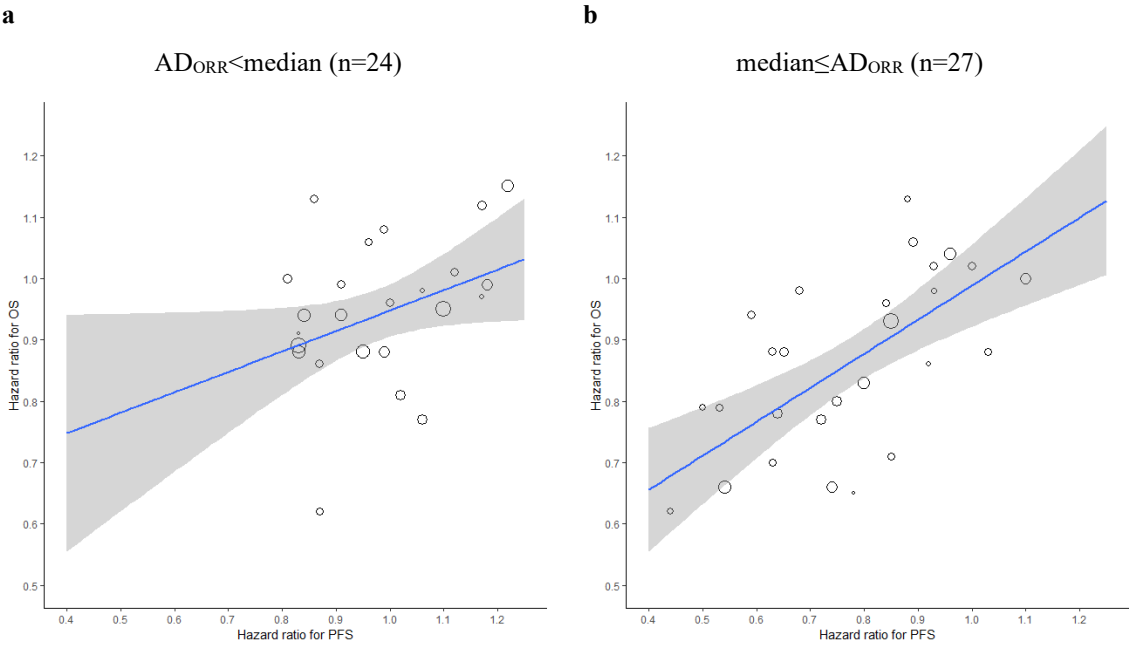
Stratification by median of absolute difference in ORR

To investigate the impact of ORR as an indicator of tumor shrinkage on the correlation between improvements in PFS and OS, we stratified the trials by the mAD_{ORR} and evaluated correlations between HR_{PFS} and HR_{OS} in each trial set. The mAD_{ORR} among the data reported in the selected trials was 7.0. After stratifying the trials with the mAD_{ORR}, demographics of each trial set were summarized in Table 1. Of note, a significant difference in post-progression survival (PPS) was not identified between the groups.

Impact of advantage in ORR on the correlation between improvements in OS and PFS

We evaluated correlations of HR_{PFS} and HR_{OS} in each trial set divided by mAD_{ORR}. The correlation coefficient of HR_{PFS} and HR_{OS} in trials with AD_{ORR} less than the mAD_{ORR} ($<mAD_{ORR}$) and that in trials with AD_{ORR} equal to or greater than the mAD_{ORR}

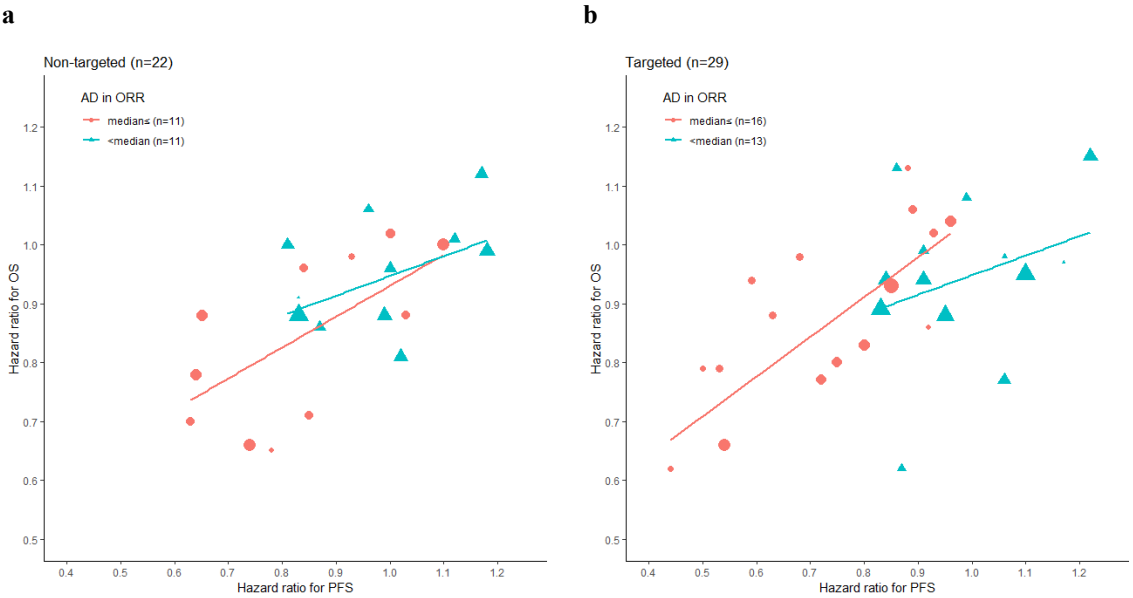
($mAD_{ORR}\leq$) were r_s=0.32 (95% CI: -0.09, 0.64, p-value=0.124) and r_s=0.63 (95% CI: 0.33, 0.81, p-value<0.001), respectively. The trial set of $mAD_{ORR}\leq$ showed stronger correlation between HR_{PFS} and HR_{OS} compared to $<mAD_{ORR}$ trials. (Fig. 2) The adjusted R^2 was 0.13 for $<mAD_{ORR}$ trials and 0.45 for $mAD_{ORR}\leq$ trials.



The solid blue line represents the change in PFS according to a change in OS; gray area indicates 95% confidence intervals of the regression line. Each trial is represented by a circle with symbol size proportional to number of patients. **(a)** Correlation within 1st line trials with a result of absolute difference in ORR between treatment arms less than 7 points. **(b)** Correlation within 1st line trials with a result of absolute difference in ORR between treatment arms equal to or greater than 7 points.

Figure 2 Correlation between HR_{PFS} and HR_{OS} in 1st line treatment for mCRC

Next, we performed sensitivity analyses by the types of treatment agents. Same analyses were carried out within trial sets of targeted agents or non-targeted agents. The subgroup analysis with non-targeted agent trials showed correlation coefficients of r_s=0.28 for <mAD$_{ORR}$ trials and r_s=0.65 for mAD$_{ORR}$≤ trials. Among the targeted agent trials, correlation coefficients were r_s=0.32 and r_s=0.72, respectively. As is the case in the analysis performed in the all trial sets, mAD$_{ORR}$≤ trials showed higher correlation between HR$_{PFS}$ and HR$_{OS}$ both in non-targeted and targeted agent trial sets. (Fig. 3, Table 3)



The solid line represents the change in PFS according to a change in OS. Each trial is represented by a circle or triangle with symbol size proportional to number of patients. Red circles represent trials with results of absolute difference in ORR between treatment arms less than 7 points. Blue triangles represent trials with results of absolute difference in ORR between treatment arms equal to or greater than 7 points. **(a)** Correlation within non-targeted 1st line trials. **(b)** Correlation within targeted 1st line trials.

Figure 3 Correlation between hazard ratios for PFS and OS in 1st line non-targeted or targeted treatment for mCRC

Table 3 Correlation between HR_{PFS} and HR_{OS} by AD_{ORR} and type of treatment agent

Therapy	Subgroup	No. of comparisons	r_s	95% CI	p-value	Adjusted R^2
Non-targeted	AD_{ORR}<median	11	0.28	-0.39, 0.75	0.41	0.16
	median≤AD_{ORR}	11	0.65	0.08, 0.90	0.030	0.39
Targeted	AD_{ORR}<median	16	0.32	-0.27, 0.74	0.28	0.06
	median≤AD_{ORR}	13	0.72	0.34, 0.90	0.002	0.58

AD_{ORR}, absolute difference in objective response rate; HR_{OS}, hazard ratio for overall survival; HR_{PFS}, hazard ratio for progression-free survival; r_s, Spearman rank correlation coefficient

2.4. Discussion

There have been several meta-analyses carried out to explore surrogate endpoints for OS in clinical trials for patients with mCRC. Shi et al. [71] found a correlation coefficient of 0.68 between PFS and OS by individual patient data (IPD)-based meta-analysis with data of mCRC patients participated in first-line clinical trials. Giessen et al. [20] reported that the correlation coefficient between PFS and OS was 0.86 for first-line trials with chemotherapies and 0.47 for those with monoclonal antibodies. While several studies revealed potential surrogate endpoints for OS in patients with mCRC, these endpoints have yet to be reliably validated. The correlations found in the present study were generally consistent with those reported in previous researches. The result that ORR poorly correlates with OS was also consistent with other insights provided previously. [24]

Although ETS and DpR have been reported to be strongly associated with OS in patients with mCRC by IPD-based retrospective analyses [10,12,14-16], they have yet to be validated as reliable surrogate endpoints for OS. [17] In the present study, with an approach distinguished from previous ones, we evaluated how the magnitude of advantage in ORR, which could be considered to be substitutable of ETS [17] or DpR based on its concept, affects the correlation between treatment effects in PFS and OS. This was done by utilizing published clinical trial data including those in which neither ETS nor DpR were reported.

In our analyses, correlation between HR_{OS} and HR_{PFS} was found to be stronger in

the $mAD_{ORR}\leq$ trials compared to that in the $<mAD_{ORR}$ trials. This tendency was also observed in the either subgroup of studies with targeted or non-targeted drugs. These results imply that PFS benefit can be reflected to OS benefit in a relatively strong manner when there is a large difference in tumor response between the treatment arms. As it was discussed in the publications suggesting the association between ETS or DpR and OS, when a definitive advantage in tumor shrinkage is observed, there could also be a difference in total tumor volume burden in patients at the time of disease progression, which could result in a difference in time for tumors to grow until lethal volume, which is known as PPS. [67] On the contrary, tumor shrinkage endpoints such as ORR, ETS, and DpR were not shown to solely have sufficient surrogacy for OS as found in the present study. One of the possibilities implied from these results is that, when there is a large difference in tumor response and the advantage in shrinkage converts to PPS benefit, PFS benefit can be transferred to OS benefit without being thoroughly diluted by confounding factors such as subsequent therapies. Conversely, when the difference in response is minimal, as in the case of $<mAD_{ORR}$ trials in the present study, the tumor volumes in patients at the time of disease progression (i.e. the time of moving to next treatment option in most case) are assumed to be almost equivalent between the treatment arms, which would make the impact of subsequent therapies on OS be more apparent. In other words, PFS benefit provided from an experimental treatment in such cases may be directly diluted by subsequent therapies.

In our analyses, clinical trials with immunotherapy such as anti-PD-1/PD-L1 antibodies, which show high effectiveness in various cancer types in recent years, were not included. Immunotherapies are often reported to show substantially longer duration of response compared to other therapies. [72,73] Considering the present results, duration of response, one of the time-based parameters, may be a reliable surrogate endpoint for OS in case where a huge benefit in tumor response is observed.

Based on the results, we concluded that the magnitude of advantage in tumor response would contribute to a better prediction of HR_{OS} based on HR_{PFS} in patients with CRC participated in clinical trials of first line treatment.

3. Research on Non-small Cell Lung Cancer (Research 2)

3.1. Background

Non-small cell lung cancer (NSCLC) is one of the most common cancers in the world. Approximately 230,000 cases are newly diagnosed and 140,000 cases die due to NSCLC per year in the United States [74]. Although the prognosis of NSCLC patients has remarkably improved with the emerging agents such as molecular targeted therapy and immunotherapy, new treatments are still desired to be developed because of its increasing number of cases and deaths.

In the clinical development of new treatment agents, PFS and ORR are broadly employed as intermediate endpoints in NSCLC field as well, however the surrogacy of those endpoints for OS have yet to be validated [75,11].

In a recent study, McCoach et al. reported that DpR is associated with OS in NSCLC patients treated with anaplastic lymphoma kinase (ALK) inhibitors or programmed cell death protein 1 (PD-1) inhibitors [76]. As DpR is considered to contribute to the survival after disease progression (i.e. post-progression survival: PPS) [77], tumor shrinkage itself is supposed to have some association with PPS. Based on this idea and the fact that OS is composed of PFS and PPS, we hypothesized that OS estimation may be improved by considering both PFS and tumor shrinkage compositely. In our Research 1, as per our hypothesis, we conducted a meta-analysis of randomized controlled trials with first-line treatment for advanced colorectal cancer, and reported that advantage in ORR, the most common endpoint for tumor shrinkage, contributed to a better correlation between HRs for PFS and OS [78].

As it is suggested that DpR is associated with survival in NSCLC patients [76], tumor shrinkage could also be considered to contribute to their PPS. Therefore, the estimation of OS benefit in NSCLC patients based on their PFS may improve by taking ORR into account, as we revealed in the research with trials for colorectal cancer. In the present study, we carried out a trial-level meta-analysis with published data of clinical trials of first-line therapy for patients with advanced NSCLC, with the aim to investigate the impact of ORR on the correlation between the treatment effects on PFS and OS.

3.2. Methods

Literature search and selection criteria

Articles on NSCLC trials published until January 30th, 2020 were identified through a systematic search in the National Library of Medicine medical literature database via PubMed gateway using the keywords: 'NSCLC' and 'randomized controlled trial' and 'overall survival' and 'progression free survival'. Inclusion criterion was first-line randomized controlled trials in patients with advanced NSCLC reporting HRs for both OS and PFS, and ORR. Exclusion criteria were adjuvant/neoadjuvant therapy, trials with surgical intervention or radiotherapy, small sample size (<100 patients per trial), investigating specifically sequential or maintenance therapy, meta-analysis, subgroup analysis, and trials allowing in-protocol crossover. Only articles published in English were reviewed following the PRISMA guidelines for the reporting of systematic reviews and meta-analyses [19].

Data extraction

We collected the following information from trials that met the eligibility criteria: trial phase, treatment regimen, year of trial execution, number of patients, primary endpoint, median OS (months), median PFS (months), HRs for OS and PFS, and ORR (%). Two investigators (YY and MK) independently abstracted the data from the publications. Also, as it is suggested that post-progression survival (PPS) is one of the factors which affect the correlation between PFS and OS [21,22], we calculated PPS of each trial arm by subtracting the median PFS from the median OS, to ensure that it does not complicate our results.

Statistical analysis

The surrogacy of intermediate endpoints for OS (i.e., prediction of OS) is dependent on the correlation between the treatment effect on the surrogate endpoint and its effect on OS, with a strong correlation indicating a better precision of the prediction [23]. In this analysis, nonparametric Spearman rank correlation coefficient (r_s) was used as a measure of correlation between the treatment effect on the surrogate endpoint and

OS. Linear regression analysis weighted by study sample size was performed to determine the proportion of variability explained (R^2) [24]. HRs were used to summarize the treatment effects for PFS (HR_{PFS}) and OS (HR_{OS}). Absolute differences in objective response rate (AD_{ORR}) between the treatment arms were used to summarize the treatment effect for response rate. To investigate an impact of the degree of AD_{ORR} on prediction of OS based on PFS, we evaluated the correlation between HR_{PFS} and HR_{OS} in the studies stratified by the median of AD_{ORR} (mAD_{ORR}). Also, as a sensitivity analysis, similar analyses were carried out by the following type of treatment agents; 1) non-targeted, defined as studies that include only comparable chemotherapy regimens using cytotoxic drugs, 2) anti-angiogenic, 3) EGFR-targeted, or 4) immunotherapy, defined as studies that include anti-angiogenic agent, epidermal growth factor receptor (EGFR)-targeted agent, or immunomodulatory agents such as PD-1 / programmed cell death ligand 1 (PD-L1) / cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor respectively as monotherapy or in combination with other drug(s). Studies that involve both anti-angiogenic agent and EGFR targeted agent are included into both subgroups of anti-angiogenic and EGFR-targeted. Studies that involve immunotherapy are exclusively included into the immunotherapy subgroup regardless of its combination agents.

All statistical analyses were performed using R software version 3.5.0 (http://www.r-project.org). P-values<0.05 were considered statistically significant.

3.3. Results

Trials included in the analysis

In total, 516 publications were identified through PubMed search. After reviewing titles, abstracts, and full texts, 60 articles [79-138] were selected for our analyses with 11 publications retrieved from citations in the reviewed articles. (Fig. 4, Supplementary Table 8) Of those excluded, there were small sample size (n=96), subgroup analysis reports (n=65), trials for second-line or later (n=62), and lack of information for the results (n=54). As 8 trials had 3 arms (one control arm + two experimental arms) in their studies, we performed our analyses with the data from 68 comparisons representing

29,134 participants in total. (Table 4)

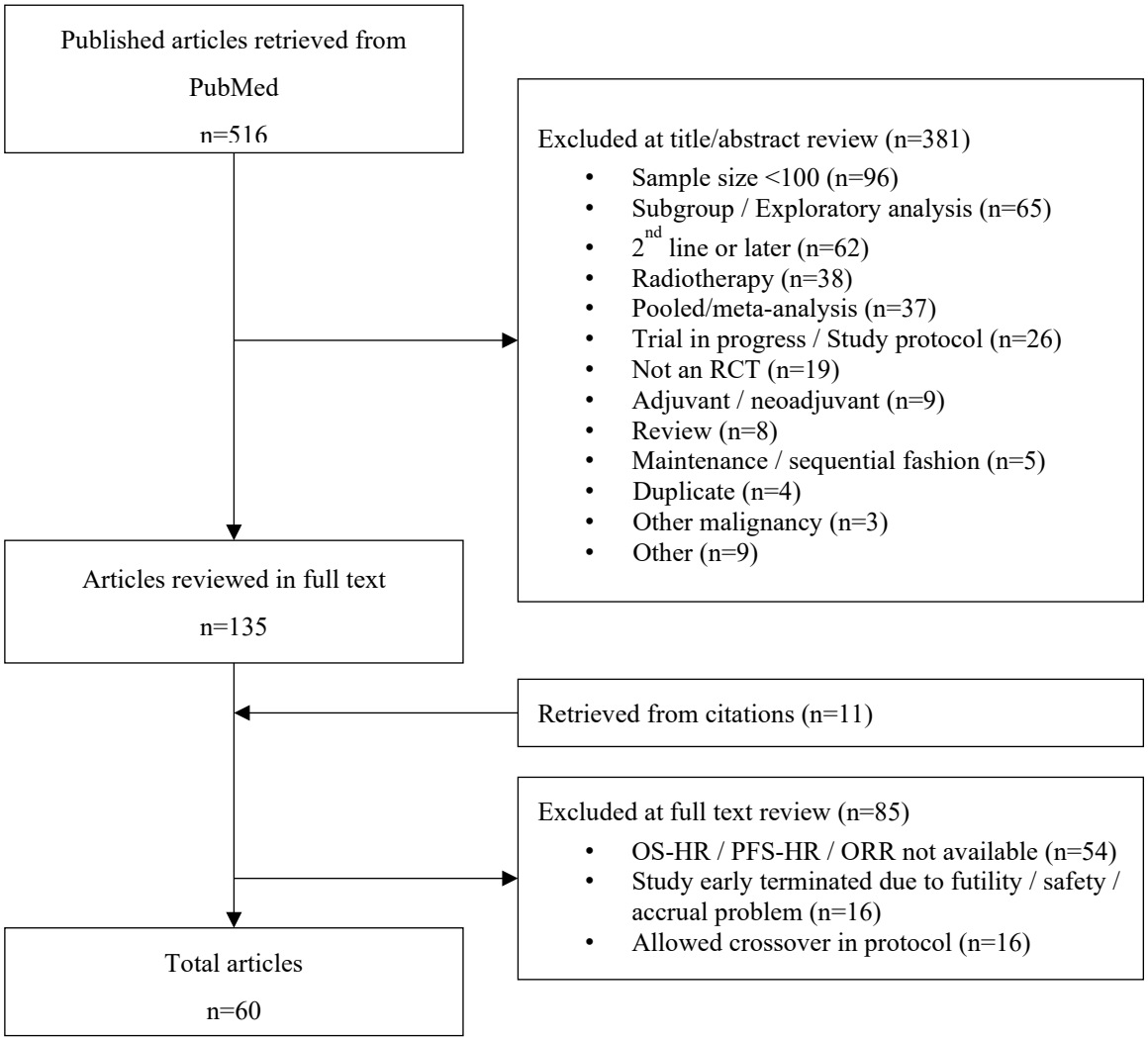


Figure 4 PRISMA diagram / literature search

Table 4 Descriptive summary of median hazard ratios (PFS, OS), response rates (ORR), and post-progression survival (months) with trial demographics

		Absolute difference in ORR	
	ALL	≤ median	median <
No. trials/comparison	60/68	31/34	29/34
No. patients	29,134	18,182	10,952
Non-targeted agents [n, (%)]	10 (15)	6 (18)	4 (12)
Targeted agents [n, (%)]	49 (72)	23 (68)	26 (76)
Anti-angiogenic containing [n, (%)]	26 (38)	8 (24)	18 (53)
EGFR targeted containing [n, (%)]	20 (29)	11 (32)	9 (27)
ALK targeted containing [n, (%)]	1 (1)	0 (0)	1 (3)
Other targeted containing [n, (%)]	7 (10)	5 (15)	2 (6)
Immunotherapy [n, (%)]	9 (13)	5 (15)	4 (12)
OS HR [median (min - max)]	0.95 (0.62 - 1.45)	0.95 (0.62 - 1.34)	0.95 (0.68 - 1.45)
PFS HR [median (min - max)]	0.90 (0.40 - 1.85)	0.95 (0.59 - 1.25)	0.85 (0.40 - 1.85)
ORR difference [median (min - max)]	6.85 (0.0 - 29.7)	3.0 (0.0 - 6.7)	14.0 (7.0 - 29.7)
PPS-ctr (months) [median (min - max)]	6.15 (2.16 – 31.0)	6.06 (2.16 - 19.4)	6.3 (3.4 – 31.0)
PPS-exp (months) [median (min - max)]	5.7 (1.34 - 37.7)	5.53 (1.34 - 18.27)	6.85 (4.07 - 37.7)

Note: PPS is calculated by subtracting median PFS (months) from median OS (months) within each control (ctr) and experimental (exp) arm.

EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PPS, post progression survival

Correlation between PFS, ORR, and OS

First, we evaluated correlations between treatment effects in PFS, ORR, and OS each other in the data set of all the included trials to see how these were associated to each other. The correlation coefficient of HR_{PFS} and HR_{OS} was r_s=0.69, AD_{ORR} and HR_{OS} was r_s=0.02, and AD_{ORR} and HR_{PFS} was r_s=-0.20. Although PFS showed a moderate correlation with OS, ORR barely correlated with either OS or PFS. (Table 5)

Table 5 Correlation between treatment effects in each endpoint (PFS, ORR, and OS)

No. of comparisons	Endpoints	r_s	95% CI	p-value	Adjusted R^2
68	HR_{PFS} vs HR_{OS}	0.69	0.55, 0.80	<0.001	0.46
	AD_{ORR} vs HR_{OS}	0.02	-0.22, 0.26	0.86	0.004
	AD_{ORR} vs HR_{PFS}	-0.20	-0.42, 0.04	0.10	0.09

AD_{ORR}, absolute difference in objective response rate; HR_{OS}, hazard ratio for overall survival; HR_{PFS}, hazard ratio for progression-free survival; r_s, Spearman rank correlation coefficient

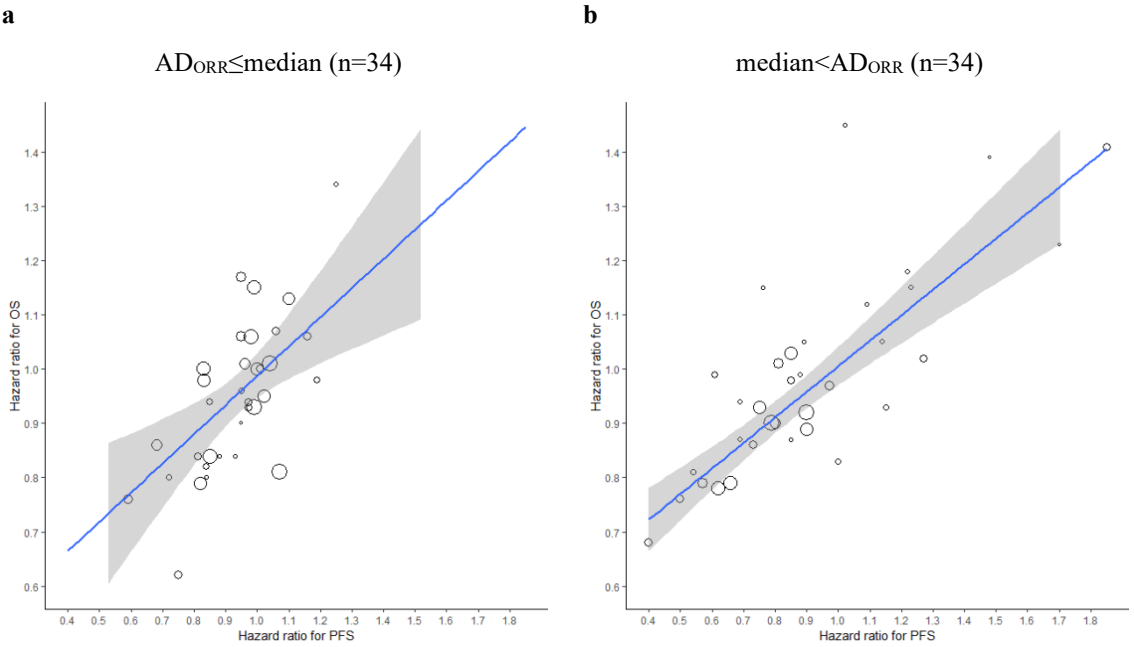
Stratification by median of absolute difference in ORR

To investigate an impact of ORR on the correlation between improvements in PFS and OS, we stratified the trials by the mAD_{ORR} and evaluated correlations between HR_{PFS} and HR_{OS} in each trial set. The mAD_{ORR} among the data reported in the selected trials was 6.85. After stratifying the trials with the mAD_{ORR}, demographics of each trial set were summarized in Table 1. Of note, no significant difference in PPS was identified between the groups.

Impact of advantage in ORR on the correlation between improvements in PFS and OS

We evaluated correlations of HR_{PFS} and HR_{OS} in each trial set divided by mAD_{ORR}. The correlation coefficient of HR_{PFS} and HR_{OS} in trials with AD_{ORR} less than or equal to the mAD_{ORR} ($\leq mAD_{ORR}$) and that in trials with AD_{ORR} greater than the mAD_{ORR}

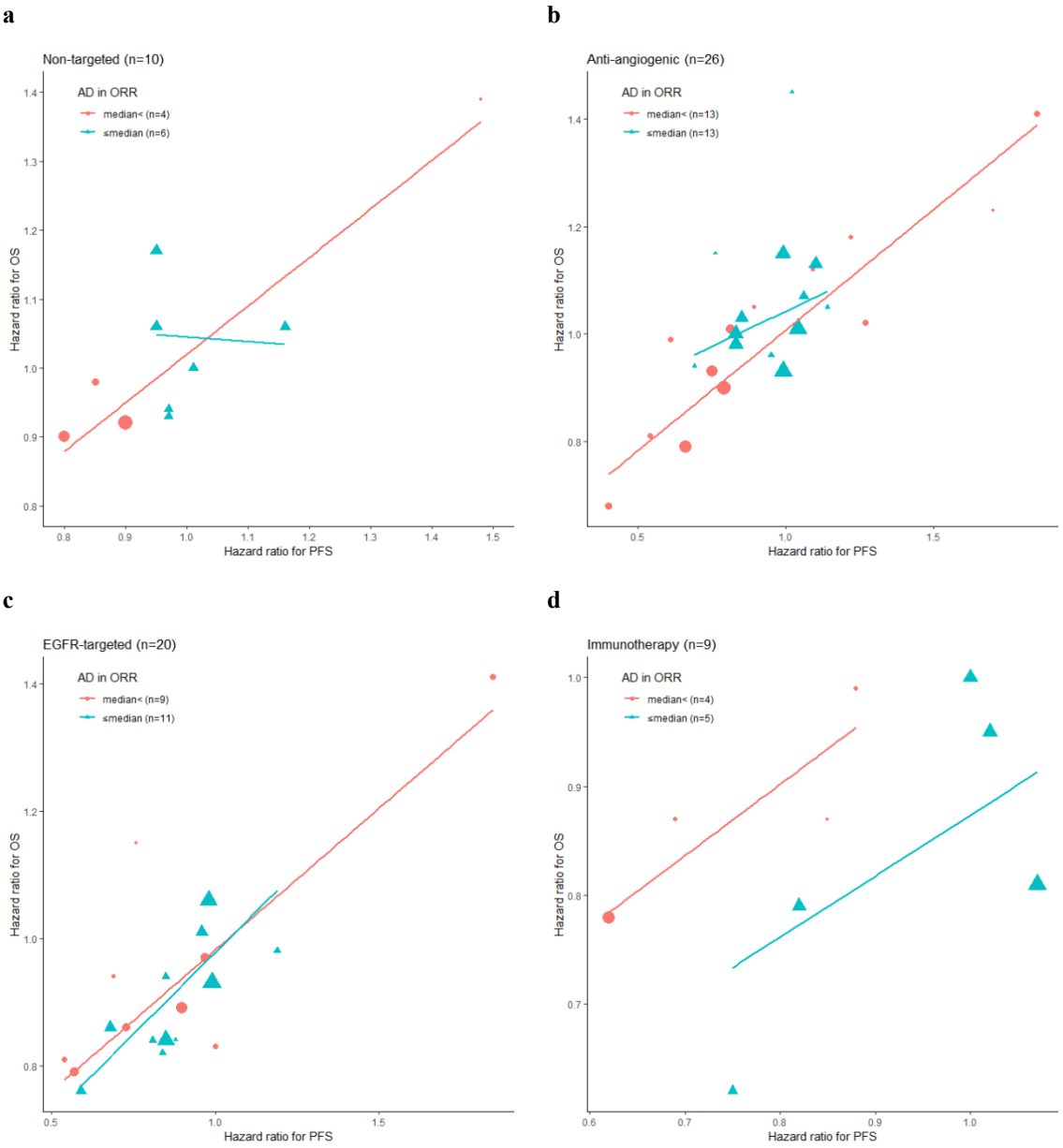
(mAD$_{ORR}$<) were r_s=0.66 (95% CI: 0.42, 0.82, p-value<0.001) and r_s=0.75 (95% CI: 0.56, 0.87, p-value<0.001), respectively. The trial set of mAD$_{ORR}$< showed relatively stronger correlation between HR$_{PFS}$ and HR$_{OS}$ compared to ≤mAD$_{ORR}$ trials. (Fig. 2) The adjusted R^2 was 0.28 for ≤mAD$_{ORR}$ trials and 0.67 for mAD$_{ORR}$< trials.



The solid blue line represents the change in PFS according to a change in OS; gray area indicates 95% confidence intervals of the regression line. Each trial is represented by a circle with symbol size proportional to number of patients. **(a)** Correlation within 1st line trials with a result of absolute difference in ORR between treatment arms less than or equal to 6.85 points. **(b)** Correlation within 1st line trials with a result of absolute difference in ORR between treatment arms greater than 6.85 points.

Figure 5 Correlation between HR$_{PFS}$ and HR$_{OS}$ in 1st line treatment for advanced NSCLC

Next, we performed sensitivity analyses by the types of treatment agents. Same analyses were carried out within each trial set of non-targeted agents, anti-angiogenic agents, EGFR-targeted agents, or immunotherapy. mAD_{ORR} was individually identified within each group and employed as cut-off values for each stratification. The subgroup analysis with non-targeted agent trials showed correlation coefficients of r_s=-0.31 for $\leq mAD_{ORR}$ trials and r_s=0.80 for $mAD_{ORR}<$ trials. Similarly, anti-angiogenic agent trials and immunotherapy trials showed higher correlation coefficients in $mAD_{ORR}<$ trials group (r_s were 0.37 and 0.92 in anti-angiogenic agent trials, and 0.60 and 0.95 in immunotherapy trials, respectively). On the contrary, among the trials that involve EGFR-targeted agents, correlation coefficient was higher in $\leq mAD_{ORR}$ trials (r_s were 0.73 and 0.62). (Fig. 6, Table 6)



The solid line represents the change in PFS according to a change in OS. Each trial is represented by a circle or triangle with symbol size proportional to number of patients. Red circles represent trials with results of absolute difference in ORR between treatment arms less than or equal to mAD_{ORR} identified within each agent group. Blue triangles represent trials with results of absolute difference in ORR between treatment arms greater than mAD_{ORR} identified within each agent group. mAD_{ORR} for non-targeted: 5.0, anti-angiogenic: 13.7, EGFR-targeted: 6.0, immunotherapy: 5.9. **(a)** Correlation within non-targeted 1st line trials. **(b)** Correlation within anti-angiogenic agent 1st line trials. **(c)** Correlation within EGFR-targeted 1st line trials. **(d)** Correlation within immunotherapy 1st line trials.

Figure 6 Correlation between hazard ratios for PFS and OS in 1st line non-targeted, anti-angiogenic, EGFR-targeted or immunotherapy treatment for advanced NSCLC

Table 6 Correlation between HR_{PFS} and HR_{OS} by AD_{ORR} and type of treatment agent

Therapy	Subgroup	No. of comparisons	r_s	95% CI	p-value	Adjusted R^2
Non-targeted	ALL	10	0.61	-0.03, 0.90	0.06	0.43
	median<AD_{ORR}	4	0.80	-0.70, 1.00	0.33	0.85
	AD_{ORR}≤median	6	-0.31	-0.90, 0.67	0.55	-0.25
Anti-angiogenic	ALL	26	0.75	0.51, 0.88	<0.001	0.58
	median<AD_{ORR}	13	0.92	0.74, 0.98	<0.001	0.82
	AD_{ORR}≤median	13	0.37	-0.23, 0.76	0.23	0.01
EGFR-targeted	ALL	20	0.58	0.18, 0.81	0.01	0.67
	median<AD_{ORR}	9	0.62	-0.08, 0.91	0.09	0.76
	AD_{ORR}≤median	11	0.73	0.22, 0.92	0.01	0.51
Immunotherapy	ALL	9	0.56	-0.16, 0.89	0.11	0.14
	median<AD_{ORR}	4	0.95	-0.14, 1.00	0.051	0.78
	AD_{ORR}≤median	5	0.60	-0.60, 0.97	0.35	0.09

mAD_{ORR} was individually identified within each treatment group; non-targeted: 5.0, anti-angiogenic: 13.7, EGFR-targeted: 6.0, immunotherapy: 5.9

mAD_{ORR}, median of absolute difference in objective response rate; AD_{ORR}, absolute difference in objective response rate; HR_{OS}, hazard ratio for overall survival; HR_{PFS}, hazard ratio for progression-free survival; r_s, Spearman rank correlation coefficient.

3.4. Discussion

Surrogate endpoints for OS in patients with advanced NSCLC have been investigated in several studies. Moderate correlations between HR_{PFS} and HR_{OS} were reported in the meta-analysis of clinical trials with first-line chemotherapy for advanced NSCLC [139] and the meta-analysis of trials with molecular targeted agents without cross over [140]. In recent studies with immunotherapy for NSCLC, correlation between HR_{PFS} and HR_{OS} was reported as moderate [141] or strong [142]. The correlations found in the present study were generally consistent with those reported in previous studies. The result that ORR poorly correlates with OS was also consistent with other insights provided previously [75,11,141,142].

In our analyses, we evaluated correlations between HR_{OS} and HR_{PFS} within each trial group stratified by mAD_{ORR} of studies identified through the systematic search. The

correlation was found to be stronger in the $mAD_{ORR}<$ trials compared to that in the $\leq mAD_{ORR}$ trials. These results imply that PFS benefit can be reflected to OS benefit in a relatively strong manner when there is a large difference in tumor response between the treatment arms. As it was discussed in the publications suggesting the association between DpR and OS, when a definitive advantage in tumor shrinkage is observed, there could also be a difference in total tumor volume burden in patients at the time of disease progression, which could result in a difference in time for tumors to grow until lethal volume, which is known as PPS [77]. On the other hand, tumor shrinkage endpoints such as ORR were not shown to solely have sufficient surrogacy for OS as found in the present study [75,11,141,142]. One of the possibilities implied from these results is that it is important to take into account both tumor shrinkage and PFS compositely, not independently, for the prediction of OS. Also it is suggested that, when there is a large difference in tumor response between the treatment arms and the advantage in tumor shrinkage is converted to PPS benefit, PFS benefit can be translated to OS benefit without being thoroughly diluted by confounding factors such as subsequent therapies. Conversely, when the difference in response is minimal, as in the case of $\leq mAD_{ORR}$ trials in the present study, the tumor volumes in patients at the time of disease progression (i.e. the time of moving to next treatment option in most of the cases) are assumed to be almost equivalent between the treatment arms, which may make the impact of subsequent therapies on OS be more apparent. In other words, PFS benefit provided by an experimental treatment in such cases may be directly diluted by subsequent therapies. This may suggest that the study result in which significant PFS benefit was observed with a small advantage in ORR need to be assessed carefully.

The tendency of stronger correlation between HR_{PFS} and HR_{OS} in trials with $mAD_{ORR}<$ was also observed in most of the subgroup analyses including the trial group with immunotherapy. In clinical trials with immunotherapies that are actively developed in recent years, while some research suggest that neither PFS nor ORR would be a reliable surrogate endpoint for OS [143-145], the tendency observed in the present study may be suggesting a meaningful perspective for designing future trial or strategy of clinical development. Meanwhile, only the subgroup of EGFR inhibitors did not show stronger correlation of HR_{PFS} and HR_{OS} in $mAD_{ORR}<$ trials. The trials identified in our

research included those with patients who were genetically unselected by EGFR mutation status or those involving anti-EGFR antibody besides the studies with EGFR tyrosine kinase inhibitors (TKI). These trials appear to have been conducted with patients who respond to study treatments differently. Because of this various population settings, it is considered that the relationship between ORR, PFS and OS may not be uniform and the impact of ORR on the correlation of HR_{PFS} and HR_{OS} did not become obvious. In the present study, we were not able to carry out an analysis with only the trials in which patients are limited to those harboring EGFR mutation as there were merely four trials. The tumor shrinkage dynamics in EGFR mutation positive patients treated with EGFR-TKI is, as discussed in following, estimated to differ from other populations or other EGFR-targeted agents. Further investigation is warranted to examine the impact of ORR on the relationship between PFS and OS in trials with EGFR mutant NSCLC patients.

Potential indicators of tumor shrinkage dynamics have been suggested to be associated with survival in patients with advanced NSCLC. DpR was reported to be associated with OS in NSCLC patients treated with first-line chemotherapy [146] and early depth of response, defined as percent tumor reductions from baseline to the first evaluation at 8-12 weeks after starting treatment, was also suggested to have strong association with OS in patients treated with nivolumab, a PD-1 inhibitor [147]. On the other hand, it was reported that early depth of response was not associated with OS in EGFR mutant NSCLC patients [148], and that neither time-to-response (TTR) nor DpR was a factor for prolonged survival among the patients who achieved complete response or partial response with EGFR-TKI, while PFS and OS in responders were significantly longer compared to non-responders [149]. Based on these insights, the tumor shrinkage dynamics in patients treated with EGFR inhibitors appears to have, comparing to other agents, a unique relationship with survival. However, the association between tumor shrinkage and survival itself is suggested in either type of therapies in their respective ways, and therefore the accuracy and reliability of OS estimation on the basis of intermediate endpoints is expected to be improved by further investigating and identifying each form of relationship between tumor shrinkage dynamics and OS in each type of therapies for patients with advanced NSCLC.

Based on our analyses, we concluded that the improvement in tumor response would contribute to a better prediction of HR_{OS} based on HR_{PFS} in patients with NSCLC participated in clinical trials of first line treatment.

4. Overall Discussion

Based on the results in Research 1 and Research 2, it was suggested that the prediction of OS benefit based on PFS in first-line clinical trials either in patients with CRC or NSCLC would be improved by considering the magnitude of improvement in ORR. It was also suggested that the correlation between HR_{PFS} and HR_{OS} may be weak in the trials where a difference in ORR between the treatment arms was small. Since we observed almost similar outcomes in both studies on patients with CRC and NSCLC, there may be other types of cancers to which our insights can be applied.

There are some limitations in our research that need to be noted. First, these were literature-based trial level meta-analyses and not IPD-based. Second, trials ascertained for the analyses included phase 2 studies, and the maturities of hazard ratios for OS could differ from those of phase 3 studies. This may affect the value of correlation coefficients obtained by our analyses. In addition, we excluded the trials from our analyses in which in-protocol crossover was allowed. Therefore, it is not apparent if our implication could be applied to cases where a remarkable unbalance in subsequent therapies is observed. A separate investigation may be needed to address the potential impact of crossover on our findings. Lastly, although we found out that the correlation between treatment effects in HR_{PFS} and HR_{OS} varied in each trial set stratified by mAD_{ORR}, we didn't determine a cut-off value of AD_{ORR} which enables us to assume that the correlation between HR_{PFS} and HR_{OS} is reliably improved. This is expected to be elucidated by further investigation of tumor shrinkage dynamics/kinetics assessment including ETS and DpR. However, the purpose of the present study was to explore, through trial-level meta-analyses, the importance of considering both time-to-event efficacy endpoint and tumor shrinkage-based endpoint for a better prediction of OS benefit, rather than estimating it from one single endpoint. Our results suggest, from a perspective of drug development, a possibility to provide more accuracy or reliability in the estimation of OS benefit, and thus of sample size, for future pivotal studies to be planned, by considering both PFS and ORR demonstrated in early phase studies. As for the clinical implication, our results may indicate that, even at the individual patient level, prognosis of patients with the same PFS needs to be estimated differently depending on their response to a first line treatment. To elucidate this, however, IPD level research is

required.

We expect that our research will generate interest in tumor shrinkage dynamics among researchers and motivate them to explore the relationships between tumor shrinkage dynamics and survival of cancer patients in future clinical trials. We believe that the more we collect sufficient detailed data on tumor shrinkage dynamics, the more we understand its relationship with survival, which finally would enable us to predict OS benefit at trial level and also at individual patient level.

5. Conclusion

Based on our analyses, we conclude that the magnitude of advantage in tumor response would contribute to a better prediction of HR_{OS} based on HR_{PFS} in either patients with CRC or NSCLC participated in clinical trials of first line treatment. The accuracy of OS estimation is expected to be improved by considering various patterns of tumor shrinkage dynamics in conjunction with PFS at each type of treatment agent and study population.

6. References

1. Collaboration GBoDC (2019) Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncology 5 (12):1749-1768. doi:10.1001/jamaoncol.2019.2996

2. Siegel RL, Miller KD, Goding Sauer A et al. (2020) Colorectal cancer statistics, 2020. CA: A Cancer Journal for Clinicians 70 (3):145-164. doi:https://doi.org/10.3322/caac.21601

3. Torre LA, Siegel RL, Jemal A (2016) Lung Cancer Statistics. Adv Exp Med Biol 893:1-19. doi:10.1007/978-3-319-24223-1_1

4. Hay M, Thomas DW, Craighead JL et al. (2014) Clinical development success rates for investigational drugs. Nature Biotechnology 32 (1):40-51. doi:10.1038/nbt.2786

5. Wouters OJ, McKee M, Luyten J (2020) Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA 323 (9):844-853. doi:10.1001/jama.2020.1166

6. U.S. Department of Health and Human Services FaDA (2018) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry. Guidance document

7. Seruga B, Ocana A, Amir E et al. (2015) Failures in Phase III: Causes and Consequences. Clinical Cancer Research 21 (20):4552-4560. doi:10.1158/1078-0432.Ccr-15-0124

8. Douaiher J, Ravipati A, Grams B et al. (2017) Colorectal cancer—global burden, trends, and geographical variations. Journal of Surgical Oncology 115 (5):619-630. doi:10.1002/jso.24578

9. Schwartzberg LS, Rivera F, Karthaus M et al. (2014) PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. Journal of Clinical Oncology 32 (21):2240-2247. doi:10.1200/jco.2013.53.2473

10. Stintzing S, Modest DP, Rossius L et al. (2016) FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. The Lancet Oncology 17 (10):1426-1434. doi:https://doi.org/10.1016/S1470-2045(16)30269-8

11. Haslam A, Hey SP, Gill J et al. (2019) A systematic review of trial-level

meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. European Journal of Cancer 106:196-211. doi:https://doi.org/10.1016/j.ejca.2018.11.012
12. Piessevaux H, Buyse M, Schlichting M et al. (2013) Use of Early Tumor Shrinkage to Predict Long-Term Outcome in Metastatic Colorectal Cancer Treated With Cetuximab. Journal of Clinical Oncology 31 (30):3764-3775. doi:10.1200/jco.2012.42.8532
13. Mansmann UR, Sartorius U, Laubender RP et al. (2013) Quantitative analysis of the impact of deepness of response on post-progression survival time following first-line treatment in patients with mCRC. Journal of Clinical Oncology 31 (15_suppl):3630-3630. doi:10.1200/jco.2013.31.15_suppl.3630
14. Cremolini C, Loupakis F, Antoniotti C et al. (2015) Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. Annals of Oncology 26 (6):1188-1194. doi:https://doi.org/10.1093/annonc/mdv112
15. Douillard J-Y, Siena S, Peeters M et al. (2015) Impact of early tumour shrinkage and resection on outcomes in patients with wild-type RAS metastatic colorectal cancer. European Journal of Cancer 51 (10):1231-1242. doi:https://doi.org/10.1016/j.ejca.2015.03.026
16. Tsuji A, Sunakawa Y, Ichikawa W et al. (2016) Early Tumor Shrinkage and Depth of Response as Predictors of Favorable Treatment Outcomes in Patients with Metastatic Colorectal Cancer Treated with FOLFOX Plus Cetuximab (JACCRO CC-05). Targeted Oncology 11 (6):799-806. doi:10.1007/s11523-016-0445-6
17. Petrelli F, Pietrantonio F, Cremolini C et al. (2015) Early tumour shrinkage as a prognostic factor and surrogate end-point in colorectal cancer: A systematic review and pooled-analysis. European Journal of Cancer 51 (7):800-807. doi:https://doi.org/10.1016/j.ejca.2015.02.011
18. Nakayama G, Fujii T, Murotani K et al. (2016) Modified two-dimensional response as surrogate marker of overall survival in patients with metastatic colorectal cancer. Cancer Science 107 (10):1492-1498. doi:10.1111/cas.13023
19. Hutton B, Salanti G, Caldwell DM et al. (2015) The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Annals of Internal Medicine 162 (11):777-784. doi:10.7326/m14-2385
20. Giessen C, Laubender RP, Ankerst DP et al. (2013) Progression-Free Survival as a

Surrogate Endpoint for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis from 50 Randomized First-Line Trials. Clinical Cancer Research 19 (1):225-235. doi:10.1158/1078-0432.Ccr-12-1515
21. Broglio KR, Berry DA (2009) Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival. JNCI: Journal of the National Cancer Institute 101 (23):1642-1649. doi:10.1093/jnci/djp369
22. Morita S, Sakamaki K, Yin G (2015) Detecting Overall Survival Benefit Derived From Survival Postprogression Rather Than Progression-Free Survival. JNCI: Journal of the National Cancer Institute 107 (8). doi:10.1093/jnci/djv133
23. Burzykowski T, Buyse M, Piccart-Gebhart MJ et al. (2008) Evaluation of Tumor Response, Disease Control, Progression-Free Survival, and Time to Progression As Potential Surrogate End Points in Metastatic Breast Cancer. Journal of Clinical Oncology 26 (12):1987-1992. doi:10.1200/jco.2007.10.8407
24. Tang PA, Bentzen SM, Chen EX et al. (2007) Surrogate End Points for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis From 39 Randomized Controlled Trials of First-Line Chemotherapy. Journal of Clinical Oncology 25 (29):4562-4568. doi:10.1200/jco.2006.08.1935
25. Aparicio T, Lavau-Denes S, Phelip JM et al. (2016) Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001–02)†. Annals of Oncology 27 (1):121-127. doi:https://doi.org/10.1093/annonc/mdv491
26. Passardi A, Nanni O, Tassinari D et al. (2015) Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. Annals of Oncology 26 (6):1201-1207. doi:https://doi.org/10.1093/annonc/mdv130
27. Brodowicz T, Ciuleanu TE, Radosavljevic D et al. (2013) FOLFOX4 plus cetuximab administered weekly or every second week in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer: a randomized phase II CECOG study. Annals of Oncology 24 (7):1769-1777. doi:https://doi.org/10.1093/annonc/mdt116
28. Labianca R, Sobrero A, Isa L et al. (2011) Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. Annals of Oncology 22 (5):1236-1242. doi:https://doi.org/10.1093/annonc/mdq580
29. Bokemeyer C, Bondarenko I, Hartmann JT et al. (2011) Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Annals of Oncology 22 (7):1535-1546.

doi:https://doi.org/10.1093/annonc/mdq632
30. Glimelius B, Sørbye H, Balteskard L et al. (2008) A randomized phase III multicenter trial comparing irinotecan in combination with the Nordic bolus 5-FU and folinic acid schedule or the bolus/infused de Gramont schedule (Lv5FU2) in patients with metastatic colorectal cancer. Annals of Oncology 19 (5):909-914. doi:https://doi.org/10.1093/annonc/mdm588
31. Punt CJA, Keizer HJ, Douma J et al. (2002) Trimetrexate as biochemical modulator of 5-fluorouracil/leucovorin in advanced colorectal cancer: final results of a randomised European study. Annals of Oncology 13 (1):81-86. doi:https://doi.org/10.1093/annonc/mdf045
32. Blanke CD, Shultz J, Cox J et al. (2002) A double-blind placebo-controlled randomized phase III trial of 5-fluorouracil and leucovorin, plus or minus trimetrexate, in previously untreated patients with advanced colorectal cancer. Annals of Oncology 13 (1):87-91. doi:https://doi.org/10.1093/annonc/mdf043
33. KALOFONOS HP, PAPAKOSTAS P, MAKATSORIS T et al. (2010) Irinotecan/Fluorouracil/Leucovorin or the Same Regimen Followed by Oxaliplatin/Fluorouracil/Leucovorin in Metastatic Colorectal Cancer. Anticancer Research 30 (10):4325-4333
34. Souglakos J, Ziras N, Kakolyris S et al. (2012) Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC). British Journal of Cancer 106 (3):453-459. doi:10.1038/bjc.2011.594
35. Yamazaki K, Kuwano H, Ojima H et al. (2015) A randomized phase II study of combination therapy with S-1, oral leucovorin, and oxaliplatin (SOL) and mFOLFOX6 in patients with previously untreated metastatic colorectal cancer. Cancer Chemotherapy and Pharmacology 75 (3):569-577. doi:10.1007/s00280-015-2676-0
36. Guan Z-Z, Xu J-M, Luo R-C et al. (2011) Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. Chin J Cancer 30 (10):682-689. doi:10.5732/cjc.011.10188
37. Cao B, Li S-t, Li Z et al. (2011) Yiqi Zhuyu Decoction (益气逐瘀汤) Combined with FOLFOX-4 as first-line therapy in metastatic colorectal cancer. Chinese Journal of Integrative Medicine 17 (8):593. doi:10.1007/s11655-011-0822-z
38. Tabernero J, Garcia-Carbonero R, Cassidy J et al. (2013) Sorafenib in Combination with Oxaliplatin, Leucovorin, and Fluorouracil (Modified FOLFOX6) as First-line Treatment of Metastatic Colorectal Cancer: The RESPECT Trial. Clinical Cancer

Research 19 (9):2541-2550. doi:10.1158/1078-0432.Ccr-13-0107
39. Douillard J-Y, Zemelka T, Fountzilas G et al. (2014) FOLFOX4 With Cetuximab vs. UFOX With Cetuximab as First-Line Therapy in Metastatic Colorectal Cancer: The Randomized Phase II FUTURE Study. Clinical Colorectal Cancer 13 (1):14-26.e11. doi:https://doi.org/10.1016/j.clcc.2013.11.009
40. Gravalos C, Salut A, García-Girón C et al. (2012) A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. Clinical and Translational Oncology 14 (8):606-612. doi:10.1007/s12094-012-0843-x
41. Ducreux M, Bennouna J, Hebbar M et al. (2011) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. International Journal of Cancer 128 (3):682-690. doi:10.1002/ijc.25369
42. Comella P, Massidda B, Filippelli G et al. (2009) Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus i.v. bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology study 0401. Journal of Cancer Research and Clinical Oncology 135 (2):217-226. doi:10.1007/s00432-008-0454-7
43. Hoff PM, Hochhaus A, Pestalozzi BC et al. (2012) Cediranib Plus FOLFOX/CAPOX Versus Placebo Plus FOLFOX/CAPOX in Patients With Previously Untreated Metastatic Colorectal Cancer: A Randomized, Double-Blind, Phase III Study (HORIZON II). Journal of Clinical Oncology 30 (29):3596-3603. doi:10.1200/jco.2012.42.6031
44. Schmoll H-J, Cunningham D, Sobrero A et al. (2012) Cediranib With mFOLFOX6 Versus Bevacizumab With mFOLFOX6 As First-Line Treatment for Patients With Advanced Colorectal Cancer: A Double-Blind, Randomized Phase III Study (HORIZON III). Journal of Clinical Oncology 30 (29):3588-3595. doi:10.1200/jco.2012.42.5355
45. Tveit KM, Guren T, Glimelius B et al. (2012) Phase III Trial of Cetuximab With Continuous or Intermittent Fluorouracil, Leucovorin, and Oxaliplatin (Nordic FLOX) Versus FLOX Alone in First-Line Treatment of Metastatic Colorectal Cancer: The NORDIC-VII Study. Journal of Clinical Oncology 30 (15):1755-1762. doi:10.1200/jco.2011.38.0915
46. Douillard J-Y, Siena S, Cassidy J et al. (2010) Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated

Metastatic Colorectal Cancer: The PRIME Study. Journal of Clinical Oncology 28 (31):4697-4705. doi:10.1200/jco.2009.27.4860
47. Tebbutt NC, Wilson K, Gebski VJ et al. (2010) Capecitabine, Bevacizumab, and Mitomycin in First-Line Treatment of Metastatic Colorectal Cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. Journal of Clinical Oncology 28 (19):3191-3198. doi:10.1200/jco.2009.27.7723
48. Saltz LB, Clarke S, Díaz-Rubio E et al. (2008) Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. Journal of Clinical Oncology 26 (12):2013-2019. doi:10.1200/jco.2007.14.9930
49. Porschen R, Arkenau H-T, Kubicka S et al. (2007) Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Leucovorin Plus Oxaliplatin in Metastatic Colorectal Cancer: A Final Report of the AIO Colorectal Study Group. Journal of Clinical Oncology 25 (27):4217-4223. doi:10.1200/jco.2006.09.2684
50. Falcone A, Ricci S, Brunetti I et al. (2007) Phase III Trial of Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared With Infusional Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) As First-Line Treatment for Metastatic Colorectal Cancer: The Gruppo Oncologico Nord Ovest. Journal of Clinical Oncology 25 (13):1670-1676. doi:10.1200/jco.2006.09.0928
51. Kabbinavar FF, Schulz J, McCleod M et al. (2005) Addition of Bevacizumab to Bolus Fluorouracil and Leucovorin in First-Line Metastatic Colorectal Cancer: Results of a Randomized Phase II Trial. Journal of Clinical Oncology 23 (16):3697-3705. doi:10.1200/jco.2005.05.112
52. Köhne C-H, Cutsem Ev, Wils J et al. (2005) Phase III Study of Weekly High-Dose Infusional Fluorouracil Plus Folinic Acid With or Without Irinotecan in Patients With Metastatic Colorectal Cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. Journal of Clinical Oncology 23 (22):4856-4865. doi:10.1200/jco.2005.05.546
53. Schilsky RL, Levin J, West WH et al. (2002) Randomized, Open-Label, Phase III Study of a 28-Day Oral Regimen of Eniluracil Plus Fluorouracil Versus Intravenous Fluorouracil Plus Leucovorin as First-Line Therapy in Patients With Metastatic/Advanced Colorectal Cancer. Journal of Clinical Oncology 20 (6):1519-1526. doi:10.1200/jco.2002.20.6.1519
54. Seymour MT, Slevin ML, Kerr DJ et al. (1996) Randomized trial assessing the addition of interferon alpha-2a to fluorouracil and leucovorin in advanced colorectal cancer. Colorectal Cancer Working Party of the United Kingdom Medical Research

Council. Journal of Clinical Oncology 14 (8):2280-2288. doi:10.1200/jco.1996.14.8.2280
55. Venook AP, Niedzwiecki D, Lenz H-J et al. (2017) Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA 317 (23):2392-2401. doi:10.1001/jama.2017.7105
56. Maughan TS, Adams RA, Smith CG et al. (2011) Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. The Lancet 377 (9783):2103-2114. doi:https://doi.org/10.1016/S0140-6736(11)60613-2
57. Maughan TS, James RD, Kerr DJ et al. (2002) Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. The Lancet 359 (9317):1555-1563. doi:https://doi.org/10.1016/S0140-6736(02)08514-8
58. Heinemann V, von Weikersthal LF, Decker T et al. (2014) FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. The Lancet Oncology 15 (10):1065-1075. doi:https://doi.org/10.1016/S1470-2045(14)70330-4
59. Loupakis F, Cremolini C, Masi G et al. (2014) Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer. New England Journal of Medicine 371 (17):1609-1618. doi:10.1056/NEJMoa1403108
60. Douillard J-Y, Oliner KS, Siena S et al. (2013) Panitumumab–FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer. New England Journal of Medicine 369 (11):1023-1034. doi:10.1056/NEJMoa1305275
61. Tol J, Koopman M, Cats A et al. (2009) Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer. New England Journal of Medicine 360 (6):563-572. doi:10.1056/NEJMoa0808268
62. Van Cutsem E, Köhne C-H, Hitre E et al. (2009) Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. New England Journal of Medicine 360 (14):1408-1417. doi:10.1056/NEJMoa0805019
63. Hurwitz H, Fehrenbacher L, Novotny W et al. (2004) Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. New England Journal of Medicine 350 (23):2335-2342. doi:10.1056/NEJMoa032691
64. Saltz LB, Cox JV, Blanke C et al. (2000) Irinotecan plus Fluorouracil and Leucovorin for Metastatic Colorectal Cancer. New England Journal of Medicine 343 (13):905-914. doi:10.1056/nejm200009283431302

65. Ocvirk J, Brodowicz T, Wrba F et al. (2010) Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. World J Gastroenterol 16 (25):3133-3143. doi:10.3748/wjg.v16.i25.3133
66. Cunningham D, Lang I, Marcuello E et al. (2013) Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. The Lancet Oncology 14 (11):1077-1085. doi:https://doi.org/10.1016/S1470-2045(13)70154-2
67. Goldberg RM, Sargent DJ, Morton RF et al. (2004) A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer. Journal of Clinical Oncology 22 (1):23-30. doi:10.1200/jco.2004.09.046
68. Yamazaki K, Nagase M, Tamagawa H et al. (2016) Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). Annals of Oncology 27 (8):1539-1546. doi:https://doi.org/10.1093/annonc/mdw206
69. García-Carbonero R, van Cutsem E, Rivera F et al. (2017) Randomized Phase II Trial of Parsatuzumab (Anti-EGFL7) or Placebo in Combination with FOLFOX and Bevacizumab for First-Line Metastatic Colorectal Cancer. The Oncologist 22 (4):375-e330. doi:10.1634/theoncologist.2016-0133
70. Pinter T, Klippel Z, Cesas A et al. (2017) A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Pegfilgrastim in Patients Receiving First-Line FOLFOX/Bevacizumab or FOLFIRI/Bevacizumab for Locally Advanced or Metastatic Colorectal Cancer: Final Results of the Pegfilgrastim and Anti-VEGF Evaluation Study (PAVES). Clinical Colorectal Cancer 16 (2):103-114.e103. doi:https://doi.org/10.1016/j.clcc.2016.08.008
71. Shi Q, Gramont Ad, Grothey A et al. (2015) Individual Patient Data Analysis of Progression-Free Survival Versus Overall Survival As a First-Line End Point for Metastatic Colorectal Cancer in Modern Randomized Trials: Findings From the Analysis and Research in Cancers of the Digestive System Database. Journal of Clinical Oncology 33 (1):22-28. doi:10.1200/jco.2014.56.5887
72. Topalian SL, Sznol M, McDermott DF et al. (2014) Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. Journal of Clinical Oncology 32 (10):1020-1030. doi:10.1200/jco.2013.53.0105
73. Daud A, Ribas A, Robert C et al. (2015) Long-term efficacy of pembrolizumab (pembro; MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma

(MEL) enrolled in KEYNOTE-001. Journal of Clinical Oncology 33 (15_suppl):9005-9005. doi:10.1200/jco.2015.33.15_suppl.9005
74. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA: A Cancer Journal for Clinicians 69 (1):7-34. doi:10.3322/caac.21551
75. Blumenthal GM, Karuri SW, Zhang H et al. (2015) Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer: US Food and Drug Administration Trial-Level and Patient-Level Analyses. Journal of Clinical Oncology 33 (9):1008-1014. doi:10.1200/jco.2014.59.0489
76. McCoach CE, Blumenthal GM, Zhang L et al. (2017) Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy. Ann Oncol 28 (11):2707-2714. doi:10.1093/annonc/mdx414
77. Heinemann V, Stintzing S, Modest DP et al. (2015) Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). European Journal of Cancer 51 (14):1927-1936. doi:https://doi.org/10.1016/j.ejca.2015.06.116
78. Yoshida Y, Kaneko M, Narukawa M (2020) Magnitude of advantage in tumor response contributes to a better correlation between treatment effects on overall survival and progression-free survival: a literature-based meta-analysis of clinical trials in patients with metastatic colorectal cancer. International Journal of Clinical Oncology. doi:10.1007/s10147-020-01619-8
79. Socinski MA, Jotte RM, Cappuzzo F et al. (2018) Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. New England Journal of Medicine 378 (24):2288-2301. doi:10.1056/NEJMoa1716948
80. Kubota K, Yoshioka H, Oshita F et al. (2017) Phase III, Randomized, Placebo-Controlled, Double-Blind Trial of Motesanib (AMG-706) in Combination With Paclitaxel and Carboplatin in East Asian Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 35 (32):3662-3670. doi:10.1200/jco.2017.72.7297
81. Peters S, Camidge DR, Shaw AT et al. (2017) Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine 377 (9):829-838. doi:10.1056/NEJMoa1704795
82. Paz-Ares L, Tan EH, O'Byrne K et al. (2017) Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Annals of Oncology 28 (2):270-277.

doi:https://doi.org/10.1093/annonc/mdw611
83. Spigel DR, Luft A, Depenbrock H et al. (2017) An Open-Label, Randomized, Controlled Phase II Study of Paclitaxel-Carboplatin Chemotherapy With Necitumumab Versus Paclitaxel-Carboplatin Alone in First-Line Treatment of Patients With Stage IV Squamous Non–Small-Cell Lung Cancer. Clinical Lung Cancer 18 (5):480-488. doi:https://doi.org/10.1016/j.cllc.2017.02.002
84. Yang JJ, Zhou Q, Yan HH et al. (2017) A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. British Journal of Cancer 116 (5):568-574. doi:10.1038/bjc.2016.456
85. Wakelee H, Zvirbule Z, De Braud F et al. (2017) Efficacy and Safety of Onartuzumab in Combination With First-Line Bevacizumab- or Pemetrexed-Based Chemotherapy Regimens in Advanced Non-Squamous Non–Small-Cell Lung Cancer. Clinical Lung Cancer 18 (1):50-59. doi:https://doi.org/10.1016/j.cllc.2016.09.013
86. Ramalingam SS, Blais N, Mazieres J et al. (2017) Randomized, Placebo-Controlled, Phase II Study of Veliparib in Combination with Carboplatin and Paclitaxel for Advanced/Metastatic Non–Small Cell Lung Cancer. Clinical Cancer Research 23 (8):1937-1944. doi:10.1158/1078-0432.Ccr-15-3069
87. Joerger M, von Pawel J, Kraff S et al. (2016) Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC)†. Annals of Oncology 27 (10):1895-1902. doi:https://doi.org/10.1093/annonc/mdw290
88. Novello S, Scagliotti G, de Castro G et al. (2017) An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as a First-Line Therapy in Patients With Advanced Nonsquamous Non–Small Cell Lung Cancer. Journal of Thoracic Oncology 12 (2):383-389. doi:https://doi.org/10.1016/j.jtho.2016.07.013
89. Hirsch FR, Govindan R, Zvirbule Z et al. (2017) Efficacy and Safety Results From a Phase II, Placebo-Controlled Study of Onartuzumab Plus First-Line Platinum-Doublet Chemotherapy for Advanced Squamous Cell Non–Small-Cell Lung Cancer. Clinical Lung Cancer 18 (1):43-49. doi:https://doi.org/10.1016/j.cllc.2016.05.011
90. Yang JC-H, Srimuninnimit V, Ahn M-J et al. (2016) First-Line Pemetrexed plus Cisplatin followed by Gefitinib Maintenance Therapy versus Gefitinib Monotherapy in East Asian Never-Smoker Patients with Locally Advanced or Metastatic Nonsquamous Non–Small Cell Lung Cancer: Final Overall Survival Results from a Randomized Phase 3 Study. Journal of Thoracic Oncology 11 (3):370-379. doi:https://doi.org/10.1016/j.jtho.2015.11.008

91. Zhou C, Wu Y-L, Chen G et al. (2015) BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 33 (19):2197-2204. doi:10.1200/jco.2014.59.4424
92. Zinner RG, Obasaju CK, Spigel DR et al. (2015) PRONOUNCE: Randomized, Open-Label, Phase III Study of First-Line Pemetrexed + Carboplatin Followed by Maintenance Pemetrexed versus Paclitaxel + Carboplatin + Bevacizumab Followed by Maintenance Bevacizumab in Patients ith Advanced Nonsquamous Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology 10 (1):134-142. doi:https://doi.org/10.1097/JTO.0000000000000366
93. Seto T, Kato T, Nishio M et al. (2014) Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. The Lancet Oncology 15 (11):1236-1244. doi:https://doi.org/10.1016/S1470-2045(14)70381-X
94. von Pawel J, Gorbounova V, Reck M et al. (2014) DISRUPT: A randomised phase 2 trial of ombrabulin (AVE8062) plus a taxane–platinum regimen as first-line therapy for metastatic non-small cell lung cancer. Lung Cancer 85 (2):224-229. doi:https://doi.org/10.1016/j.lungcan.2014.05.013
95. Belani CP, Yamamoto N, Bondarenko IM et al. (2014) Randomized phase II study of pemetrexed/cisplatin with or without axitinib for non-squamous non-small-cell lung cancer. BMC Cancer 14 (1):290. doi:10.1186/1471-2407-14-290
96. Yu H, Zhang J, Wu X et al. (2014) A phase II randomized trial evaluating gefitinib intercalated with pemetrexed/platinum chemotherapy or pemetrexed/platinum chemotherapy alone in unselected patients with advanced non-squamous non-small cell lung cancer. Cancer Biology & Therapy 15 (7):832-839. doi:10.4161/cbt.28874
97. Twelves C, Chmielowska E, Havel L et al. (2014) Randomised phase II study of axitinib or bevacizumab combined with paclitaxel/carboplatin as first-line therapy for patients with advanced non-small-cell lung cancer. Annals of Oncology 25 (1):132-138. doi:https://doi.org/10.1093/annonc/mdt489
98. Patel JD, Socinski MA, Garon EB et al. (2013) PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 31

(34):4349-4357. doi:10.1200/jco.2012.47.9626
99. Wu Y-L, Lee JS, Thongprasert S et al. (2013) Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. The Lancet Oncology 14 (8):777-786. doi:https://doi.org/10.1016/S1470-2045(13)70254-7
100. Bonomi PD, Mace J, Mandanas RA et al. (2013) Randomized Phase II Study of Cetuximab and Bevacizumab in Combination with Two Regimens of Paclitaxel and Carboplatin in Chemonaive Patients with Stage IIIB/IV Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology 8 (3):338-345. doi:https://doi.org/10.1097/JTO.0b013e318282ded5
101. Paz-Ares L, Bálint B, de Boer RH et al. (2013) A Randomized Phase 2 Study of Paclitaxel and Carboplatin with or without Conatumumab for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology 8 (3):329-337. doi:https://doi.org/10.1097/JTO.0b013e31827ce554
102. Lee SY, Park HS, Lee KY et al. (2013) Paclitaxel-Loaded Polymeric Micelle (230 mg/m2) and Cisplatin (60 mg/m2) vs. Paclitaxel (175 mg/m2) and Cisplatin (60 mg/m2) in Advanced Non–Small-Cell Lung Cancer: A Multicenter Randomized Phase IIB Trial. Clinical Lung Cancer 14 (3):275-282. doi:https://doi.org/10.1016/j.cllc.2012.11.005
103. Paz-Ares LG, Biesma B, Heigener D et al. (2012) Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Gemcitabine/Cisplatin Alone or With Sorafenib for the First-Line Treatment of Advanced, Nonsquamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 30 (25):3084-3092. doi:10.1200/jco.2011.39.7646
104. Scagliotti GV, Vynnychenko I, Park K et al. (2012) International, Randomized, Placebo-Controlled, Double-Blind Phase III Study of Motesanib Plus Carboplatin/Paclitaxel in Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer: MONET1. Journal of Clinical Oncology 30 (23):2829-2836. doi:10.1200/jco.2011.41.4987
105. Lynch TJ, Bondarenko I, Luft A et al. (2012) Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. Journal of Clinical Oncology 30 (17):2046-2054. doi:10.1200/jco.2011.38.4032
106. Socinski MA, Bondarenko I, Karaseva NA et al. (2012) Weekly nab-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Final Results of a Phase III Trial. Journal of Clinical Oncology 30 (17):2055-2062.

doi:10.1200/jco.2011.39.5848
107. Niho S, Kunitoh H, Nokihara H et al. (2012) Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer 76 (3):362-367. doi:https://doi.org/10.1016/j.lungcan.2011.12.005
108. Groen HJM, Sietsma H, Vincent A et al. (2011) Randomized, Placebo-Controlled Phase III Study of Docetaxel Plus Carboplatin With Celecoxib and Cyclooxygenase-2 Expression As a Biomarker for Patients With Advanced Non–Small-Cell Lung Cancer: The NVALT-4 Study. Journal of Clinical Oncology 29 (32):4320-4326. doi:10.1200/jco.2011.35.5214
109. Jr PNL, Douillard J-Y, Nakagawa K et al. (2011) Randomized Phase III Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the Vascular Disrupting Agent Vadimezan (ASA404) in Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 29 (22):2965-2971. doi:10.1200/jco.2011.35.0660
110. Hirsh V, Paz-Ares L, Boyer M et al. (2011) Randomized Phase III Trial of Paclitaxel/Carboplatin With or Without PF-3512676 (Toll-Like Receptor 9 Agonist) As First-Line Treatment for Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 29 (19):2667-2674. doi:10.1200/jco.2010.32.8971
111. Koch A, Bergman B, Holmberg E et al. (2011) Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: A double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group. European Journal of Cancer 47 (10):1546-1555. doi:https://doi.org/10.1016/j.ejca.2011.03.035
112. Digumarti R, Wang Y, Raman G et al. (2011) A Randomized, Double-Blind, Placebo-Controlled, Phase II Study of Oral Talactoferrin in Combination with Carboplatin and Paclitaxel in Previously Untreated Locally Advanced or Metastatic Non-small Cell Lung Cancer. Journal of Thoracic Oncology 6 (6):1098-1103. doi:https://doi.org/10.1097/JTO.0b013e3182156250
113. Manegold C, van Zandwijk N, Szczesna A et al. (2012) A phase III randomized study of gemcitabine and cisplatin with or without PF-3512676 (TLR9 agonist) as first-line treatment of advanced non-small-cell lung cancer. Annals of Oncology 23 (1):72-77. doi:https://doi.org/10.1093/annonc/mdr030
114. Blumenschein Jr GR, Kabbinavar F, Menon H et al. (2011) A phase II, multicenter, open-label randomized study of motesanib or bevacizumab in combination with paclitaxel and carboplatin for advanced nonsquamous non-small-cell lung cancer. Annals of Oncology 22 (9):2057-2067. doi:https://doi.org/10.1093/annonc/mdq731
115. Scagliotti G, Novello S, Pawel Jv et al. (2010) Phase III Study of Carboplatin and

Paclitaxel Alone or With Sorafenib in Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 28 (11):1835-1842. doi:10.1200/jco.2009.26.1321
116. Reck M, von Pawel J, Zatloukal P et al. (2010) Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Annals of Oncology 21 (9):1804-1809. doi:https://doi.org/10.1093/annonc/mdq020
117. Lynch TJ, Patel T, Dreisbach L et al. (2010) Cetuximab and First-Line Taxane/Carboplatin Chemotherapy in Advanced Non–Small-Cell Lung Cancer: Results of the Randomized Multicenter Phase III Trial BMS099. Journal of Clinical Oncology 28 (6):911-917. doi:10.1200/jco.2009.21.9618
118. Takeda K, Hida T, Sato T et al. (2010) Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203). Journal of Clinical Oncology 28 (5):753-760. doi:10.1200/jco.2009.23.3445
119. Lee SM, Rudd R, Woll PJ et al. (2009) Randomized Double-Blind Placebo-Controlled Trial of Thalidomide in Combination With Gemcitabine and Carboplatin in Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 27 (31):5248-5254. doi:10.1200/jco.2009.21.9733
120. Zwitter M, Kovac V, Smrdel U et al. (2009) Gemcitabine in Brief versus Prolonged Low-Dose Infusion, both Combined with Cisplatin, for Advanced Non-small Cell Lung Cancer: A Randomized Phase II Clinical Trial. Journal of Thoracic Oncology 4 (9):1148-1155. doi:https://doi.org/10.1097/JTO.0b013e3181ae280f
121. Comella P, Chiuri VE, De Cataldis G et al. (2010) Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer: A randomized phase II SICOG trial. Lung Cancer 68 (1):94-98. doi:https://doi.org/10.1016/j.lungcan.2009.05.008
122. Goss G, Ferry D, Wierzbicki R et al. (2009) Randomized Phase II Study of Gefitinib Compared With Placebo in Chemotherapy-Naive Patients With Advanced Non–Small-Cell Lung Cancer and Poor Performance Status. Journal of Clinical Oncology 27 (13):2253-2260. doi:10.1200/jco.2008.18.4408
123. Kubota K, Kawahara M, Ogawara M et al. (2008) Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. The Lancet Oncology 9 (12):1135-1142. doi:https://doi.org/10.1016/S1470-2045(08)70261-4
124. Heymach JV, Paz-Ares L, Braud FD et al. (2008) Randomized Phase II Study of

Vandetanib Alone or With Paclitaxel and Carboplatin as First-Line Treatment for Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 26 (33):5407-5415. doi:10.1200/jco.2008.17.3138
125. Crinò L, Cappuzzo F, Zatloukal P et al. (2008) Gefitinib Versus Vinorelbine in Chemotherapy-Naïve Elderly Patients With Advanced Non–Small-Cell Lung Cancer (INVITE): A Randomized, Phase II Study. Journal of Clinical Oncology 26 (26):4253-4260. doi:10.1200/jco.2007.15.0672
126. Gridelli C, Gallo C, Ceribelli A et al. (2007) Factorial phase III randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: the GEmcitabine-COxib in NSCLC (GECO) study. The Lancet Oncology 8 (6):500-512. doi:https://doi.org/10.1016/S1470-2045(07)70146-8
127. Gatzemeier U, Pluzanska A, Szczesna A et al. (2007) Phase III Study of Erlotinib in Combination With Cisplatin and Gemcitabine in Advanced Non–Small-Cell Lung Cancer: The Tarceva Lung Cancer Investigation Trial. Journal of Clinical Oncology 25 (12):1545-1552. doi:10.1200/jco.2005.05.1474
128. Sandler A, Gray R, Perry MC et al. (2006) Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. New England Journal of Medicine 355 (24):2542-2550. doi:10.1056/NEJMoa061884
129. Mok TSK, Wu Y-L, Kudaba I et al. (2019) Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet 393 (10183):1819-1830. doi:https://doi.org/10.1016/S0140-6736(18)32409-7
130. Herbst RS, Redman MW, Kim ES et al. (2018) Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. The Lancet Oncology 19 (1):101-114. doi:https://doi.org/10.1016/S1470-2045(17)30694-0
131. Thatcher N, Hirsch FR, Luft AV et al. (2015) Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. The Lancet Oncology 16 (7):763-774. doi:https://doi.org/10.1016/S1470-2045(15)00021-2
132. Paz-Ares L, Mezger J, Ciuleanu TE et al. (2015) Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. The

Lancet Oncology 16 (3):328-337. doi:https://doi.org/10.1016/S1470-2045(15)70046-X
133. von Pawel J, Spigel DR, Ervin T et al. (2018) Randomized Phase II Trial of Parsatuzumab (Anti-EGFL7) or Placebo in Combination with Carboplatin, Paclitaxel, and Bevacizumab for First-Line Nonsquamous Non-Small Cell Lung Cancer. The Oncologist 23 (6):654-e658. doi:10.1634/theoncologist.2017-0690
134. Gridelli C, Perrone F, Gallo C et al. (2003) Chemotherapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) Phase III Randomized Trial. JNCI: Journal of the National Cancer Institute 95 (5):362-372. doi:10.1093/jnci/95.5.362
135. Hellmann MD, Paz-Ares L, Bernabe Caro R et al. (2019) Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine 381 (21):2020-2031. doi:10.1056/NEJMoa1910231
136. Mok TS, Cheng Y, Zhou X et al. (2018) Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer and EGFR-Activating Mutations. Journal of Clinical Oncology 36 (22):2244-2250. doi:10.1200/jco.2018.78.7994
137. Dingemans AMC, Groen HJM, Herder GJM et al. (2015) A randomized phase II study comparing paclitaxel–carboplatin–bevacizumab with or without nitroglycerin patches in patients with stage IV nonsquamous nonsmall-cell lung cancer: NVALT12 (NCT01171170)†. Annals of Oncology 26 (11):2286-2293. doi:https://doi.org/10.1093/annonc/mdv370
138. Thomas M, Fischer J, Andreas S et al. (2015) Erlotinib and bevacizumab versus cisplatin, gemcitabine and bevacizumab in unselected nonsquamous nonsmall cell lung cancer. European Respiratory Journal 46 (1):219-229. doi:10.1183/09031936.00229014
139. Nakashima K, Horita N, Nagai K et al. (2016) Progression-Free Survival, Response Rate, and Disease Control Rate as Predictors of Overall Survival in Phase III Randomized Controlled Trials Evaluating the First-Line Chemotherapy for Advanced, Locally Advanced, and Recurrent Non–Small Cell Lung Carcinoma. Journal of Thoracic Oncology 11 (9):1574-1585. doi:https://doi.org/10.1016/j.jtho.2016.04.025
140. Hotta K, Suzuki E, Di Maio M et al. (2013) Progression-free survival and overall survival in phase III trials of molecular-targeted agents in advanced non-small-cell lung cancer. Lung Cancer 79 (1):20-26. doi:https://doi.org/10.1016/j.lungcan.2012.10.007
141. Ritchie G, Gasper H, Man J et al. (2018) Defining the Most Appropriate Primary End Point in Phase 2 Trials of Immune Checkpoint Inhibitors for Advanced Solid Cancers: A Systematic Review and Meta-analysis. JAMA Oncology 4 (4):522-528.

doi:10.1001/jamaoncol.2017.5236
142. Ito K, Miura S, Sakaguchi T et al. (2019) The impact of high PD-L1 expression on the surrogate endpoints and clinical outcomes of anti-PD-1/PD-L1 antibodies in non-small cell lung cancer. Lung Cancer 128:113-119. doi:https://doi.org/10.1016/j.lungcan.2018.12.023
143. Nie R-C, Chen F-P, Yuan S-Q et al. (2019) Evaluation of objective response, disease control and progression-free survival as surrogate end-points for overall survival in anti–programmed death-1 and anti–programmed death ligand 1 trials. European Journal of Cancer 106:1-11. doi:https://doi.org/10.1016/j.ejca.2018.10.011
144. Gyawali B, Hey SP, Kesselheim AS (2018) A Comparison of Response Patterns for Progression-Free Survival and Overall Survival Following Treatment for Cancer With PD-1 Inhibitors: A Meta-analysis of Correlation and Differences in Effect Sizes. JAMA Netw Open 1 (2):e180416. doi:10.1001/jamanetworkopen.2018.0416
145. Kaufman HL, Schwartz LH, William WN, Jr. et al. (2018) Evaluation of classical clinical endpoints as surrogates for overall survival in patients treated with immune checkpoint blockers: a systematic review and meta-analysis. J Cancer Res Clin Oncol 144 (11):2245-2261. doi:10.1007/s00432-018-2738-x
146. Morgensztern D, Ko A, O'Brien M et al. (2019) Association between depth of response and survival in patients with advanced-stage non–small cell lung cancer treated with first-line chemotherapy. Cancer 125 (14):2394-2399. doi:10.1002/cncr.32114
147. Kawachi H, Fujimoto D, Morimoto T et al. (2019) Early depth of tumor shrinkage and treatment outcomes in non-small cell lung cancer treated using Nivolumab. Investigational New Drugs 37 (6):1257-1265. doi:10.1007/s10637-019-00770-y
148. Lee CK, Lord S, Marschner I et al. (2018) The Value of Early Depth of Response in Predicting Long-Term Outcome in EGFR-Mutant Lung Cancer. Journal of Thoracic Oncology 13 (6):792-800. doi:https://doi.org/10.1016/j.jtho.2018.03.010
149. Takeda M, Okamoto I, Nakagawa K (2014) Survival Outcome Assessed According to Tumor Response and Shrinkage Pattern in Patients with EGFR Mutation–Positive Non–Small-Cell Lung Cancer Treated with Gefitinib or Erlotinib. Journal of Thoracic Oncology 9 (2):200-204. doi:https://doi.org/10.1097/JTO.0000000000000053

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8. Appendix

Table 7 Supplementary Table: Trials included in the analyses for Research 1

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR (Exp-Ctr)
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Aparicio et al. 2016 [25]	140	142	LV5FU2-IRI or FOLFIRI	LV5FU2 or Simplified LV5FU2	PFS	-0.9	0.96	2.1	0.84	20.6
Aparicio et al. 2016 [25]	141	141	LV5FU2 or LV5FU2-IRI	FOLFIRI or Simplified LV5FU2	PFS	3.8	0.71	0.5	0.85	11.5
Passardi et al. 2015 [26]	176	194	FOLFIRI or FOLFOX4 + Bevacizumab	FOLFIRI or FOLFOX4	PFS	-0.5	1.13	1.2	0.86	0.6
Brodowicz et al. 2013 [27]	75	77	FOLOFX4 + Cetuximab Q1W	FOLOFX4 + Cetuximab Q2W	ORR	2.8	0.86	0.3	0.92	-9.0
Labianca et al. 2011 [28]	147	146	Intermittent FOLFIRI	continuous FOLFIRI	OS	1	0.88	0	1.03	-8.0
Bokemeyer et al. 2011 [29]	169	168	FOLFOX-4 +Cetuximab	FOLFOX-4	ORR	0.3	1.015	0	0.931	10.0
Glimelius et al. 2008 [30]	281	286	FLIRI	Lv5FU2-IRI	PFS	0.4	1	0.4	1.1	-14.0
Punt et al. 2002 [31]	182	182	Trimetrexate + FULV	FULV	PFS	2.9	0.86	1.3	0.87	1.0
Blanke et al. 2002 [32]	191	191	Trimetrexate + FULV	FULV + placebo	PFS	-1	0.96	0.9	1	2.0
Kalofonos et al 2010 [33]	206	211	FOLFIRI followed by FOLFOX	FOLFIRI	ORR	-0.6	1	0.9	0.81	2.0
Souglakos et al. 2012	167	166	FOLFIRI +	CAPIRI + Bevacizumab	PFS	-1.8	1.08	1.1	0.99	5.7

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR (Exp-Ctr)
	Exp arm	Ctr arm	Exp arm	Ctr arm						
[34]			Bevacizumab							
Yamazaki et al. 2015 [35]	56	49	SOL	mFOLFOX6	PFS	4	0.91	2.7	0.83	0.3
Guan et al. 2011 [36]	139	64	mIFL + Bevacizumab	mIFL	PFS	5.3	0.62	4.1	0.44	18.1
Cao et al. 2011 [37]	60	60	FOLFOX-4 + Yiqi Zhuyu	FOLOFX-4 + placebo	NR	3	0.65	1	0.78	7.5
Tabernero et al. 2013 [38]	97	101	mFOLFOX6 + Sorafenib	mFOLFOX6 + Placebo	PFS	-0.5	1.13	0.4	0.88	-14.0
Douillard et al. 2014 [39]	150	150	FOLFOX4 + Cetuximab	UFOX + Cetuximab	PFS	1.6	0.98	1.6	0.68	13.8
Gravalos et al. 2012 [40]	92	91	Oxaliplatin + raltritrexed	FOLFOX-4	ORR	-1.5	0.975	-1	0.927	9.3
Ducreux et al. 2011 [41]	156	150	FOLFOX6	XELOX	ORR	-0.6	1.02	-0.5	1	-7.0
Comella et al. 2009 [42]	164	158	OXXEL	OXAFAFU	ORR	-1.1	1.01	0.1	1.12	1.0
Schwartzberg et al. 2014 [9]	142	143	mFOLFOX6 + Panitumumab	mFOLFOX6 + Bevacizumab	PFS	9.9	0.62	0.8	0.87	4.5
Hoff et al. 2012 [43]	502	358	FOLFIRI/CAPOX + cediranib	FOLFIRI/CAPOX + placebo	PFS/OS	0.8	0.94	0.3	0.84	0.9
Schmoll et al. 2012 [44]	709	713	mFOLFOX6 + Cediranib	mFOLFOX6 + Bevacizumab	PFS	1.4	0.95	-0.4	1.1	-1.0
Tveit et al. 2012 [45]	194	185	Nordic FLOX +	Nordic FLOX	PFS	-0.7	1.06	0.4	0.89	8.0

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR (Exp-Ctr)
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Douillard 2010 [46]	325	331	Cetuximab FOLFOX4 + Panitumumab	FOLFOX4	PFS	4.2	0.83	1.6	0.8	7.0
Tebbutt et al. 2010 [47]	158	156	Capecitabine + Bevacizumab + Mitomycin	Capecitabine	PFS	-2.5	0.942	2.7	0.59	15.6
Tebbutt et al. 2010 [47]	157	156	Capecitabine + Bevacizumab	Capecitabine	PFS	0	0.875	2.8	0.63	7.8
Saltz et al. 2008 [48]	699	701	FOLFOX-4 or XELOX + Bevacizumab	FOLFOX-4 or XELOX + placebo	PFS	1.4	0.89	1.4	0.83	0.0
Porschen et al. 2007 [49]	242	234	CAPOX	FUFOX	PFS	-2	1.12	-0.9	1.17	-6.0
Falcone et al. 2007 [50]	122	122	FOLFOXIRI	FOLFIRI	ORR	5.9	0.7	2.9	0.63	21.2
Kabbinavar et al. 2005 [51]	104	105	FULV + Bevacizumab	FULV + placebo	OS	3.7	0.79	3.7	0.5	10.8
Köhne et al. 2005 [52]	216	214	FOLFIRI	FULV	PFS	3.2	0.88	2.1	0.65	27.8
Schilsky et al. 2002 [53]	485	479	Eniluracil + FU	FULV	OS	-1.2	0.88	-0.45	0.832	-0.5
Seymour et al. 1996 [54]	128	132	FULV + IFNα	FULV	ORR	0	1.06	0.0	0.96	1.0
Venook et al. 2017 [55]	578	559	mFOLFOX6/FOLFIRI + Cetuximab	mFOLFOX6/FOLFIRI + Bevacizumab	OS	1	0.88	-0.1	0.95	4.4

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR (Exp-Ctr)
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Maughan et al. 2011 [56]	362	367	Oxaliplatin + Fluoropyrimidine + Cetuximab	Oxaliplatin + Fluoropyrimidine	OS	-0.9	1.04	0	0.96	7.0
Maughan et al. 2002 [57]	301	303	FULV (Lokich regimen)	FULV (de Gramont regimen)	OS	0.27	0.88	0	0.99	2.0
Maughan et al. 2002 [57]	301	303	Raltitrexed	FULV (de Gramont regimen)	OS	-0.93	0.99	-1	1.18	-5.0
Heinemann et al. 2014 [58]	297	295	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	ORR	3.7	0.77	-0.3	1.06	4.0
Loupakis et al. 2014 [59]	252	256	FOLFOXIRI + Bevacizumab	FOLFIRI + Bevacizumab	PFS	4	0.8	2.4	0.75	12.0
Douillard et al. 2013 [60]	259	253	Panitumumab + FOLFOX4	FOLFOX4	PFS	5.6	0.77	2.2	0.72	9.0
Tol et al. 2009 [61]	368	368	XELOX + Bevacizumab + Cetuximab	XELOX + Bevacizumab	PFS	-0.9	1.15	-1.3	1.22	2.7
Van Cutsem et al. 2009 [62]	599	599	FOLFIRI + Cetuximab	FOLFIRI	PFS	1.3	0.93	0.9	0.85	8.2
Hurwitz et al. 2004 [63]	402	411	FOLFIRI + Bevacizumab	FOLFIRI + Placebo	OS	4.7	0.66	4.4	0.54	10.0
Saltz et al. 2000 [64]	231	226	FOLFIRI	FULV	PFS	2.2	0.78	2.7	0.64	18.0

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR (Exp-Ctr)
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Ocvirk et al. 2010 [65]	77	74	FOLFOX6 + Cetuximab	FOLFIRI + Cetuximab	PFS rate at 9months	-1.5	0.98	0.3	1.06	-2.0
Cunningham et al. 2013 [66]	140	140	Capecitabine + Bevacizumab	Capecitabine	PFS	3.9	0.79	4	0.53	9.0
Goldberg et al. 2004 [67]	267	264	FOLFOX	FOLFIRI	TTP	4.5	0.66	1.8	0.74	14.0
Goldberg et al. 2004 [67]	264	264	IROX	FOLFIRI	TTP	2.4	0.81	-0.4	1.02	4.0
Yamazaki et al. 2016 [68]	197	198	FOLFIRI + Bevacizumab	mFOLFOX6 + Bevacizumab	PFS	1.3	0.99	1.4	0.905	2.0
García-Carbonero et al. 2017 [69]	63	64	mFOLFOX6 + Bevacizumab + Parsatuzumab	mFOLFOX6 + Bevacizumab + Placebo	PFS	-	0.97	0.1	1.17	-5.0
Pinter et al. 2017 [70]	423	424	FOLFOX/FOLFIRI + Bevacizumab + Pegfilgrastim	FOLFOX/FOLFIRI + Bevacizumab + Placebo	safety	0.9	0.94	0.2	0.91	3.4

Ctr, control; Exp, experimental; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Table 8 Supplementary Table: Trials included in the analyses for Research 2

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Socinski et al. 2018 [79]	400	400	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	Bevacizumab + Carboplatin + Paclitaxel	OS and PFS	4.50	0.78	1.50	0.62	15.5
Kubota et al. 2017 [80]	197	204	Carboplatin + Paclitaxel + Motesanib	Carboplatin + Paclitaxel + Placebo	PFS	1.20	1.01	0.50	0.81	18.5
Peters et al. 2017 [81]	152	151	Alectinib	Crizotinib	PFS	NR	0.76	15.30	0.50	7.4
Paz-Ares et al. 2017 [82]	160	159	Afatinib	Gefitinib	PFS	3.40	0.86	0.10	0.73	14.0
Spigel et al. 2017 [83]	110	57	Carboplatin + Paclitaxel + Necitumumab	Carboplatin + Paclitaxel	ORR	2.00	0.83	-0.20	1.00	8.9
Yang et al. 2017 [84]	128	128	Erlotinib	Gefitinib	PFS	2.80	0.84	2.60	0.81	4.0
Wakelee et al. 2017 [85]	69	70	Bevacizumab + Paclitaxel + Platinum + Onartuzumab	Bevacizumab + Paclitaxel + Platinum + Placebo	PFS	NR	1.34	-1.80	1.25	6.7
Wakelee et al. 2017 [85]	59	61	Pemetrexed + Platinum + Onartuzumab	Pemetrexed + Platinum + Placebo	PFS	-5.20	1.15	-0.20	1.23	-7.5
Ramalingam et al. 2017	105	53	Carboplatin + Paclitaxel + Veliparib	Carboplatin + Paclitaxel + Placebo	PFS	2.60	0.80	1.60	0.72	0.3

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
[86] Joerger et al. 2016 [87]	183	182	Platinum + Paclitaxel (PK guided)	Platinum + Paclitaxel (Fixed)	Safety	-0.60	1.06	-0.60	1.16	-4.0
Novello et al. 2017 [88]	85	81	Pemetrexed + Cisplatin + Cixutumumab	Pemetrexed + Cisplatin	PFS	0.95	0.93	0.23	1.15	7.3
Hirsch et al. 2017 [89]	55	54	Platinum + Paclitaxel + Onartuzumab	Platinum + Paclitaxel + Placebo	PFS	0.60	0.90	0.00	0.95	-3.4
Yang et al. 2016 [90]	118	118	Pemetrexed + Platinum followed by Gefitinib	Gefitinib	PFS	-1.00	0.94	-1.25	0.85	-6.0
Zhou et al. 2015 [91]	138	138	Carboplatin + Paclitaxel + Bevacizumab	Carboplatin + Paclitaxel + Placebo	PFS	6.60	0.68	2.70	0.40	28.0
Zinner et al. 2015 [92]	182	179	Pemetrexed + Carboplatin followed by Pemetrexed	Carboplatin + Paclitaxel + Bevacizumab followed by Bevacizumab	PFS	-1.20	1.07	-1.05	1.06	-4.3
Seto et al. 2014 [93]	77	77	Erlotinib + Bevacizumab	Erlotinib	PFS	-0.40	0.81	6.30	0.54	20.0
von Pawel et al. 2014 [94]	88	88	Docetaxel + Cisplatin / Paclitaxel + Carboplatin + Ombrabulin	Docetaxel + Cisplatin / Paclitaxel + Carboplatin	PFS	0.00	0.96	0.20	0.95	1.0
Belani et al. 2014 [95]	55	57	Pemetrexed + Cisplatin + Axitinib (continuous)	Pemetrexed + Cisplatin	PFS	1.10	1.05	0.90	0.89	19.2

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Belani et al. 2014 [95]	58	57	Pemetrexed + Cisplatin + Axitinib (modified)	Pemetrexed + Cisplatin	PFS	-1.20	1.45	0.80	1.02	13.4
Yu et al. 2014 [96]	58	59	Pemetrexed + Platinum + Gefitinib	Pemetrexed + Platinum	non progression rate	4.60	0.84	0.90	0.88	2.6
Twelves et al. 2014 [97]	58	60	Carboplatin + Paclitaxel + Axitinib	Carboplatin + Paclitaxel + Bevacizumab	PFS	-2.70	1.12	-0.40	1.09	-14.0
Patel et al. 2013 [98]	472	467	Pemetrexed + Carboplatin + Bevacizumab followed by Pemetrexed + Bevacizumab	Paclitaxel + Carboplatin + Bevacizumab followed by Bevacizumab	OS	-0.80	1.00	0.40	0.83	1.1
Wu et al. 2013 [99]	226	225	Gemcitabine + Platinum + Erlotinib	Gemcitabine + Platinum + Placebo	PFS	3.10	0.79	1.60	0.57	24.7
Bonomi et al. 2013 [100]	60	61	Carboplatin + Paclitaxel (~6cycle) + Bevacizumab + Cetuzimab (~6cycle)	Carboplatin + Paclitaxel (~3cycle) + Bevacizumab + Cetuzimab (~6cycle)	PFS	0.43	0.94	1.55	0.69	7.4
Paz-Ares et al. 2013 [101]	57	59	Carboplatin + Paclitaxel + Conatumumab (3mg)	Carboplatin + Paclitaxel + Placebo	PFS	4.50	0.80	-0.10	0.84	2.0
Paz-Ares et al. 2013 [101]	56	59	Carboplatin + Paclitaxel + Conatumumab (15mg)	Carboplatin + Paclitaxel + Placebo	PFS	3.60	0.84	-0.70	0.93	2.0
Lee et al. 2013 [102]	134	136	Cisplatin + Paclitaxel-loaded polymeric micelle	Cisplatin + Paclitaxel	ORR	1.10	0.94	-0.10	0.97	1.7

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Paz-Ares et al. 2012 [103]	452	452	Gemcitabine + Cisplatin + Sorafenib	Gemcitabine + Cisplatin + Placebo	OS	-0.10	0.98	0.50	0.83	2.0
Scagliotti et al. 2012 [104]	541	549	Carboplatin + Paclitaxel + Motesanib	Carboplatin + Paclitaxel + Placebo	OS	2.00	0.90	0.20	0.79	14.0
Lynch et al. 2012 [105]	70	66	Carboplatin + Paclitaxel + Ipilimumab (concurrent)	Carboplatin + Paclitaxel + Placebo	irPFS	1.41	0.99	-0.10	0.88	7.0
Lynch et al. 2012 [105]	68	66	Carboplatin + Paclitaxel + Ipilimumab (phased)	Carboplatin + Paclitaxel + Placebo	irPFS	3.94	0.87	0.92	0.69	18.0
Socinski et al. 2012 [106]	521	531	Nab-paclitaxel + Carboplatin	Sb-paclitaxel + Carboplatin	ORR	0.90	0.92	0.50	0.90	8.0
Niho et al. 2012 [107]	121	59	Carboplatin + Paclitaxel + Bevacizumab	Carboplatin + Paclitaxel	PFS	-0.60	0.99	1.00	0.61	29.7
Groen et al. 2011 [108]	281	280	Carboplatin + Docetaxel + Celecoxib	Carboplatin + Docetaxel + Placebo	OS	0.00	0.90	0.50	0.80	8.0
Jr, P et al 2011 [109]	649	650	Carboplatin + Paclitaxel + Vadimezan	Carboplatin + Paclitaxel + Placebo	OS	0.70	1.01	0.00	1.04	0.1
Hirsh et al. 2011 [110]	408	420	Paclitaxel + Carboplatin + PF-3512676	Paclitaxel + Carboplatin	OS	0.20	0.95	0.10	1.02	5.0
Koch et al.	159	160	Platinum + Gemcitabine/Vinorelbine	Platinum + Gemcitabine/Vinorelbine +	OS	1.00	1.00	-0.40	1.01	5.0

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
2011 [111]			+ Celecoxib	Placebo						
Digumarti et al. 2011 [112]	55	55	Carboplatin + Paclitaxel + Talactoferrin	Carboplatin + Paclitaxel + Placebo	ORR	1.90	0.87	2.80	0.85	15.0
Manegold et al. 2012 [113]	416	423	Gemcitabine + Cisplatin + PF-3512676	Gemcitabin + Cisplatin	OS	0.30	1.00	0.00	1.00	1.2
Blumenschein Jr et al. 2011 [114]	61	63	Carboplatin + Paclitaxel + Motesanib (125mg QD)	Carboplatin + Paclitaxel + Bevacizumab	ORR	0.00	1.05	-0.60	1.14	-7.0
Blumenschein Jr et al. 2011 [114]	62	63	Carboplatin + Paclitaxel + Motesanib (75mg BID)	Carboplatin + Paclitaxel + Bevacizumab	ORR	-2.00	1.18	-2.50	1.22	-14.0
Scagliotti et al. 2010 [115]	464	462	Carboplatin + Paclitaxel + Sorafenib	Carboplatin + Paclitaxel	OS	0.10	1.15	-0.80	0.99	3.0
Reck et al. 2010 [116]	345	347	Cisplatin + Gemcitabine + Bevacizumab (7.5mg/kg)	Cisplatin + Gemcitabine + Placebo	PFS	0.50	0.93	0.60	0.75	16.2
Reck et al. 2010 [116]	351	347	Cisplatin + Gemcitabine + Bevacizumab (15mg/kg)	Cisplatin + Gemcitabine + Placebo	PFS	0.30	1.03	0.40	0.85	13.0
Lynch et al. 2010 [117]	338	338	Taxane + Carboplatin + Cetuximab	Taxane + Carboplatin	PFS	1.31	0.89	0.16	0.90	8.5

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Takeda et al. 2010 [118]	300	298	Platinum doublet followed by Gefitinib	Platinum doublet	OS	0.80	0.86	0.30	0.68	4.9
Lee et al. 2009 [119]	372	350	Gemcitabine + Carboplatin + Thalidomide	Gemcitabine + Carboplatin + Placebo	OS	-0.40	1.13	-0.70	1.10	-2.0
Zwitter et al. 2009 [120]	124	125	Gemcitabine (prolonged) + Cisplatin	Gemcitabine (brief) + Cisplatin	OS and PFS	-0.10	0.98	0.50	0.85	14.0
Comella et al. 2010 [121]	51	54	Gemcitabine + Pemetrexed	Gemcitabine + Paclitaxel	ORR and safety	-2.80	1.39	-3.20	1.48	-12.0
Goss et al. 2009 [122]	100	101	Gefitinib	Placebo	PFS	0.90	0.82	0.07	0.84	5.0
Kubota et al. 2008 [123]	196	197	Vinorelbine + Gefitinib followed by Docetaxel	Vinorelbine + Gefitinib followed by Carboplatin + Paclitaxel	OS	-0.50	0.97	-0.30	0.97	-12.1
Heymach et al. 2008 [124]	56	52	Carboplatin + Paclitaxel + Vandetainib	Carboplatin + Paclitaxel + Placebo	PFS	-2.40	1.15	0.25	0.76	7.0
Crinò et al. 2008 [125]	97	99	Gefitinib	Vinorelbine	PFS	-2.10	0.98	-0.20	1.19	-2.0
Gridelli et al. 2007 [126]	126	125	Cisplatin + Gemcitabine (prolonged-constant infusion)	Cisplatin + Gemcitabine (standard)	OS	0.75	0.93	0.25	0.97	-5.0
Gatzemeier et	586	586	Gemcitabine + Cisplatin + Erlotinib	Gemcitabine + Cisplatin + Placebo	OS	-0.28	1.06	-0.23	0.98	1.6

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
al. 2007 [127]										
Sandler et al. 2006 [128]	434	444	Carboplatin + Paclitaxel + Bevacizumab	Carboplatin + Paclitaxel	OS	2.00	0.79	1.70	0.66	20.0
Mok et al. 2019 [129]	637	637	Pembrolizumab	Platinum-based chemotherapy	OS	4.60	0.81	-1.10	1.07	0.0
Herbst et al. 2018 [130]	656	657	Cetuximab + Carboplatin + Paclitaxel +/- Bevacizumab	Carboplatin + Paclitaxel +/- Bevacizumab	OS and PFS	1.70	0.93	0.10	0.99	6.0
Thatcher et al. 2015 [131]	545	548	Necitumumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin	OS	1.60	0.84	0.20	0.85	2.0
Paz-Ares et al. 2015 [132]	315	318	Necitumumab + Pemetrexed + Cisplatin	Pemetrexed + Cisplatin	OS	-0.20	1.01	0.00	0.96	-1.0
von Pawel et al. 2018 [133]	52	52	Carboplatin + Paclitaxel + Bevacizumab + Parsatuzumab	Carboplatin + Paclitaxel + Bevacizumab + Placebo	PFS	0.00	1.23	-1.40	1.70	-27.0
Gridelli et al. 2003 [134]	232	233	Vinorelbine + Gefitinib	Vinorelbine	OS	-1.50	1.17	0.25	0.95	3.0
Gridelli et al. 2003 [134]	232	233	Vinorelbine + Gefitinib	Gefitinib	OS	0.50	1.06	0.50	0.95	5.0
Hellmann et al. 2019 [135]	396	397	Nivolumab + Ipilimumab	Platinum-based chemotherapy	OS and PFS	2.20	0.79	-0.50	0.82	5.9

Trial	No. of patients		Treatments		Primary endpoint	Delta OS (month)	OS HR	Delta PFS (month)	PFS HR	Delta ORR
	Exp arm	Ctr arm	Exp arm	Ctr arm						
Hellmann et al. 2019 [135]	187	186	Nivolumab + Ipilimumab	Platinum-based chemotherapy	OS and PFS	5.00	0.62	0.40	0.75	4.2
Mok et al. 2018 [136]	227	225	Dacomitinib	Gefitinib	PFS	7.30	0.76	5.50	0.59	3.3
Dingemans et al. 2015 [137]	111	112	Paclitaxel + Carboplatin + Bevacizumab + Nitroglycerin	Paclitaxel + Carboplatin + Bevacizumab	PFS	-2.20	1.02	-1.70	1.27	16.0
Thomas et al. 2015 [138]	111	113	Erlotinib + Bevacizumab	Cisplatin + Gemcitabine + Bevacizumab	PFS	-5.10	1.41	-3.40	1.85	-24.0

Ctr, control; Exp, experimental; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression free survival