International Journal of Clinical Oncology (2019) 24:1406–1411
https://doi.org/10.1007/s10147-019-01504-z

ORIGINAL ARTICLE

Analysis of response-related endpoints in trials of first-line medical treatment of metastatic colorectal cancer

Giuseppe A. Colloca[1] · **Antonella Venturino**[1] · **Domenico Guarneri**[1]

Received: 20 May 2019 / Accepted: 30 June 2019 / Published online: 9 July 2019

Abstract

Background Tumor radiologic response after systemic chemotherapy has been used as endpoint of trials of patients with metastatic colorectal cancer (mCRC), which can report the best overall response rate (ORR) and the disease control rate (DCR) by RECIST criteria as well as the early tumor shrinkage (ETS). The present study perform a trial-level analysis to verify whether such response-related endpoints are predictive of overall survival (OS).

Methods After a systematic search, randomized clinical trials (RCTs) were selected each time they evaluated the three response endpoints and progression-free survival (PFS). Two arms per trial were selected, and the correlation between the difference in each endpoint and the difference in OS was calculated. The analysis then evaluated the effects of treatment on ΔORR, or ΔDCR, ΔETS, ΔPFS, and on ΔOS, using separate linear regressions for each of them, and the proportion of variability explained (R^2_{trial}) on OS for each of the four endpoints was calculated.

Results The systematic review of the literature led to the selection of 12 RCTs, 7 phase-3 and 5 phase-2. ETS reported a different performance in the entire sample compared to phase-3 trials ($R^2_{\text{trial}}=0.172$ vs. 0.842), differently from DCR ($R^2_{\text{trial}}=0.541$ vs. 0.816) and ORR ($R^2_{\text{trial}}=0.349$ vs. 0.740). Surprisingly, PFS predicted OS with a weak correlation, which was not significant in the subgroup of phase-3 studies ($R^2_{\text{trial}}=0.455$ vs. 0.466).

Conclusion The results of the present trial-level analysis report a good performance of two response-related endpoints, DCR and ETS, and suggest that they could be differently used depending on the setting of disease and the type of medical treatment.

Keywords Overall response rate · Disease control rate · Early tumor shrinkage · Prognosis · Overall survival

Introduction

In European Union, colorectal cancer (CRC) is the second and the third most common cause of cancer-specific mortality in men and women, respectively, and a major cause of cancer-specific mortality [1], with a 5-year overall survival (OS) of 10% for patients with a metastatic colorectal cancer (mCRC) [2].

Median OS of patients with mCRC has greatly improved from 6 to over 30 months, thanks to the introduction of new drugs. As a rule, tumor response continues to be evaluated by imaging, and the change of tumor size after chemotherapy has been the most used criterion for evaluating the activity of chemotherapy in solid tumors, leading to the definition of standardized criteria such as the response evaluation criteria in solid tumors (RECIST) [3, 4]. Targeted therapies, alone or in combination with cytotoxic chemotherapy, have prolonged the OS, but also the survival after the first progression (post-progression survival), negatively modifying the strong relationship between progression-free survival and OS. As a result, response-related endpoints, such as best overall response rate (ORR) and disease control rate (DCR), are increasing their reliability in clinical trials of mCRC [5]. Biologic drugs and technological improvements have also allowed the development of new methods to redefine the tumor regression after the medical therapy, with the definition of morphological, functional, or metabolic criteria, which have proved to be effective in some groups of patients or after some treatments [6, 7]. Among these, the early tumor shrinkage (ETS) was particularly successful, although it was only studied retrospectively: it appears as a refinement of the concept of ORR and is characterized by

✉ Giuseppe A. Colloca
g.colloca@katamail.com

[1] Department of Oncology, Ospedale Civile di Sanremo, Via G. Borea n. 56, 18038 Sanremo, Imperia, Italy

a uni-dimensional reduction of at least 20% of the baseline tumor size after 8 weeks of medical treatment [8].

The aim of the current paper is to perform a trial-level analysis to verify whether ORR, DCR, ETS, and PFS, after a first-line medical treatment, are effective predictors of OS in patients with mCRC.

Methods

A literature search of randomized trials of first-line medical treatment in patients with mCRC was undertaken in February 2018, as it has been reported elsewhere [9]. The definition of the four endpoints is reported in Table 1.

After a systematic search of studies reporting ORR, DCR, ETS, and PFS, randomized trials (RCTs) were selected each time they evaluated these endpoints in relation to overall survival (OS). Two arms per trial were selected, and the differences in the results of these two arms (Δ, delta) were calculated for every endpoint. The nonparametric Spearman ρ (r) was used as a measure of the correlation between the difference in each endpoint and the difference in OS. The analysis then evaluated the effects of treatment on ΔORR, or ΔDCR, ΔETS, and ΔPFS on ΔOS, using separate linear regressions for each of them, and the proportions of variability explained (R^2_{trial}) on OS for the four endpoints have been calculated. An exploratory analysis of treatment arms by type of regimen (chemotherapy plus EGFR-inhibitor vs. chemotherapy plus antiangiogenetics) has been done to test any difference Sin the effects of the four variables on OS by drug regimen.

Results

The search results and the review process have been reported in a previous article [9]. The final analysis included 18 selected articles and 4 abstracts, for a total of 22 reports about the results of 12 RCTs [10–31].

The systematic review of the literature led to the selection of 12 RCTs, 7 phase-3 and 5 phase-2. Characteristics and results of the selected trials are listed in Table 2. For only 3117/4327 patients (72%), the ETS was available.

Table 3 summarizes the results of both the planned analyses.

In all 12 studies, the correlation coefficient of the 4 endpoints, each with OS, was significant for all of them except for ETS, which however was only evaluated in 10/12 trials. Instead, in the subgroup of the seven phase-3 studies only DCR maintained a positive correlation with OS (Spearman rho = 0.821; p value = 0.023).

Linear regressions have documented that ETS reported a very different performance in the entire sample compared to the phase-3 trials ($R^2_{\text{trial}} = 0.172$ vs. 0.842), in contrast to ORR ($R^2_{\text{trial}} = -0.349$ vs. 0.740). Even after this statistical test, DCR was most closely associated with OS ($R^2_{\text{trial}} = 0.541$ vs. 0.816) of the response-related endpoints, whereas PFS predicted OS significantly but with a lower effect and failing in the subgroup of phase-3 trials ($R^2_{\text{trial}} = 0.455$ vs. 0.466).

Discussion

The current trial-level analysis has confirmed that ETS and DCR could be good early predictor of survival, performing better than PFS and ORR. Among RECIST variables, DCR appears as the most reliable intermediate end point of OS after first-line medical therapy. The results are

Table 1 Definition of the response-related variables and of progression-free survival

Variables
Overall response rate (ORR)
Proportion of patients with at least a 30% decrease in the sum of diameters of target lesions at any time point after the beginning of the treatment, taking as reference the baseline sum diameters
Disease control rate (DCR)
Proportion of patients with neither sufficient shrinkage to qualify for response nor at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, or the appearance of new lesions
Early tumor shrinkage rate (ETS)
Proportion of patients with at least a 20% decrease in the sum of diameters of target lesions after a time point of 8 weeks from the beginning of the treatment, taking as reference the baseline sum diameters
Progression-free survival (PFS)
Time (months) from the beginning of the treatment to progression or death

DCR disease control rate, *ETS* early tumor shrinkage, *ORR* overall response rate, *PFS* progression-free survival

Table 2 Results of trials and patients' characteristics

Trial [ref]	Trial arms	No. pts	ORR (%)	ETS (%)	DCR (%)	PFS (m)	OS (m)
Phase III							
CRYSTAL	FOLFIRI + C	316	57.3	61.5	88.9	9.9	23.5
[10, 11]	FOLFIRI	350	39.7	50.6	86.0	8.4	20.0
PRIME	FOLFOX + P	325	57	71.9	86	10.0	23.9
[12, 13]	FOLFOX	331	48	57.0	84	8.6	19.7
FIRE 1	mIROX	241	41	53.2	68	8.2	19
[14, 15]	FUFIRI	238	41		81	7.2	22
Chinese	CHT + C	70	57.1	66.2	78.0	10.2	30.9
[16, 17]	CHT	68	29.4	73.4	63.2	5.8	21.0
FIRE 3	FOLFIRI + C	297	62.0	68.2	80.0	10.0	28.7
[18, 19]	FOLFIRI + B	295	58.0	49.1	87.0	10.3	25.0
TRIBE	FOLFOXIRI + B	256	65.1	57.8	89.7	12.1	31.0
[20, 21]	FOLFIRI + B	252	53.1		85.1	9.7	25.8
WJOG4407G	FOLFIRI + B	197	64	63.1	92	12.1	31.4
[22, 23]	FOLFOX + B	198	62	57.1	92	10.7	30.1
Phase II							
OPUS	FOLFIRI + C	61	61	53.8	92	7.7	22.8
[10, 24]	FOLFIRI	73	37	45.5	78	7.2	18.5
AIO KRK 0104	CAPIRI + C	89	46.1	59.2	74.2	6.2	21.1
[25, 26]	CAPOX + C	88	47.7		77.2	7.1	23.5
ACCORD 13	XELIRI + B	72	62	60.8	83	9	23
[27, 28]	FOLFIRI + B	73	63		86	9	23
PEAK	FOLFOX + P	142	57.8	75.0	89.8	10.9	34.2
[29, 30]	FOLFOX + B	143	53.5	62.2	85.5	10.1	24.3
PLANET TTD	FOLFOX + P	38	74	76.9	NR	13	37
[31]	FOLFIRI + P	39	67	77.2	NR	14	41

B bevacizumab, *C* cetuximab, *CHT* cytotoxic chemotherapy, *DCR* disease control rate, *ETS* early tumor shrinkage rate, *FUFIRI* 5-fluorouracil, leucovorin and irinotecan, *mIROX* modified irinotecan plus oxaliplatin, *NR* not reported, *ORR* overall response rate, *OS* overall survival, *P* panitumumab, *PFS* progression-free survival

Table 3 Correlation coefficients and logistic regressions between endpoints and OS in all trials (A) and in phase III trials (B)

	No. trials	Spearman rho	*p* value	R^2_{trial}	*p* value
A. All trials (12)					
Response-related end point					
ORR	12	0.585	0.046	0.349	0.043
ETS	10	0.456	0.185	0.170	0.237
DCR	11	0.840	0.001	0.541	0.010
Time-to-event end point					
PFS	12	0.586	0.045	0.455	0.016
B. Phase III trials (7)					
Response-related end point					
ORR	7	0.643	0.119	0.740	0.013
ETS	7	0.750	0.052	0.842	0.004
DCR	7	0.821	0.023	0.816	0.005
Time-to-event end point					
PFS	7	0.667	0.102	0.466	0.091

DCR disease control rate, *ETS* early tumor shrinkage, *m* months, *ORR* overall response rate, *PFS* progression-free survival

limited to few studies, but confirm the weak effect of PFS on OS, and support some change in the current definition of the RECIST criteria of response, by including at least the dimension of the timing. The lower number of studies and patients evaluated could explain the low correlation coefficient of ETS with OS and, given the retrospective evaluation of ETS, a selection bias cannot be excluded. However, when we assess phase-3 trials only, ETS is the best predictor of OS ($R^2_{trial} = 0.842$; p value = 0.004), while PFS is not ($R^2_{trial} = 0.466$; p value = 0.091). The optimal cutoff for ETS varies with the disease, but it was recently confirmed for mCRC at the value of at least 20% reduction after 8 weeks [8], definitely shorter than the median of 14 weeks needed to assign ORR.

From the analysis of phase-3 trials, DCR showed to be a very interesting intermediate endpoint too ($R^2_{trial} = 0.816$; p value = 0.005). Although it also has the advantage of an earlier determination compared to ORR, on the other hand, however, the effectiveness of first-line treatments suggests that DCR will approach soon 100%, becoming useful only after late chemotherapy lines. Even though the discussion can be still limited to the mCRC sub-population with a

deficit of mismatch repair system, DCR could be an ideal endpoint after immunotherapy, probably resetting the timing after 14–15 weeks, as suggested by the immuno-related response criteria [32].

ORR is not considered a reliable intermediate endpoint [33] and appears to be the least effective of the response-related variables. This limited predictive power on OS has been attributed to the possible too high cutoff [34], but probably ORR does not capture many elements of the phenomenon. In particular, among patients with an RAS wild-type mCRC, while in those with unresectable disease ORR correlates with conversion rate and R0 resection [35], in those ones with a resectable disease a higher response rate from the addition of cetuximab to chemotherapy did not correlate with the prognosis [36], and the same advantage in OS detected for chemotherapy plus anti-EGFR vs chemotherapy plus bevacizumab did not show a corresponding increase of ORR [10].

What differentiates ETS from ORR is certainly the timing of evaluation (6–8 vs. 14 weeks). And it seems by now established that is relevant for prognosis, regardless of the type of drug, as it works in other tumors [37–39], where ORR does not correlate with OS [40].

The kinetics of the response detected by ETS is by itself a prognostic factor, given that ETS after the first-line chemotherapy correlates effectively with the outcome after the second-line [41]. However, ETS probably does not include all the information that characterizes the kinetics of the tumor response, as it is suggested by the prognostic role of the deep of response [42, 43], the role of two-dimensionality [44], the pattern of concentric shrinkage [45], and the same morphological response [46].

Although ETS among patients with an RAS wild-type mCRC was studied with anti-EGFR-based regimens and it is a prognostic factor after chemotherapy plus anti-EGFR [47], ETS predicts the prognosis even after chemotherapy plus antiangiogenics [48], so much to suggest that the prognostic effect is more related to the efficacy of the combination than to the mechanism of action of the single biological drug [9], similar to what was suggested for the complete responses [49]. Moreover, from the current available data for mCRC, it is not known if ETS has a different meaning for some subgroups, such as patients with a BRAF-mutated mCRC, or with a liver limited disease, or with a right-sided tumor, and few data have been published about patients with RAS-mutated mCRC.

The results of the relationships between the four variables and OS in the subgroups of trial arms receiving chemotherapy plus anti-EGFR antibody or chemotherapy plus bevacizumab should be considered cautiously due to the low number of the arms and to the lack of any effect of PFS on OS within the subgroup of the five trial arms receiving chemotherapy only ($R^2_{\text{trial}} = 0.034$). This result could be the effect of a sequential administration of biologic drugs, with a consequent prolongation of the post-progression survival.

The most important limitation of the present analysis, beyond the trial-level type, is in the retrospective and partial data regarding ETS, which was available in 72% only of the patients enrolled in the selected studies. This exposes to possible inhomogeneities of the study arms, but should not interfere with the analysis of the individual arms per treatment group that was performed.

Up to date, we believe that the absence of prospective data does not allow conclusions on the possible surrogacy of ETS after a first-line medical treatment for patients with a RAS wild-type mCRC, while DCR should be compared with PFS and implemented in studies of subsequent lines. On the other hand an ideal condition of surrogate endpoint is rare in medicine and, therefore both, ETS and DCR, could be much better than the available alternatives for the evaluation of the first-line treatments, as well as being applicable to most patients and treatments.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent For this type of study, formal consent is not required.

References

1. Malvezzi M, Carioli G, Bertuccio P et al (2018) European cancer mortality predictions for the year 2018 with focus on colorectal cancer. Ann Oncol 29:1016–1022
2. Siegel R, Ma J, Zou Z et al (2014) Cancer statistics, 2014. CA Cancer J Clin 64:9–29
3. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
4. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
5. Colloca G, Venturino A, Guarneri D (2016) Analysis of clinical end points of randomised trials including bevacizumab and chemotherapy versus chemotherapy as first-line treatment of metastatic colorectal cancer. Clin Oncol 28(10):e155–e164
6. Choi H, Charnsangavej C, Faria SC et al (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal

of new computed tomography response criteria. J Clin Oncol 25(13):1753–1759
7. Chun YS, Vauthey JN, Boonsirikamchai P et al (2009) Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. J Am Med Assoc 302(21):2338–2344
8. Sakamaki K, Kito Y, Yamazaki K et al (2017) Exploration of time points and cut-off values for early tumor shrinkage to predict survival outcomes of patients with metastatic colorectal cancer treated with first-line chemotherapy using a biexponential model for change in tumour size. ESMO Open 2:e000275
9. Colloca GA, Venturino A, Guarneri D (2019) Early tumor shrinkage after first-line medical treatment of colorectal cancer: a meta-analysis. Int J Clin Oncol 24:231–240
10. 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. J Clin Oncol 31:3764–3775
11. Van Cutsem E, Kohne C-H, Lang I et al (2011) Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 29:2011–2019
12. Douillard JY, Siena S, Cassidy J et al (2014) Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25:1346–1355
13. Douillard JY, 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. Eur J Cancer 51:1231–1242
14. Fischer von Weikersthal L, Schalhorn A, Stauch M et al (2011) Phase III trial of irinotecan plus infusional 5-fluorouracil/folinic acid versus irinotecan plus oxaliplatin as first-line treatment of advanced colorectal cancer. Eur J Cancer 47:206–214
15. Giessen C, Laubender RP, Fischer von Weikersthal L et al (2013) Early tumor shrinkage in metastatic colorectal cancer: retrospective analysis from an irinotecan-based randomized first-line trial. Cancer Sci 104:718–724
16. Ye LC, Liu TS, Ren L et al (2013) Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 31:1931–1938
17. Ye LC, Wei Y, Zhu DX et al (2015) Impact of early tumor shrinkage on clinical outcome in wild-type KRAS colorectal liver metastases treated with cetuximab. J Gastroenterol Hepatol 30:674–679
18. Heinemann V, Fischer von Weikersthal L, 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. Lancet Oncol 15:1065–1075
19. Stintzing S, Modest DP, von Fischer Weikersthal L et al (2014) Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. Ann Oncol 25(suppl 5):LBA11
20. Loupakis F, Cremolini C, Masi G et al (2014) Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 371:1609–1618
21. Cremolini C, Loupakis F, Lonardi S et al (2014) Early tumor shrinkage (ETS) and deepness of response (DoR) to predict progression-free, postprogression, and overall survival: results from the phase III TRIBE trial. J Clin Oncol 32(suppl 3):521
22. 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). Ann Oncol 27:1539–1546
23. Nagase M, Yamazaki K, Tamagawa H et al (2015) The impact of early tumor shrinkage on survival in WJOG4407G trial, a randomized phase III trial of mFOLFOX6 plus bevacizumab versus FOLFIRI plus bevacizumab in first-line treatment for metastatic colorectal cancer. J Clin Oncol 33(suppl 3):679
24. Bokemeyer C, Bondarenko I, Makhson A et al (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27:663–671
25. Moosmann N, Fischer von Weikersthal L, Vehling-Kaiser U et al (2011) Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104—a randomized trial of the German AIO CRC study group. J Clin Oncol 29:1050–1058
26. Modest DP, Laubender RP, Stintzing S et al (2013) Early tumor shrinkage in patients with metastatic colorectal cancer receiving first-line treatment with cetuximab combined with either CAPIRI or CAPOX: an analysis of the German AIO KRK 0104 trial. Acta Oncol 52:956–962
27. Ducreux M, Adenis A, Pignon J-P et al (2013) Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomized phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). Eur J Cancer 49:1236–1245
28. Ichante J, Adenis A, Malka D et al (2011) Impact of early tumor shrinkage on long-term outcome in metastatic colorectal cancer (mCRC) treated with 5FU plus irinotecan plus leucovorin (FOLFIRI) or capecitabine plus irinotecan XELIRI plus bevacizumab. J Clin Oncol 29(suppl):e14041
29. Schwartzberg LS, Rivera F, Karthaus M et al (2014) PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorinm and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 32:2240–2247
30. Rivera F, Karthaus M, Hecht JR et al (2017) Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. Int J Colorectal Dis 32:1179–1190
31. Carrato A, Abad A, Massuti B et al (2017) First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: a randomised, phase II trial (PLANET-TTD). Eur J Cancer 81:191–202
32. Wolchock JD, Hoos A, O'Day S et al (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15:7412–7420
33. Ciani O, Buyse M, Garside R et al (2015) Meta-analyses of randomized controlled trials show suboptimal validity of surrogate outcomes for overall survival in advanced colorectal cancer. J Clin Epidemiol 68(7):833–842
34. Lamarca A, Barriuso J, Kulke M et al (2018) Determination of an optimal response cut-off able to predict progression-free survival in patients with well-differentiated advanced pancreatic neuroendocrine tumours treated with sunitinib: an alternative to the current RECIST-defined response. Br J Cancer 118:181–188
35. Okuno M, Hatano E, Nishino H et al (2017) Does response rate of chemotherapy with molecular target agents correlate with the conversion rate and survival in patients with unresectable colorectal liver metastases? A systematic review. Eur J Surg Oncol 43(6):1003–1012
36. Primrose J, Falk S, Finch-Jones M et al (2014) Systemic chemotherapy with or without cetuximab in patients with resectable

colorectal liver metastasis: the new EPOC randomised controlled trial. Lancet Oncol 15(6):601–611
37. Masaki C, Sugino K, Saito N et al (2017) Lenvatinib induces early tumor shrinkage in patients with advanced thyroid carcinoma. Endocrine J 64(8):819–826
38. Kim ST, Jang K-T, Lee SJ et al (2015) Tumor shrinkage at 6 weeks predicts favorable clinical outcomes in a phase III study of gemcitabine and oxaliplatin with or without erlotinib for advanced biliary tract cancer. BMC Cancer 15:530
39. Krajewski KM, Guo M, Van den Abbeele AD et al (2011) Comparison of four early posttherapy imaging changes (EPTIC; RECIST 1.0; tumor shrinkage, computed tomography tumor density, Choi criteria) in assessing outcome to vasculare endothelial growth factor-targeted therapy in patients with advanced renal cell carcinoma. Eur Urol 59:562–586
40. Krajewski KM, Franketti Y, Nishino M et al (2014) 10% tumor diameter shrinkage on the first follow-up computed tomography predicts clinical outcome in patients with advanced renal cell carcinoma treated with angiogenesis inhibitors: a follow-up validation study. Oncologist 19:507–514
41. Modest DP, Stintzing S, Fischer von Weikersthal L et al (2017) Relation of early tumor shrinkage (ETS) observed in first-line treatment to efficacy parameters of subsequent treatment in FIRE-3 (AIOKRK0306). Int J Cancer 140(8):1918–1925
42. Taieb J, Rivera F, Siena S et al (2018) Exploratory analyses assessing the impact of early tumour shrinkage and depth of response on survival outcomes in patients with RAS wild-type metastatica colorectal cancer receiving treatment in three randomised panitumumab trials. J Cancer Res Clin Oncol 144(2):321–335
43. 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). Eur J Cancer 51:1927–1936
44. Nakayama G, Gujii T, Murotani K et al (2016) Modified two-dimensional response as surrogate marker of overall survival in patients with metastatic colorectal cancer. Cancer Sci 107:1492–1498
45. Fukada I, Araki K, Kobayashi K et al (2018) Pattern of tumor shrinkage during neoadjuvant chemotherapy is associated with prognosis in low-grade luminal early brast cancer. Radiology 286(1):49–57
46. Shindoh J, Loyer EM, Kopetz S et al (2012) Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol 30:4566–4572
47. Heinemann V, Rivera F, O'Neil BH et al (2016) A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with RAS wild-type metastatic colorectal cancer. Eur J Cancer 67:11–20
48. Ito M, Kusaba H, Mukaide S et al (2017) Early tumor shrinkage indicates a favorable response to bevacizumab-based first-line chemotherapy for metastatic colorectal cancer. Anticancer Drugs 28(10):1166–1173
49. Qi W-X, Shen Z, Tang L-N et al (2014) Does the addition of targeted biological agents to first-line chemotherapy for advanced colorectal cancer increase complete response? A systematic review and meta-analysis. Colorectal Dis 16:O300–O307