
Article:
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Table 1. Summary of the characteristics of included meta-analyses, N=31

	Frequency (%)
Type of meta-analysis	
Aggregate data	18 (58)
IPD	13 (42)
Number of trials, Median (IQR)	28 (9 - 51)
Aggregate data	39 (31 - 67)
IPD	4 (4 - 10)
Number of patients, Median (IQR)	*4138 (1167 - 15262)*
Aggregate data	15850 (10714 - 23492)
IPD	1158 (642 - 1280)
Advanced tumour types	
Colorectal cancer	12 (39)
Ovarian cancer	7 (23)
Breast cancer	8 (26)
Lung cancer	9 (29)
Renal cell carcinoma	3 (10)
Prostate cancer	2 (6)
Glioblastoma multiforme	2 (6)
Gastric cancer	1 (3)
Head and neck cancer	1 (3)
Pancreatic cancer	1 (3)
Number of tumour types examined	
1	24 (77)
2	4 (13)
> 2	3 (10)
Surrogate endpoint considered	
PFS	15 (48)
TTP	6 (19)
PFS and TTP[*]	3 (10)
PFS/TTP[§]	5 (16)
PFS and TTP and PFS/TTP	2 (6)

IPD = Individual patient data; NSCLC = non-small-cell lung cancer; PFS = Progression-free survival; TTP = Time to progression

[*] PFS and TTP analysed as two distinct endpoints

[§] PFS and TTP analysed as single endpoint

Table 2. Assessment of the validity of PFS as surrogate for OS: comparison of meta-analyses by tumour type across evaluation frameworks. Shaded cells indicate meta-analyses using individual patient data.

Tumour type	Meta-analysis	Elston and Taylor framework[a]	IQWiG framework[b]			BSES3[c]		Authors' conclusions
			Reliability	Correlation	Conclusion	Overall Score /12	Level of Evidence	
Colorectal cancer	Louvet 2001[43]	Level 2	Low	-	No proof	7	D	"In conclusion, PFS certainly deserves further evaluation as an endpoint measure."
	Tang 2007[44]	Level 1	Moderate	Medium	Hint	10	C	"In first-line chemotherapy trials for metastatic CRC, improvements in PFS are strongly associated with improvements in OS. In this patient population, PFS may be an appropriate surrogate for OS."
	Wilkerson 2009[40]	Level 1	Moderate	Low	No Proof	8	D+	"We conclude that PFS is not a surrogate for OS; rather it is a straightforward measure of on-therapy benefit."
	Chirila 2012[25]	Level 1	Limited	Medium	Indication	9	C-	"We have shown that the correlation of OS with PFS, either alone or aggregated with TTP, in clinical trials of patients with metastatic CRC is robust across lines of therapy and provides a useful means of predicting improvements in OS."
	Burzykowski 2001[38]	Level 1	Limited	Low	No Proof	7	D	"These results suggest that PFS is neither trial level nor individual level valid"
	Burzykowski 2006[24]	Level 1	Limited	Medium	Indication	8	D+	"This clearly illustrates that PFS would not be an acceptable, even 'potentially', surrogate for survival in the set of trials analysed here. [However] the association between the treatment effects on both endpoints may

								have been dominated by random noise."
	Buyse 2007[45]	Level 1	Limited	High	Indication	10	C	"The analyses presented here show that, in historical trials comparing FU leucovorin with single-agent FU or with raltitrexed, PFS was an acceptable surrogate for OS"
	Green 2008[26]	Level 1	Limited	Medium	Indication	10	C-	"We conclude that there is modest evidence for surrogacy between one-year PFS and two-year OS."
Lung cancer	Hotta 2011[50]	Level 2	Low	-	No Proof	8	D+	"A PFS advantage is unlikely to be associated with an OS advantage any longer due to this increasing impact of PPS on OS."
	Li 2012[47]	Level 2	Low	-	No Proof	7	D	"Our data suggest that PFS is appropriate survival marker in the clinical trials of EGFR-TKIs for advanced NSCLC."
	Mandrekar 2010[48]	Level 2	Low	-	No Proof	6	D-	"Our present findings (based on data from phase II trials) demonstrate that PFS is a significant predictor of patient survival in advanced NSCLC."
	Foster 2011[57]	Level 1	Limited	Medium	Indication	8	D+	"PFS showed the most promise as a surrogate endpoint for OS (in SCLC) at the patient and the trial-level across all the statistical methods assessed."
Breast cancer	Miksad 2008[53]	Level 1	Limited	Low	No Proof	8* 9**	D+ C-	"This meta-analysis suggests that the trial-level TE on PFS is significantly associated with the trial-level TE on OS. However, prediction of OS based on PFS is surrounded with uncertainty."
	Wilkerson 2009[40]	Level 1	Moderate	Low	No Proof	8	D+	"We conclude that PFS is not a surrogate for OS; rather it is a straightforward measure of on-therapy benefit."

	Burzykowski 2008[51]	Level 1	High	Low	No Proof	7	D	"No end point could be demonstrated as a good surrogate for OS in these trials."
Ovarian cancer	Wilkerson 2009[40]	Level 1	Moderate	Low	No Proof	8	D+	"We conclude that PFS is not a surrogate for OS; rather it is a straightforward measure of on-therapy benefit."
	Rose 2010[54]	Level 2	Low	-	No Proof	5	E+	"We studied the correlation between PFS at six months and survival and found measures of PFS at six months correlated better than response rate to OS."
	Burzykowski 2001[38]	Level 1	Limited	High	Indication	8	D+	"It seems plausible to conclude that PFS is a valid surrogate for survival in advanced ovarian cancer for treatments of the type used in the trials analysed."
	Burzykowski 2006[24]	Level 1	Limited	High	Indication	8	D+	"Consequently, we suggest a better validity of the surrogate (PFS) [than in CRC]."
Renal cell carcinoma	Heng 2011[59]	Level 2	Low	-	No Proof	5	E+	"PFS may be a meaningful intermediate endpoint for OS in patients with metastatic RCC who receive treatment with novel agents."
Prostate cancer	Halabi 2009[58]	Level 2	Low	-	No Proof	6	D-	"PFS seems to be associated with OS. These data need to be validated prospectively before it can be used routinely as an intermediate end point in phase II trials in CRPC."
GBM	Ballman 2007[42]	Level 2	Low	-	No Proof	6	D-	"In light of our assessment of the relationship between PFS and OS, it appears that PFS provides only a moderately reliable estimate of survival."
	Polley 2010[41]	Level 2	Low	-	No Proof	5	E+	"Our analysis suggested that PFS at 6 months may be an appropriate primary endpoint in the context of phase II trials evaluating treatment regimen in newly diagnosed

								GBM patients. Future research is needed to validate our findings in a larger population.”

CRC = colorectal cancer; CRPC = castrate-resistant prostate cancer; EGFR-TKIs = epidermal growth factor receptor tyrosine-kinase inhibitors; FU = fluorouracil; GBM = Glioblastoma multiforme; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PPS = post-progression survival; RCC = renal cell carcinoma; RCT = randomised controlled trial; SCLC = small-cell lung cancer; TE = Treatment effect, TTP = time to progression.

*Taxanes; ** Anthracyclines.

[a] Level 1 corresponds to treatment-level association, i.e. evidence showing treatment effects on the surrogate correspond to treatment effects on the final patient-relevant endpoint. Level 2 corresponds to evidence showing association between the two endpoints.

[b]Reliability is assessed according to (i) use of appropriate statistical approach, (ii) robustness and generalisability of results, (iii) systematic compilation of data, (iv) sufficient restriction of indications, degrees of disease severity, interventions and (v) clear definitions of endpoints. Low, moderate, limited and high indicate growing level of reliability. High correlation corresponds to $R \geq 0.85$ whilst low correlation to $R \leq 0.70$. Correlation is not even assessed if the study is of low reliability. The conclusion about the effect on the final endpoint drawn from the effect observed on the surrogate can be a no proof, hint, indication or proof according to increasing level of validity of the surrogate endpoint.

[c]Overall score sums up scores from 0 to 3 obtained in each of the four domain (i.e., study design, target endpoint, statistical evaluation and generalisability). Category A and B of level of evidence correspond to good evidence for validity of the surrogate endpoint. If the score is lower than 2 in any domain, the level of evidence drops by one alphabetic category.

Table 3 Assessment of the validity of TTP as surrogate for OS: comparison of meta-analyses by tumour type across evaluation frameworks

Tumour type	Meta-analysis	Elston and Taylor framework[a]	IQWiG framework[b]			BSES3[c]		Authors' conclusions
			Reliability	Correlation	Conclusion	Overall Score /12	Level of Evidence	
Colorectal cancer	Johnson 2006[27]	Level 1	Limited	Low	No proof	8	D+	"Our findings support the use of time to progression as a surrogate for survival in metastatic lung cancer and colorectal cancer."
	Tang 2007[44]	Level 1	Moderate	Medium	No Proof	7	D	"Our analysis showed that improvements in PFS, TTP, and RR were all strongly associated with an improvement in OS in randomized control trials of first-line chemotherapy for metastatic CRC. […] The overlapping definitions of PFS and OS may account for the superiority of PFS as a surrogate for OS, as compared with TTP or RR."
	Bowater 2008[23]	Level 1	Low	-	No proof	8	D+	"The relationship between PFS and PPS in cancer treatment that have been examined in this study are worthy of further investigation."
	Bowater 2011[37]	Level 1	Low	-	No proof	7	D	"It would appear that drugs for metastatic breast or CRC that extend, by a given amount, the TTP have a strong tendency to extend, by roughly the same amount, the OS."
	Chirila 2012[25]	Level 1	Limited	Low	No proof	8	D+	"The weighted correlation value did not change for PFS and it was somewhat lower for TTP (although

								with confidence limits that overlap those of PFS/TTP) […] the correlation of OS with PFS, either alone or aggregated with TTP, in clinical trials of patients with metastatic CRC is [...] a useful means of predicting improvements in OS."
NSCLC	Johnson 2006[27]	Level 1	Limited	Low	No proof	8	D+	"Our findings support the use of time to progression as a surrogate for survival in metastatic lung cancer and colorectal cancer."
	Bowater 2008[23]	Level 1	Low	-	No proof	8	D+	"The relationship between PFS and PPS in cancer treatment that have been examined in this study are worthy of further investigation."
	Hotta 2009[46]	Level 1	Limited	Low	No Proof	8	D+	"TTP potentially acts as a surrogate marker, but may not be still a definitive alternative in the first-line setting."
	Li 2012[47]	Level 2	Low	-	No Proof	7	D	"Our data suggest that PFS is appropriate survival marker in the clinical trials of EGFR-TKIs for advanced NSCLC."
Breast cancer	Hackshaw 2005[52]	Level 1	Moderate	Medium	Hint	9	C-	"TTP may be a useful surrogate marker for predicting survival in women receiving first-line anthracycline chemotherapy and could be used to estimate the survival benefit in future trials of first-line chemotherapy."
	Bowater 2008[23]	Level 1	Low	-	No proof	8	D+	"The relationship between PFS and PPS in cancer treatment that have been examined in this study are worthy of further investigation."

	Bowater 2011[37]	Level 1	Low	-	No proof	7	D	"It would appear that drugs for metastatic breast or CRC that extend, by a given amount, the TTP have a strong tendency to extend, by roughly the same amount, the OS."
	Burzykowski 2008[51]	Level 1	Limited	Low	No Proof	7	D	"No end point could be demonstrated as a good surrogate for OS in these trials."
Ovarian cancer	Buyse 2000[9]	Level 1	Limited	High	Indication	8	D+	"We conclude that TTP can be used as a surrogate for survival in advanced ovarian cancer."
Prostate cancer	Bowater 2008[23]	Level 1	Low	-	No Proof	8	D+	"The relationship between PFS and PPS in cancer treatment that have been examined in this study are worthy of further investigation."

CRC = colorectal cancer; EGFR-TKIs = epidermal growth factor receptor tyrosine-kinase inhibitors; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PPS = post-progression survival; RR = response rate; TTP = time to progression.
Shaded cells indicate meta-analyses using individual patient data.

[a]see Table 2.

[b]see Table 2.

[c]see Table 2.