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Meta-analysis comparing docetaxel and vinca-alkaloids in the first-line treatment of NSCLC. Comparison of results based on individual patient data, study report data, and published data

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Background: Meta-analyses based on data extracted from the literature rather than on individual patient data (IPD) must be interpreted with caution. Here we compare both these approaches with a third one, based on clinical and statistical study report data.
Material and Methods: We performed a meta-analysis of survival data to compare docetaxel and vinca-alkaloids in the first-line treatment of NSCLC. Study search and selection have been previously described [Douillard JY et al. Proc ASCO 2006]. Summary statistics to perform a meta-analysis of published data were either directly extracted (hazard ratio [HR] and 95% CI available) or derived from the number of deaths and log-rank p value [Parmar M et al. Stat Med 1998; 17: 2815−34]. Summary statistics of the study report data were either directly extracted, derived, or computed using life tables. All analyses were performed on an intention-to-treat basis when available. Logarithms of the HR were pooled by the inverse-variance weighting method. For IPD, the meta-analysis was performed by a log-rank test stratified for study.
Results: A total of 7 RCTs were identified (2,867 patients). IPD analyses are still pending for one trial. The pooled estimate for overall survival showed an improvement in favor of docetaxel whatever the data used:

Trial	No. of pts	Design	Hazard ratio [95% CI]		
			Published data	Study report data	IPD
Fossella F et al. J Clin Oncol 2003	1218	DC vs VC DCb vs VC	0.85 [0.70;1.01] 0.95 [0.80;1.14]	0.85 [0.72;0.99] 0.95 [0.81;1.12]	0.89 [0.76;1.04] 1.02 [0.88;1.20]
Douillard JY et al. Am Oncol 2005	233	DC vs VC	0.89 [0.68;1.16]	0.89 [0.66:1.19]	0.87 [0.66;1.13]
Kubota K et al. J Clin Oncol 2004	311	DC vs VdC	0.73 [0.57;0.94]	0.75 [0.58;0.97]	0.71 [0.56.0.91]
Georgoulias V et al. J Clin Oncol 2005	413	DG vs VC	1.00 [0.80;1.26]	1.00 [0.80;1.26]	1.02 [0.81;1.27]
Pujol JL et al. Ann Oncol 2005	311	DG vs VC	0.90 [0.70;1.16]	0.90 [0.70;1.16]	pending
Kudoh S et al. J Clin Oncol 2006	180	D vs VC	0.78 [0.56;1.08]	0.78 [0.56;1.08]	0.78 [0.56;1.08]
Monnier A et al. Proc ASCO 2003	201	D vs V	NA (abstract)	0.95 [0.70;1.30]	0.96 [0.70;1.31]
Overall HR			0.88 [0.81;0.96]	0.89 [0.82;0.96]	0.90 [0.82;0.98]

D: docetaxel, C: cisplatin, Cb: carboplatin, G: gemcitabine, V: vinorelbine, Vd: vindesine

Conclusions: For this meta-analysis of survival, IPD confirmed the results found with either study report data or published data. The meta-analysis is currently on-going for other less objective endpoints such as tumour response, progression-free survival and safety endpoints.

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Subgroup results from a randomised, double-blind, multicentre phase III study of bevacizumab in combination with cisplatin-gemcitabine in chemotherapy-naive patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): study BO17704

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Background: Study BO17704 demonstrated a significant improvement in PFS with bevacizumab (B) at either dose of 7.5 mg/kg or 15 mg/kg when added to cisplatin/ gemcitabine (CG) vs. CG + placebo in regions outside of the US.
Methods: Pts were randomised to low dose (LD) or high dose (HD) placebo or LD or HD B. The primary endpoint analysis for progression-free survival (PFS) compared the pooled placebo arms vs. B-LD or vs. B-HD in two pair-wise comparisons. Eligibility: previously untreated advanced or recurrent non-squamous NSCLC; ECOG PS 0–1; no brain metastases. Pts were stratified by region, ECOG PS, gender and disease stage (IIIb, IV, recurrent). B was combined with CG for up to 6 cycles followed by B-alone to disease progression. Secondary endpoints included tumour response (RR) and overall survival (OS) [Manegold ASCO 2007]. PFS results for gender, ECOG PS and stage, as well as exploratory analyses of subgroups by age (<65; ⩾65) and prior weight loss (⩽5%; >5%) for the B arms were compared with pooled placebo (i.e., HD plus LD) arms using a two-sided logrank test.
Results: PFS results for selected subgroups are presented in the table. PFS by appropriate comparison of treatment arms within LD and HD cohorts (e.g., B-LD:LD placebo and B-HD:HD placebo) yielded similar results. A positive treatment effect was observed for RR within each of these subgroups while results for OS were not yet mature for analysis due to short duration of follow-up.
Conclusions: Although conclusions are hindered by small sample size in some cases in this exploratory analysis, the treatment effect for PFS appears consistent across most pt subgroups in B-LD and B-HD. Pts with >5% weight loss in both B arms had no apparent reduction in PFS event risk. Conversely, stage IIIb pts appeared to have ~30% reduction in PFS event risk in both B arms relative to stage IV and recurrent pts. Males in the B-HD arm did not appear to have a reduction in PFS risk. This is in contrast to the OS results observed for gender in the phase III ECOG study 4599 wherein males had a greater reduction in OS event risk relative to females when treated with B at 15 mg/kg with carboplatin/paclitaxel [Ramies ASCO 2007].

	B-LD + CG N; HR*	B-HD + CG N; HR*
Female	246; 0.77	256; 0.59
Male	446; 0.74	442; 0.99
ECOG PS 0	275; 0.70	286; 0.79
1	417; 0.78	412; 0.84
Stage IIIb	103; 0.49	111; 0.58
IV	533; 0.80	535; 0.88
Recurrent	53; 0.79	51; 0.83
Age <65	491; 0.78	483; 0.86
⩾65	201; 0.68	215; 0.74
Weight Loss ⩽5%	479; 0.66	472; 0.71
>5%	187; 0.94	190; 1.12

*HR = Hazard Ratio