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Review

ANtiangiogenic Second-line Lung cancer Meta-Analysis on individual patient data in non-small cell lung cancer: ANSELMA

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Abstract ***Background:*** Now that immunotherapy plus chemotherapy (CT) is one standard option in first-line treatment of advanced non-small cell lung cancer (NSCLC), there exists a medical need to assess the efficacy of second-line treatments (2LT) with antiangiogenics (AA). We performed an individual patient data meta-analysis to validate the efficacy of these combinations as 2LT.
Methods: Randomised trials of AA plus standard 2LT compared to 2LT alone that ended accrual before 2015 were eligible. Fixed-effect models were used to compute pooled hazard ratios (HRs) for overall survival (OS, main end-point), progression-free survival (PFS) and subgroup analyses.
Results: Sixteen trials were available (8,629 patients, 64% adenocarcinoma). AA significantly prolonged OS (HR = 0.93 [95% confidence interval {CI}: 0.89; 0.98], p = 0.005) and PFS (0.80 [0.77; 0.84], p < 0.0001) compared with 2LT alone. Absolute 1-year OS and PFS benefit for AA were +1.8% [−0.4; +4.0] and +3.5% [+1.9; +5.1], respectively. The OS benefit of AA was higher in younger patients (HR = 0.87 [95% CI: 0.76; 1.00], 0.89 [0.81; 0.97], 0.94 [0.87; 1.02] and 1,04 [0.93; 1.17] for patients <50, 50–59, 60–69 and ≥ 70 years old, respectively; trend test: p = 0.02) and in patients who started AA within 9 months after starting the first-line therapy (0.88 [0.82; 0.99]) than in patients who started AA later (0.99 [0.91; 1.08]) (interaction: p = 0.03). Results were similar for PFS. AA increased the risk of hypertension (p < 0.0001), but not the risk of pulmonary thromboembolic events (p = 0.21).
Conclusions: In the 2LT of advanced NSCLC, adding AA significantly prolongs OS and PFS, but the benefit is clinically limited, mainly observed in younger patients and after shorter time since the start of first-line therapy.

1. Introduction

Tumour angiogenesis is a hallmark for cancer, being critical for tumour progression. The vascular endothelial growth factor (VEGF) has been implicated in tumorigenesis and metastasis and mediates the angiogenesis. Indeed, the overexpression of VEGF has been correlated with poor prognosis in non-small cell lung cancer (NSCLC) [1], and angiogenic factors inhibit immune cells and induce immune suppression at multiple levels [2]. Several drugs with antiangiogenic (AA) effects, either monoclonal antibodies (mAbs such as bevacizumab and ramucirumab) or tyrosine kinase inhibitors (TKIs such as nintedanib, vandetanib, sunitinib, sorafenib and anlotinib), have been developed to block this pathway. Bevacizumab in combination with platinum-based chemotherapy was the first AA drug approved in the first-line setting in advanced non-squamous NSCLC based on the improved survival compared with chemotherapy alone [3]. In patients with platinum-refractory advanced NSCLC, several clinical trials have addressed the role of adding AA drugs either to chemotherapy or to TKI. Data from two randomised phase III clinical trials reported that the addition of nintedanib or ramucirumab to docetaxel improved the outcome compared with docetaxel alone, being specially relevant for patients with shorter time since the start of first-line therapy (<9 months) [4,5]. However, data from other trials are inconsistent, with a limited clinical benefit and no clear impact on patients' quality of life, putting into question the real role of AA in the second-line setting. Previous meta-analyses have assessed the role of AA in second-line setting [6,7]. However, these meta-analyses were based on the data extracted from publications instead of individual patient data (IPD), which could offer more powerful and reliable information about the treatment effects across individuals, limiting potential publication bias. Likewise, the role of AA becomes of renewed interest now that immunotherapy plus chemotherapy is one of the new standard treatment options in the first-line setting of advanced NSCLC [8,9], with no robust clinical data about the best therapeutic strategy at the time of progression. Therefore, we performed an IPD meta-analysis to study the effect of adding AA drugs to the standard second-line treatment (2LT) of patients with advanced NSCLC on survival.

2. Methods

The methods were pre-specified in a protocol (https://www.gustaveroussy.fr/node/2784/), which was registered in Prospero (CRD42016035670).

2.1. Eligibility criteria

All trials eligible for the meta-analysis had to satisfy the following criteria: (1) included adult patients with advanced NSCLC who experienced a platinum-based chemotherapy first-line failure; (2) compared standard 2LT (pemetrexed, docetaxel and erlotinib) with standard

2LT plus AA agent (mAb or TKI against vascular pathway); (3) to be randomised in a way that precludes prior knowledge of treatment assignment and (4) have completed accrual before 31 December 2014.

2.2. Search strategy

Published and unpublished eligible phases II and III randomised clinical trials were identified using electronic database search (PubMed, Scopus, Web of Science, Embase, ClinicalTrials, CenterWatch, National Cancer Institute NIH, Cochrane) and hand search (meeting proceedings, review, articles) without language restriction (Web-Appendix 2). Experts and all trialists who took part in the meta-analysis were also asked to identify trials.

2.3. Collected data and checking

Data collected were patient and tumour characteristics, dates of randomisation and death, treatment group allocated, details about treatments received, overall response and toxicities. Trials were checked with a standard procedure [10–12], which follows the recommendations of the Cochrane Working Group on IPD Meta-analysis (Web-Appendix 3). Trials conducted by public institutions were analysed individually, and the resulting survival analyses as well as data description were sent to the trialists for review. IPD were available from two sources: sent through Gustave Roussy or through a remote access. For the latter, results were extracted and then pooled in the meta-analysis.

2.4. End-points

The primary end-point was overall survival (OS), defined as the time from randomisation to death from any cause or the last follow-up. The secondary end-points included progression-free survival (PFS), defined as the time from randomisation to disease progression, death from any cause or the last follow-up whichever occurred first; objective response rate (ORR) according to RECIST, version 1.0 or 1.1, criteria and toxicity.

2.5. Statistical analysis

All analyses were performed on the intention-to-treat principle and stratified by trial. Median follow-up was estimated with the reverse Kaplan–Meier method [13]. Individual and overall hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated with a fixed-effects model using the method developed by Richard Peto (*i.e.* log-rank expected number of events and variance) [14]. Odds ratios (ORs) were calculated for toxicities with a similar method where Kaplan–Meier was replaced by chi-square. Survival curves were estimated with a method also described by Peto, based on the survival in both treatment arms and the HR (re-estimated every 3 months in ANtiangiogenic Second-line Lung cancer Meta-Analysis [ANSELMA]) [15].

To study the robustness of the results, several sensitivity analyses were performed. In subgroup analyses, interaction between treatment effect and patients' characteristics was studied (Web-Appendix 4). Because IPD of several trials were available only remotely, our usual methodology had to be modified. In ANSELMA, a Cox model adjusted on a covariate, treatment and the interaction between those two variables were performed for each trial separately. Global interaction was calculated by pooling the interaction of each trial using the inversed variance weighted average method, as recommended by Fisher *et al.* [16]. The global HRs (*e.g.* treatment effect in male, treatment effect in female) were calculated with the same method. Sensitivity and subgroup analyses were pre-planned, except if mentioned otherwise.

Heterogeneity was estimated using I^2 and chi-square test [17]. In case of significant heterogeneity ($p > 0.10$), trials that do not include the global HR in their CIs were excluded. If heterogeneity remained significant, a random-effect model was used. ORRs of each arm were compared by the Cochran–Mantel–Haenszel chi-square test.

The percentage of toxicities in experimental arm was calculated using the Stewart & Parmar formula [18]. All p-values were two-sided.

3. Results

3.1. Study characteristics and patients' characteristics

Seventeen randomised trials (8,797 patients) met the inclusion criteria (Table 1), but IPD were not available for one trial (168 patients) [19]. IPD of the four trials conducted by public institutions were sent to Gustave Roussy (378 patients) [20–23]. The other trials were conducted by pharmaceutical companies, for which IPD were available remotely for 10 trials (6,801 patients) [4,24–32] and sent to Gustave Roussy for two trials (1,450 patients) (Fig. 1) [5,33]. Five trials assessed the combination of mAb AA plus chemotherapy [5,20,25,29,33], seven trials assessed the combination of TKI AA plus chemotherapy [4,21,22,24,26–28] and four trials assessed the combination of AA (mAb or TKI) plus erlotinib [23,30–32]. Of the 8,629 patients enrolled, 35% were female, 21% never-smokers, 81% younger than 70 years, 65% Caucasian and 13% Asian and 64% had an adenocarcinoma. Only 5% of patients had brain metastases at baseline, 40% had up to three metastatic sites at baseline and 54% of patients started the 2LT with AA within 9 months after starting the first-line treatment (Table 2). Median follow-up was estimated in each trial separately. The median of those medians was 1.85 year [min = 1.0; max = 4.3] and 1.75 year [1.1; 4.1] in control and experimental arms, respectively.

Table 1
Description of eligible trials.

Trials	Inclusion period	Adenocarcinoma	Brain metastases	Prior bevacizumab treatment	Treatments	Doses	No. patients collected/ randomised	Median fw-up (years)	
								Exp	Control
MONOCLONAL ANTIBODIES (OR PROTEINS) ADDED TO CHEMOTHERAPY									
REVEL [5] (NCT01168973) Phase III	2010–2013	60%	NA	14%	Docetaxel + ramucirumab vs. Docetaxel + placebo	Docetaxel: 75 mg/m^2 IV D1 Ramucirumab: 10 mg/kg IV D1 Cycle of 21 days	1,253/1,253	1.7	1.6
VITAL [25] (NCT00532155) Phase III	2007–2010	83%	1%	12%	Docetaxel + aflibercept[a] vs. Docetaxel + placebo	Docetaxel: 75 mg/m^2 IV D1 Aflibercept: 6 mg/kg IV D1 Cycle of 21 days	913/913	1.9	1.9
WJOG 5910 [20] Phase II	2011–2013	94%	1%	100%	Docetaxel + bevacizumab vs. Docetaxel	Docetaxel: 60 mg/m^2 D1 Bevacizumab: 15 mg/kg D1 Cycle of 21 days	100/100	1.7	2.6
Beva2L-2004 [29] (NCT00095225) Phase II	2004–2005	78%	0%	0%	Docetaxel or pemetrexed + bevacizumab vs. Docetaxel or pemetrexed + placebo	Docetaxel: 75 mg/m^2 IV D1 Pemetrexed: 500 mg/m^2 IV D1 Bevacizumab: 15 mg/kg IV D1 Cycle of 21 days	81/82	1.6	1.7
JVCG [33] (NCT01703091) Phase II	NA	NA	10%	30%	Docetaxel + ramucirumab vs. Docetaxel + placebo	Docetaxel: 60 mg/m^2 IV D1 Ramucirumab: 10 mg/kg IV D1 Cycle of 21 days	197/197	1.1	1.0
TYROSINE KINASE INHIBITORS (TKIS) ADDED TO CHEMOTHERAPY									
ZLC 2003 [27] (NCT00047840) Phase II	2003–2004	50%	NA	0%	Docetaxel + vandetanib[b] vs. Docetaxel + placebo	Docetaxel: 75 mg/m^2 IV D1 Vandetanib[b]: 100 mg or 300 mg orally, QD, D1-21 Cycle of 21 days	127/127	1.9	1.9
ZODIAC [26] (NCT00312377) Phase III	2006–2008	60%	10%	3%	Docetaxel + vandetanib vs. Docetaxel + placebo	Docetaxel: 75 mg/m^2 IV D1 Vandetanib: 100 mg orally, QD, D1-21 Cycle of 21 days	1,391/1,391	2.2	2.1
ZEAL [28] (NCT00418886) Phase III	2007–2008	63%	8%	8%	Pemetrexed + vandetanib vs. Pemetrexed + placebo	Pemetrexed: 500 mg/m^2 IV D1 Vandetanib: 100 mg orally, QD, D1-21 Cycle of 21 days	534/534	1.6	1.6
N0626 [22] (NCT00454194) Phase II	2007–2010	68%	5%	43%	Pemetrexed + sorafenib vs. Pemetrexed	Pemetrexed: 500 mg/m^2 IV D1 Sorafenib: 400 mg orally, BID, D1-21 Cycle of 21 days	110/110	4.1	3.4
LUME-Lung 1[4] (NCT00805194) Phase III	2008–2011	50%	6%	4%	Docetaxel + nintedanib *vs.* Docetaxel + placebo	Docetaxel: 75 mg/m^2 IV D1 Nintedanib: 200 mg orally, BID, D2-21 Cycles of 21 days	1314/1314	2.7	2.6

(*continued on next page*)

Table 1 (*continued*)

Trials	Inclusion period	Adenocarcinoma	Brain metastases	Prior bevacizumab treatment	Treatments	Doses	No. patients collected/ randomised	Median fw-up (years)	
								Exp	Control
LUME-Lung 2 [24] (NCT00806819) Phase III	2008–2011	94%	10%	8%	Pemetrexed + nintedanib vs. Pemetrexed + placebo	Pemetrexed: 500 mg/m^2 IV D1 Nintedanib: 200 mg orally, BID, D2-21 Cycle of 21 days	713/713	2.2	2.4
CALGB 30704 [21] (NCT00698815) Phase II	2008–2011	66%	2%	NA	Pemetrexed + sunitinib vs. Pemetrexed	Pemetrexed: 500 mg/m^2 IV D1 Sunitinib: 37.5 mg orally, QD, D1-21 Cycle of 21 days	83/83	4.1	4.3
Antiangiogenic (monoclonal antibodies or TKI) added to Erlotinib									
BeTa [30] (NCT00130728) Phase III	2005–2008	75%	7%	0%	Erlotinib + bevacizumab vs. Erlotinib + placebo	Erlotinib: 150 mg orally, QD, D1-21 Bevacizumab: 15 mg/kg IV D1 Cycles of 21 days	636/636	1.5	1.6
SUN1058 [31] (NCT00265317) Phase II	2007–2009	49%	0%	11%	Erlotinib + sunitinib> *vs.* Erlotinib + placebo	Erlotinib: 150 mg orally, QD, D1-28 Sunitinib: 37.5 mg orally, QD, D1-28 Cycle of 28 days	132/132	1.3	1.6
SUN1087 [32] (NCT00457392) Phase III	2007–2009	53%	0%	10%	Erlotinib + sunitinib vs. Erlotinib + placebo	Erlotinib: 150 mg orally, QD, D1-28 Sunitinib: 37.5 mg orally, QD, D1-28 Cycles of 28 days	960/960	1.8	1.8
LUN160 [19] (NCT00600015) Phase II	2008–2009	NA	0%	35%	Erlotinib + sorafenib vs. Erlotinib + placebo	Erlotinib: 150 mg orally, QD Sorafenib: 400 mg orally, BID	0/168 (IPD not available)	NA	NA
ECOG 1512 [23] (NCT01708954) Phase II	2013–2014	91%	14%	NA	Erlotinib + cabozantinib vs. Erlotinib	Erlotinib: 150 mg orally, QD, D1-28 Cabozantinib: 40 mg orally, QD, D1-28 Cycle of 28 days	85/85	1.2	1.3

QD: once a day; BID: twice a day; Exp: experimental; Fw-up: follow up; NA: not available; *vs.*: versus.

[a] Aflibercept is a recombinant human fusion protein blocking the VEGF-A and -B isoforms and the placental growth factor 1 and 2 isoforms. We report the median follow-up of the experimental arm.

[b] Randomisation in two experimental arms: vandetanib 100 mg or vandetanib 300 mg. Analysed as one experimental arm in the meta-analysis. Beva2L: Bevacizumab 2nd line; CALGB: Cancer and Leukaemia Group B; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; NA: not available; NC: not collected; SUN: sunitinib; WJOG: West Japan Oncology Group; ZEAL: Zactima Efficacy with Alimta in Lung cancer; ZODIAC: Zactima in combination with Docetaxel in non-small cell lung cancer.

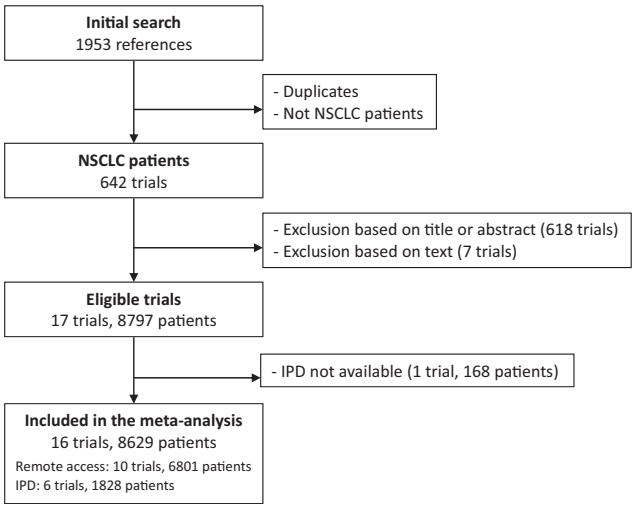


Fig. 1. Flowchart of ANSELMA. ANSELMA: ANtiangiogenic Second-line Lung cancer Meta-Analysis; NSCLC: non-small cell lung cancer; IPD: individual patient data.

3.2. Overall survival

With 6,459 deaths (75%) (Web-Table 1), the addition of AA significantly prolonged OS, reducing the risk of death by 7% (HR = 0.93 [95% CI: 0.89; 0.98], p = 0.005) compared with 2LT alone. There was no significant variation of AA effect on OS according to the three types of combinations (interaction test: p = 0.54) (Fig. 2A). Absolute 1-year OS benefit for AA were +1.8% [95% CI: −0.4; +4.0] (Fig. 3A). At 3 years, 10.5% of patients were alive in both arms. There was no significant heterogeneity between trials (I^2 = 30%, p = 0.12). Sensitivity analyses led to similar results (Web-Table 2).

3.3. Progression-free survival

With 7,730 events (90%), the addition of AA significantly prolonged PFS (HR = 0.80 [95% CI: 0.77; 0.84], p < 0.0001) compared with standard second-line alone. This positive effect was significantly different between the three types of combinations (interaction test: p = 0.0004). The strongest effect was in the combination 'mAb (or TKI) added to erlotinib' (HR = 0.70 [95% CI: 0.63; 0.77]), whereas the effect of mAb or TKI added to chemotherapy was HR = 0.79 ([0.73; 0.86]) and HR = 0.85 ([0.90; 0.91]), respectively (Fig. 2B). Heterogeneity between trials was borderline (p = 0.06), caused by the significant interaction (residual heterogeneity: p = 0.40, I^2 = 5%). Absolute 1-year PFS benefit was equal to +3.5% [+1.9; +5.1] in all trials (Fig. 3B) and was the largest in 'mAb (or TKI) added to erlotinib' group, 7.3% [+3.0; +11.6] (Web-Fig. 1). Sensitivity analyses led to similar results (Web-Table 2).

3.4. Objective response rate

Six trials (2,405 patients) were excluded from the analysis because of missing information [4,20–24]. The addition of AA significantly improved the ORR compared to standard second-line treatment alone (24% vs. 14.0%, p < 0.0001). This benefit occurred regardless of the type of combinations (mAb plus chemotherapy added to chemotherapy: 26% vs. 14%, p < 0.0001; TKI added to chemotherapy: 29% vs. 19.4%, p < 0.0001; and mAb or TKI added to erlotinib: 14.0% vs. 8.0%, p = 0.0001).

A sensitivity analysis, not planned in the protocol, including published data for those six trials led to similar results (Web-Table 3).

3.5. Interaction between patient characteristics and treatment effect

Compared with the standard 2LT alone, a better effect with the addition of AA was observed on OS amongst younger patients (HR = 0.87 [95% CI: 0.76; 1.00], 0.89 [0.81; 0.97], 0.94 [0.87; 1.02] and 1,04 [0.93; 1.17] for patients <50, 50–59, 60–69 and ≥ 70 years old, respectively; trend test: p = 0.02) and for patients who started second-line treatment with AA within the 9 months after starting first-line treatment (<9 vs. ≥9 months: HR = 0.88 [0.82; 0.99] vs. 0.99 [0.91; 1.08], interaction: p = 0.03, not planned in the protocol). The absolute difference on 1-year OS between arms ranged from 6.1% in favour of AA for the youngest to 1.6% in favour of the control arm for the oldest. Conclusions were similar on PFS (age: trend test p = 0.02, time between the first-line treatment and 2LT: p = 0.0001). None of the other patients' characteristics studied such as the number of metastatic sites at inclusion (<3 vs. ≥ 3), brain metastases status at inclusion and prior use of bevacizumab had an impact on the benefit of AA neither for OS nor PFS (Table 3).

3.6. Toxicity

Grade ≥3 toxicity was higher in the addition of AA than with standard 2LT salone (66.2% vs. 55.0%, OR = 1.57 [95% CI: 1.42; 1.73] p < 0.0001). The risk of grade ≥3 toxicity was significantly different between the three types of combinations (interaction: p = 0.008), with the highest risk in the combination 'monoclonal antibodies or TKI added to erlotinib' (61% vs. 45%, OR = 2.00 [1.66; 2.42]).

The AA induces a higher risk of asthenia (1.44 [1.21; 1.70], p < 0.0001) and neutropenia (1.25 [1.09; 1.42], p = 0.0009) and higher risk of some specific toxicities related to AA effect such as hypertension (2.04 [1.47; 2.85]; p < 0.0001) and proteinuria (3.44 [2.02; 5.87], p < 0.0001). AA did not increase the risk of deep vein thrombosis (being less frequent with AA; OR = 0.55

Table 2
Baseline patients' characteristics by treatment arm.

	Experimental arm		Control arm		All	
	N	%	N	%	N	%
Sex						
Male	2803	*64.9*	2767	*64.2*	5570	*64.5*
Female	1514	*35.1*	1544	*35.8*	3058	*35.4*
Missing	1	*<1*	0	*0*	1	*<1*
Age, years						
<50	589	*13.6*	573	13.3	1162	*13.5*
50–59	1325	*30.7*	1327	30.8	2652	*30.7*
60–69	1573	*36.4*	1595	*37.0*	3168	*36.7*
≥70	830	*19.2*	816	*18.9*	1646	*19.1*
Missing	1	*<1*	0	*0*	1	*<1*
Mean [95% CI]	60.4 [60.1; 60.7]		60.4 [60.1; 60.7]		60.4 [60.1; 60.7]	
Body mass index (kg/m^2)						
No. missing	71		71		142	
No. Patients	4247		4240		8487	
Mean [95% CI]	25.1 [25.0; 25.3]		25.1 [25.0; 25.3]		25.1 [25.0; 25.3]	
Ethnic origin						
Black	88	*2.0*	97	*2.3*	185	*2.1*
Asian	557	*12.9*	592	*13.7*	1149	*13.3*
White	2824	*65.4*	2774	*64.3*	5598	*64.9*
Other	111	*2.6*	107	*2.5*	218	*2.5*
Missing	738	*17.1*	741	*17.2*	1479	*17.1*
Tobacco status						
Current smoker[a]	3,317	*76.8*	3,258	*75.6*	6575	*76.2*
Never smoker	895	*20.7*	942	*21.9*	1837	*21.3*
Missing	106	*2.5*	111	*2.6*	217	*2.5*
Performance status						
0	1,175	*27.2*	1,136	*26.4*	2,311	*26.8*
1	2,136	*49.5*	2,144	*49.7*	4,280	*49.6*
≥2	51	*1.2*	52	*1.2*	103	*1.2*
Missing	956	*22.1*	979	*22.7*	1,935	*22.4*
Histology						
Adenocarcinoma	2,758	*63.9*	2,726	*63.2*	5,484	*63.6*
Squamous cell carcinoma	863	*20.0*	844	*19.6*	1,707	*19.8*
Other	692	*16.0*	737	*17.1*	1,429	*16.6*
Missing	5	*0.1*	4	*0.1*	9	*0.1*
No. metastases						
0	91	*2.1*	73	*1.7*	164	*1.9*
1	509	*11.8*	541	*12.5*	1,050	*12.2*
2	691	*16.0*	715	*16.6*	1,406	*16.3*
3	507	*11.7*	439	*10.2*	946	*11.0*
4	215	*5.0*	227	*5.3*	442	*5.1*
5	89	*2.1*	88	*2.0*	177	*2.1*
≥6	41	*0.9*	46	*1.1*	87	*1.0*
Missing	2,175	*50.4*	2,182	*50.6*	4,357	*50.5*
Brain metastases						
No	3,398	*78.7*	3,420	*79.3*	6,818	*79.0*
Yes	206	*4.8*	223	*5.2*	429	*5.0*
Missing	714	*16.5*	668	*15.5*	1,382	*16.0*
Time first to second line						
<9 months	2,336	*54.1*	2,316	*53.7*	4,652	*53.9*
≥9 months	1,481	*34.3*	1,496	*34.7*	2,977	*34.5*
Missing	501	*11.6*	499	*11.6*	1,000	*11.6*
TOTAL	4,318	*100*	4,311	*100*	8,629	*100*

No.: number of, NSCLC: non-small cell lung cancer.
[a] Includes current smokers and former smokers.

[0.33; 0.89], p = 0.02), gastrointestinal bleeding (p = 0.75), pulmonary emboli (p = 0.20), pulmonary bleeding (p = 0.59) or central nervous system ischaemic events (p = 0.81) (Web-Table 4).

4. Discussion

This is the first IPD meta-analysis reporting that the addition of AA drugs to standard 2LT in patients with advanced NSCLC reduces 20% the risk of progression

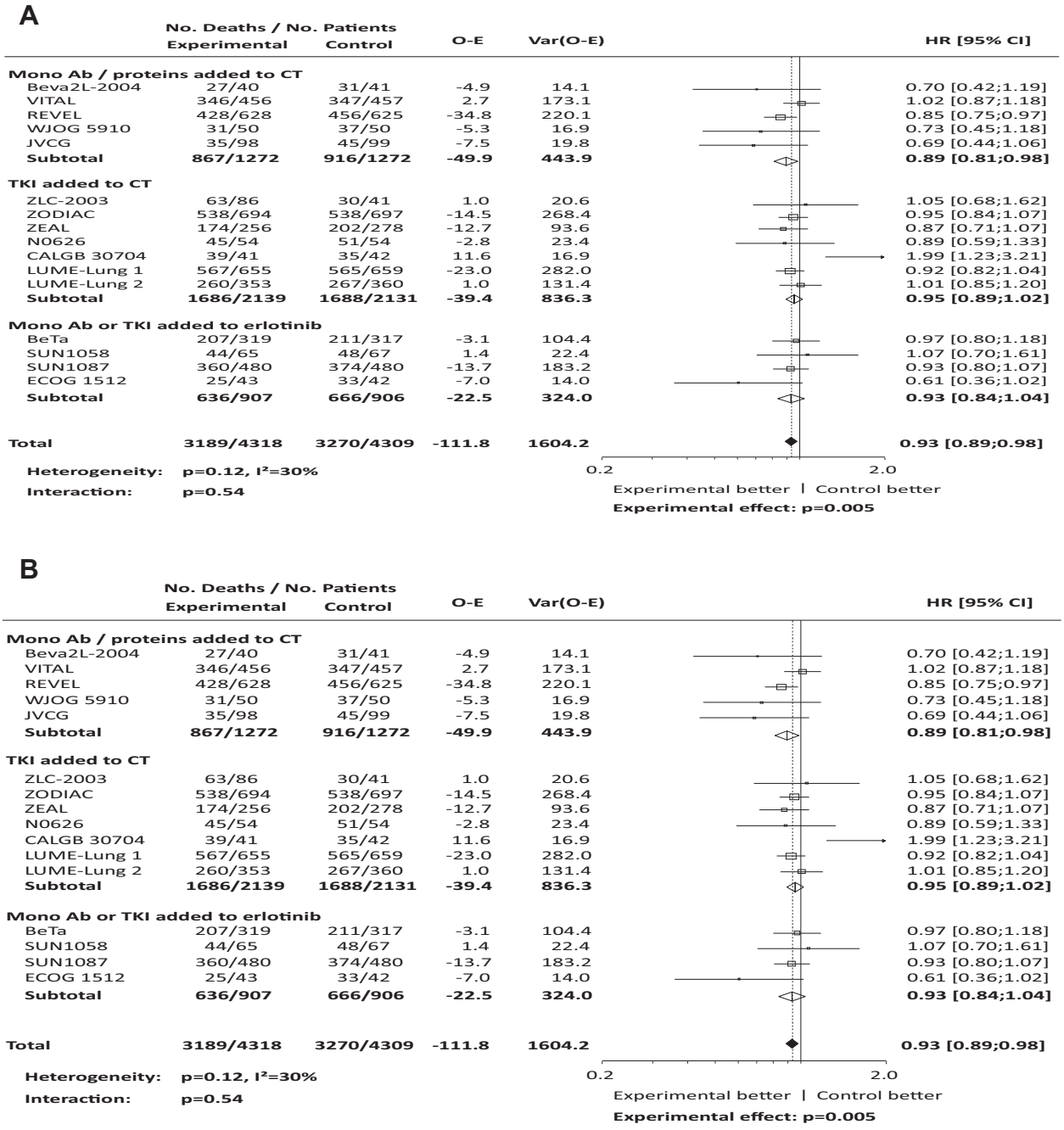
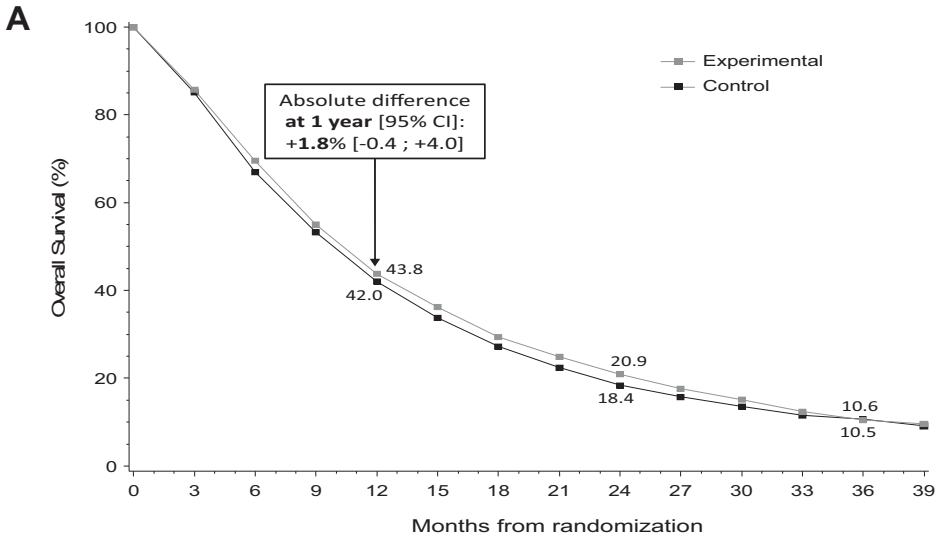


Fig. 2. (**A**) Forest plot of overall survival. Two patients excluded because of missing survival data. (B) Forest plot of progression-free survival. Four patients excluded because of missing survival data. Mono: monoclonal; Ab: antibody; CI: confidence interval; CT: chemotherapy; E: expected; HR: hazard ratio; O: observed; TKI: tyrosine kinase inhibitor.

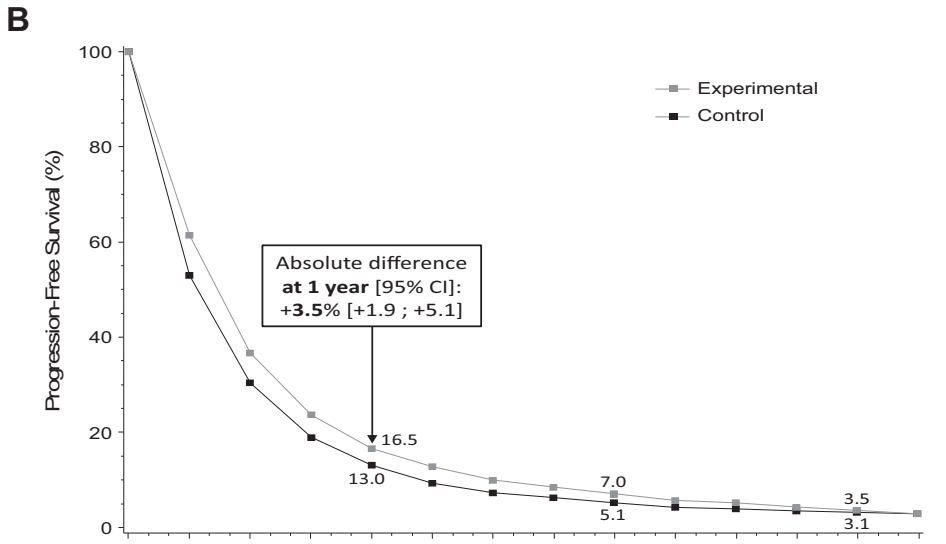
and 7% the risk of death, regardless of the AA drug subtype. This magnitude of benefit was especially significant amongst younger patients and those who started 2LT with AA within the first 9 months after first-line treatment initiation, suggesting a potential benefit of AA agents in refractory tumours. The magnitude of benefit of adding AA in second-line therapy mirrors the data reported in other meta-analysis addressing the benefit of adding bevacizumab to platinum-based chemotherapy in the first-line setting in patients with advanced NSCLC (HR for OS: 0.90 [95% CI: 0.81, 0.99]; p = 0.03, and HR for PFS: 0.72 [95% CI: 0.66, 0.79]; $p < 0.001$) [34], suggesting that AA drugs impact the outcome of patients with advanced NSCLC.

The addition of AA significantly increased the risk of grade ≥3 toxicity, especially drug-related toxicities such as hypertension and proteinuria, but did not increase clinically relevant toxicities such as deep vein thrombosis, gastrointestinal or pulmonary bleeding, pulmonary emboli and central nervous system ischaemic events, which may negatively impact patients' quality of life. The current meta-analysis did not aim to assess



Number of deaths / person-years

	Year [0;1[	Year [1;2[	Year [2;3[	Years 3+
Control	2401 / 2854	761 / 903	99 / 164	9 / 15
Experimental	2320 / 2927	744 / 988	119 / 174	6 / 15



Number of deaths / person-years

	Year [0;1[	Year [1;2[	Year [2;3[	Years 3+
Control	3681 / 1580	231 / 221	22 / 40	1 / 3
Experimental	3469 / 1857	288 / 309	37 / 51	3 / 3

Fig. 3. (A) Peto curves of overall survival. Two patients were excluded because of missing survival data. (B) Peto curves of progression-free survival. CI: confidence interval.

whether some toxicities such as hypertension could be a potential clinical predictive biomarker (*i.e.* correlated with efficacy). A previous observational study in a multi-tumour cohort did not suggest hypertension as a reliable predictive biomarker for response under bevacizumab [35]. This, along with previous published data [36,37], may suggest that toxicity profile of these drugs can be easily managed in daily clinical practice in a broad lung cancer population without limited the risk of life-threatening adverse events.

Previous meta-analyses addressing the role of AA in the second-line setting, including ours [6,7,38–40], which were based on published data, have reported similar HR outcomes for PFS and OS, but either the OS benefit of AA was restricted to docetaxel combinations and to non-squamous histology in the subgroup

Table 3
Subgroup analyses for overall survival and progression-free survival.

Characterisitics	Overall survival[a]				Progression-free survival[b]			
	No. deaths/ no. Patients	HR [95% CI]	Interaction	Heterogeneity[c]	No. events/ no. Patients	HR [95% CI]	Interaction	Heterogeneity[c]
Sex	16 trials (8,626 patients)							
Male	4,310/5,569	0.93 [0.87; 0.99]	p = 0.96	p = 0.46 I^2 = 0%	5,060/5,569	0.80 [0.76; 0.84]	p = 0.62	p = 0.79 I^2 = 0%
Female	2,149/3,057	0.94 [0.88; 1.01]			2,674/3,057	0.83 [0.78; 0.89]		
Age	16 trials (8,626 patients)							
<50	847/1,161	0.87 [0.76; 1.00]	p = 0.10 (trend:	NA[d]	1,056/1,161	0.72 [0.64; 0.82]	p = 0.15 (trend:	NA[d]
50-59	2,008/2,652	0.89 [0.81; 0.97]	p = 0.02)		2,410/2,652	0.78 [0.72; 0.84]	p = 0.02)	
60-69	2,358/3,167	0.94 [0.87; 1.02]			2,837/3,167	0.82 [0.76; 0.88]		
≥70 years	1,246/1,646	1.04 [0.93; 1.17]			1,431/1,646	0.86 [0.78; 0.96]		
Ethnic origin	12 trials (6,849 patients)							
Caucasian	4,331/5,597	0.96 [0.90; 1.02]	p = 0.28	p = 0.13 I^2 = 32%	5008/5597	0.82 [0.78; 0.87]	p = 0.62	p = 0.23 I^2 = 21%
Non-Caucasian	842/1252	0.88 [0.77; 1.01]			1086/1252	0.77 [0.68; 0.86]		
Tobacco status	14 trials (8412 patients)							
Current Smokers[e]	5063/6575	0.94 [0.90; 1.00]	p = 0.06	p = 0.92 I^2 = 0%	5936/6575	0.80 [0.76; 0.84]	p = 0.39	p = 0.23 I^2 = 21%
Never-smokers	1206/1837	0.85 [0.76; 0.95]			1591/1837	0.78 [0.71; 0.86]		
Performance status	14 trials (6692 patients)							
PS 0	1581/2310	0.95 [0.86; 1.05]	p = 0.77	p = 0.96 I^2 = 0%	1999/2310	0.81 [0.74; 0.88]	p = 0.73	p = 0.51 I^2 = 0%
PS ≥ 1	3420/4382	0.93 [0.87; 0.99]			3939/4382	0.80 [0.75; 0.85]		
Histology	15 trials (8421 patients)							
Adenocarcinoma	3986/5482	0.93 [0.87; 0.99]	p = 0.92	p = 0.15 I^2 = 28%	4895/5482	0.81 [0.77; 0.86]	p = 0.98	p = 0.98 I^2 = 0%
Non-adenocarcinoma	2389/2939	0.96 [0.88; 1.04]			2671/2939	0.79 [0.73; 0.85]		
No. metastatic sites at baseline[f,g]	6 trials (4102 patients)							
<3	1674/2257	0.96 [0.87; 1.05]	p = 0.66	p = 0.60 I^2 = 0%	1961/2257	0.80 [0.73; 0.88]	p = 0.20	p = 0.11 I^2 = 44%
≥3	1488/1845	0.93 [0.84; 1.03]			1647/1845	0.86 [0.78; 0.94]		
Brain metastasis at baseline	9 trials (5891 patients)							
Absence	4123/5463	0.94 [0.89; 1.00]	p = 0.79	p = 0.77 I^2 = 0%	5031/5463	0.82 [0.78; 0.87]	p = 0.33	p = 0.49 I^2 = 0%
Presence	333/428	0.90 [0.72; 1.12]			387/428	0.74 [0.60; 0.90]		
EGFR status	8 trials (1595 patients)							
Negative	966/1371	0.96 [0.84; 1.09]	p = 0.48	p = 0.66 I^2 = 0%	1238/1371	0.77 [0.69; 0.86]	p = 0.22	p = 0.99 I^2 = 0%
Positive	128/224	0.91 [0.64; 1.31]			170/224	0.69 [0.51; 0.94]		
Prior bevacizumab	10 trials (7452 patients)							
No	5126/6751	0.93 [0.88; 0.99]	p = 0.76	p = 0.59 I^2 = 0%	6065/6751	0.81 [0.77; 0.85]	p = 0.53	p = 0.83 I^2 = 0%
Yes	513/701	0.88 [0.74; 1.05]			635/701	0.84 [0.72; 0.98]		
Prior taxane[g]	13 trials (7518 patients)							
No	3595/4792	0.93 [0.88; 1.00]	p = 0.21	p = 0.92 I^2 = 0%	4305/4792	0.81 [0.76; 0.86]	p = 0.73	p = 0.86 I^2 = 0%
Yes	2018/2726	0.89 [0.81; 0.98]			2382/2726	0.79 [0.72; 0.86]		

(*continued on next page*)

Table 3 (*continued*)

Characterisitics	Overall survival[a]				Progression-free survival[b]			
	No. deaths/ no. Patients	HR [95% CI]	Interaction	Heterogeneity[c]	No. events/ no. Patients	HR [95% CI]	Interaction	Heterogeneity[c]
Prior maintenance therapy	4 trials (1635 patients)							
No	813/1166	0.87 [0.76; 1.00]	p = 0.25	p = 0.42 I^2 = 0%	1063/1166	0.78 [0.69; 0.88]	p = 0.40	p = 0.48 I^2 = 0%
Yes	277/469	0.70 [0.55; 0.89]			417/469	0.69 [0.57; 0.84]		
Start second-first lines[g]	12 trials (7629 patients)							
<9 months	3749/4652	0.88 [0.82; 0.93]	p = 0.03	p = 0.12 I^2 = 34%	4301/4652	0.74 [0.70; 0.79]	p = 0.0001	p = 0.16 I^2 = 29%
≥9 months	2019/2977	0.99 [0.91; 1.08]			2567/2977	0.90 [0.83; 0.97]		

CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; NA: not available.
[a] Two patients were excluded from all overall survival analyses because of missing survival data.
[b] Four patients were excluded from all progression-free survival analyses because of missing survival data. Due to an error during the extraction of PFS results, numbers of patients are equal for OS and PFS in this table. But HR was estimated on the right numbers of patients.
[c] Heterogeneity between trial interactions.
[d] Data collected did not allowed the analyses of the heterogeneity of the interaction. When only two categories were used (<70 and ≥ 70 years), the heterogeneity was not significant (data not shown).
[e] Includes current and former smokers.
[f] Number of metastases when number of metastatic sites not available.
[g] Not planned in the protocol.

analyses [7] or the OS was not significant, as pooled analysis of first and second-line trials was performed, which increased the heterogeneity [39]. In contrast, our IPD meta-analysis did not find a significant survival interaction according to the three types of combinations (mAb AA plus chemotherapy, TKI AA plus chemotherapy and AA plus erlotinib) or histological subgroups, suggesting the broad efficacy of AA in second-line NSCLC. In patients with NSCLC and disease progression after platinum-based chemotherapy, both the US Food and Drug Administration and the European Medicines Agency approved ramucirumab in combination with docetaxel in December 2014 and January 2016, respectively, regardless of the histologic subtype. Nintedanib was only approved in non-squamous NSCLC by the EMA in November 2014.

The combination of docetaxel either with ramucirumab or nintedanib was adopted as standard treatment in the second-line setting [4,5]. However, the treatment paradigm rapidly shifted in daily clinical practice with the irruption of immune checkpoint inhibitors (ICIs) in this setting based on better OS than that with docetaxel, with a 3-year OS ranging from 17% to 23%, and better toxicity profile [41–43]. In our IPD meta-analysis, 11% of patients treated with AA were alive at 3 years, suggesting a prolonged survival amongst some patients with AA drugs in second line. One recent meta-analysis reported similar efficacy of docetaxel plus AA drugs (nintedanib or ramucirumab) and nivolumab, with potential differences in subgroups according to PD-L1 expression [6]. However, second-line ICIs have not been formally compared with docetaxel plus AA, limiting firm conclusions about the long-term benefit between both therapeutic strategies. Recently, ICI plus chemotherapy with or without bevacizumab became the new standard treatment option in the first-line setting of advanced NSCLC [8,9], resulting in a dearth of robust clinical data to underpin an optimised therapeutic pathway after progression on immune chemotherapy strategy. Interestingly, angiogenesis induces immune suppression at multiple levels, and it is a potential mechanism of immune resistance [2,44], suggesting that AA drugs could be relevant for overcoming immune resistance [45–50], especially amongst those patients with primary resistance on chemotherapy immune strategy [51,52]. Although our data support the benefit of AA in second-line settings, this benefit after immune chemotherapy strategy must be confirmed in the ongoing phase III clinical trials (NCT04471428; NCT03906071; NCT03976375). While awaiting the results of these trials, in daily clinical practice, the combination of chemotherapy plus an AA agent seems feasible and safe after immune chemotherapy strategy. Indeed, indirect comparison suggests higher ORR (~20%) and longer PFS (4.4 months) with docetaxel plus nintedanib after immune chemotherapy strategy [51] than after just chemotherapy [4]. Similarly, there are initial data from the MRTX-500 phase II trial showing encouraging the outcome with the combination of sitravatinib (a multi-TKI agent with AA properties) plus nivolumab reporting a 2-year OS of 32% in non-squamous NSCLC previously treated with ICIs [50].

In our IPD meta-analysis, we found that the OS and PFS benefit with AA diminished in elderly population. The reasons remain unknown but are likely wide-ranging, such as a higher number of comorbidities [53], which can exacerbate treatment-related toxicities,

ultimately leading to decreased treatment dose or duration in older patients, as well as age-related decrease in renal function and bone marrow regeneration that may impact tolerance and response to therapy. Similarly, in the first-line setting, amongst 157 patients aged 75 years or above, the use of bevacizumab plus platinum-based chemotherapy did not confer PFS and OS benefit compared with chemotherapy alone [54]. However, we could not perform a sensitivity analysis to assess the risk of toxicity by the age. Likewise, in our IPD meta-analysis, other relevant clinical characteristics such as sex, ethnicity, the number of metastatic sites and brain metastases status at inclusion did not influence the outcome achieved with the addition of AA to the standard treatment. However, these subgroup analyses were performed in a limited number of patients.

In our IPD meta-analysis, previous treatment with bevacizumab did not impact the outcome of AA in the second-line setting. Although bevacizumab beyond disease progression did not improve the outcome in the phase III AvaALL trial [55], there is some evidence that other AA drugs subtypes may play a role at the time of bevacizumab progression. In exploratory analysis from REVEL trial, the efficacy of ramucirumab plus docetaxel occurred regardless of prior treatment with bevacizumab [56].

The strengths of this IPD meta-analysis include that most analyses, based on intention-to-treat principle, were pre-planned according to a protocol, and the high number of patients allowed rigorous assessment with adequate power association for several subgroups with treatment effect. There may exist some limitations also, such as potential heterogeneity and lack of analysis for specific subgroup of patients, and risk that broad genomic profiling of patients with advanced NSCLC enrolled into these trials was unknown in majority of cases. Likewise, the subsequent treatment lines after progression on AA were not collected in all trials, not allowing us to explore the survival impact of sequential treatment strategies. Direct access to IPD was possible only for six trials (21% of patients) [5,20–23,33]. A remote access was available for the others. Remote access was time-consuming and did not allow checking and analysis as detailed as the direct access. Results had to be extracted for each trial separately and then pooled. No contact with investigators or statistical team was possible to correct inconsistencies or update the data.

In conclusions, this meta-analysis clearly endorses that in the second-line setting of advanced NSCLCs, adding AA to standard second treatment modestly but significantly prolongs the outcome. This benefit appears independent of the type of AA drugs, but the observed benefit may be higher in younger patients and in those patients with refractory tumours with good and manageable safety profile.

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Author contribution

JR, BL, J-PP and BBE designed and supervised the study.

JR and BBE searched for and selected the trials.

BL and J-PP did the statistical analyses.

JR wrote the draft, with revisions from the other authors. All authors contributed to the interpretation of the results during the revision of the manuscript.

All investigators listed in Appendix 1 received the manuscript for revision.

The corresponding author, the first author, BL and J-PP had full access to all the data in the study and had final responsibility for the decision to submit for publication. BL and J-PP have accessed and verified the data.

Conflict of interest statement

RH, MR, EBG, GVS, RR, NH, JV, KY, HG, JH and RH are authors for some of the trials included in this meta-analysis. Other authors have not reported any conflict of interest related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.02.002

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