32P

Impact of smoking status on the relative efficacy of the EGFR TKI/angiogenesis inhibitor combination therapy in advanced NSCLC – A systematic review and meta-analysis

U. Dafni[1,2], R.A Soo[3], S. Peters[4], Z. Tsourti[2], K.Vervita[2], J-Y. Han[5], J. De Castro[6,7], L. Coate[8,9], M. Früh[10,11,12], S. M.S Hashemi[13], E. Nadal[7,14], E. Carcereny[7,15], M.A. Sala[7,16], R. Bernabé[7,17], M. Provencio Pulla[7,18], S. Cuffe[9,19], B. Ruepp[20], H.Roschitzki-Voser[20], R. Rosell[15], R.A. Stahel[20]

[1]National and Kapodistrian University of Athens, Athens, Greece; [2]Frontier Science Foundation Hellas, Athens, Greece; [3]National University Cancer Institute, Department of Haematology-Oncology, Singapore; [4]Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland; [5]National Cancer Center, Center for Lung Cancer, Goyang, Republic of Korea; [6]Hospital Universitario La Paz, Medical Oncology Department, Spain; [7]Spanish Lung Cancer Group (SLCG); [8]Mid-Western Cancer Centre and University Hospital Limerick, Limerick, Ireland; [9]Cancer Trials Ireland, Innovation House, Dublin, Ireland; [10]Cantonal Hospital St. Gallen, Oncology and Hematology, Switzerland; [11]Inselspital Bern, Department of Oncology, Bern, Switzerland; [12]Swiss Group for Clinical Cancer Research (SAKK); [13]Amsterdam UMC, VU University Medical Center, Department of Pulmonary Diseases, Amsterdam, Netherlands; [14]ICO L'Hospitalet, Medical Oncology Department, Barcelona, Spain; [15]Institut Català d'Oncologia Badalona-Hospital Germans Trias i Pujol. B-ARGO Group, Medical Oncology Department, Badalona, Spain; [16]Hospital Universitario Basurto, Medical Oncology Department, Bilbao, Spain; [17]Hospital Virgen del Rocio, Medical Oncology Department, Sevilla, Spain; [18]Hospital Puerta de Hierro, Majadahonda Medical Oncology Service, Madrid, Spain; [19]St. James's Hospital, Department of Medical Oncology, Dublin, Ireland; [20]European Thoracic Oncology Platform (ETOP), Coordinating Office, Bern, Switzerland

Background

- In the randomised BOOSTER trial *(Soo R.A. et al., 2022; Annals of Oncology)*, the primary analysis failed to show superiority of the osimertinib(osi)/bevacizumab(beva) combination versus osi alone.
- Exploratory analysis found an improvement in progression-free survival (PFS) in the subgroup of smokers treated with osi+beva.
  - HR (95% CI) → **Smokers: 0.52 (0.30-090) ; p=0.021**
    → Non-smokers: 1.47 (0.92-2.33); p=0.10
  - **Interaction p=0.0052**
- The role of smoking status on the benefit of adding an angiogenesis inhibitor to EGFR TKI therapy for EGFR-mutated non-small cell lung cancer (EGFR-NSCLC) patients (pts) is undetermined.

Methods

- A **systematic review and meta-analysis** was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement *(Page M.J. et al., 2021; PLOS Medicine)*, in order to evaluate the relative effect of adding an angiogenesis inhibitor to EGFR TKI therapy in advanced EGFR-NSCLC pts, according to their smoking status.
- **Randomised controlled trials**, administering EGFR TKI therapy with or without angiogenesis inhibitor were **eligible** for inclusion.
- **Target population** was advanced EGFR-mutated NSCLC pts.
- All randomised studies of osi/erlotinib(erlo) with or without beva/ramucirumab(ramu), appearing in recent main oncology congresses (AACR, ESMO, WCLC, ELCC) or in PubMed as of **1st November 2021**, were examined.
- The **hazard ratios (HRs)** for PFS and overall survival (OS), by smoking status, were used.
- Pooled HRs and the interaction HR, are estimated by **fixed or random effects models**, depending on the detected degree of heterogeneity (Cochran's Q).
- **Risk of bias** was assessed using the revised Cochrane tool for randomised trials (RoB2) *(Sterne J.A.C. et al., 2019; BMJ)*.

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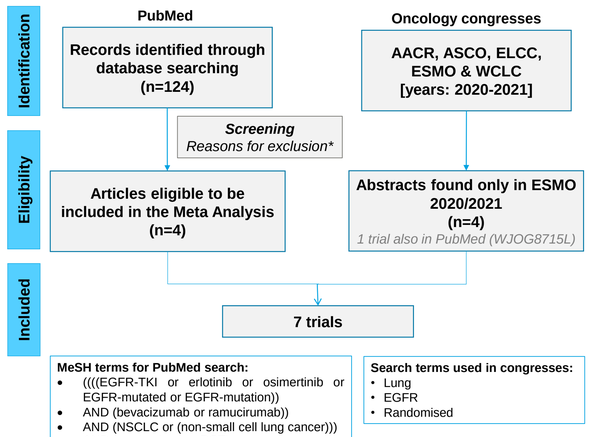
Results

Figure 1: Flowchart



**Reasons for exclusion: 38 review/meta-analysis, 36 non-randomized trial, 8 no EGFR TKI trt, 7 no survival results, 7 no results by smoking, 4 subgroup analysis, 4 study design paper, 3 no angiogenesis inhibitor trt, 2 clinical practice guidelines, 2 reply letter, 2 no comparison with EGFR TKI, 2 pooled analysis, 2 updated results, 1 case study, 1 highlights, 1 study on mice*

- **7 randomised trials** with 1,343 randomised pts
- **1,291 pts** with available results by smoking status
- 5 first-line studies (erlo/beva: 3; erlo/ramu and osi/beva: 1 each)
- 2 second-line (osi/beva)
- Monotherapy with EGFR TKI (erlo, osi) was the control arm
- PFS information: All 7 studies
- OS information: 4 studies
- **Low risk of bias** for all studies

Table 1: Baseline characteristics for each study

Study (N) *(Line, Phase)*	Treatment	n	Age	Female	Smokers	ECOG PS 0	EGFR mut. Ex19del	Stage IV
			Median	*n (%)*				
BEVERLY (N=160)	Erlo+Beva	80	66	52 (65.0)	**34 (42.5)**	52 (65.0)	44 (55.0)	77 (96.0)
(First, Phase III)	Erlo	80	68	50 (62.5)	**43 (54.0)**	47 (59.0)	44 (55.0)	75 (94.0)
JO25567 (N=152)	Erlo+Beva	75	67	45 (60.0)	**24 (32.0)**	43 (57.0)	40 (53.0)	60 (80.0)
(First, Phase II)	Erlo	77	67	51 (66.0)	**26 (34.0)**	41 (53.0)	40 (52.0)	62 (81.0)
NEJ026 (N=224)	Erlo+Beva	112	67	71 (63.0)	**41 (37.0)**	64 (57.0)	56 (50.0)	82 (73.0)
(First, Phase III)	Erlo	112	68	73 (65.0)	**41 (37.0)**	68 (61.0)	55 (49.0)	84 (75.0)
RELAY (N=449)	Erlo+Ramu	224	65	141 (63.0)	**64 (29.0)**	116 (52.0)	123 (55.0)	195 (87.0)
(First, Phase III)	Erlo+placebo	225	64	142 (63.0)	**73 (32.0)**	119 (53.0)	120 (53.0)	189 (84.0)
WJOG9717L (N=122)	Osi+Beva	61	67	37 (60.7)	**23 (38.0)**	32 (52.5)	35 (57.0)	48 (79.0)
(First, Phase II)	Osi	61	66	38 (62.3)	**31 (51.0)**	34 (56.0)	36 (59.0)	46 (75.4)
BOOSTER (N=155)	Osi+Beva	78	68	47 (60.0)	**34 (44.0)**	22 (28.0)	58 (74.0)	76 (97.0)
(Second, Phase II)	Osi	77	66	49 (64.0)	**28 (36.0)**	25 (33.0)	51 (66.0)	76 (99.0)
WJOG8715L (N=81)	Osi+Beva	40	68	24 (60.0)	**19 (48.0)**	20 (50.0)	22 (55.0)	33 (83.0)
(Second, Phase II)	Osi	41	70	24 (59.0)	**21 (51.0)**	17 (42.0)	28 (68.0)	26 (63.0)

Figure 2: Forest plot for PFS

Interaction by smoking: HR=0.62, p=0.020

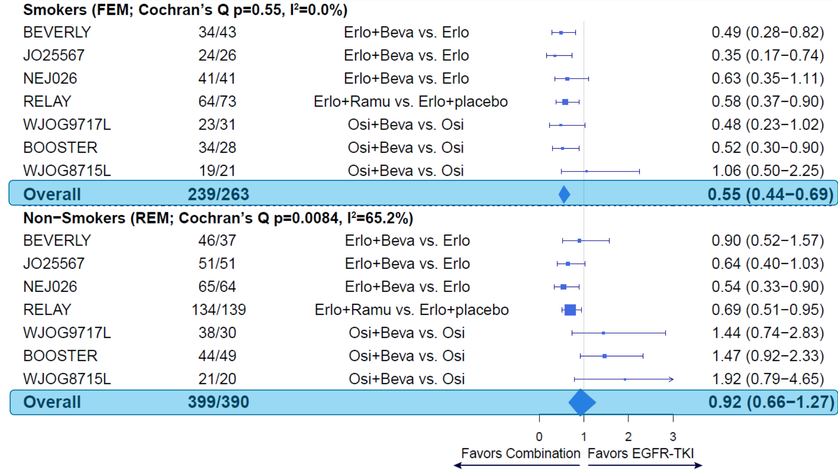
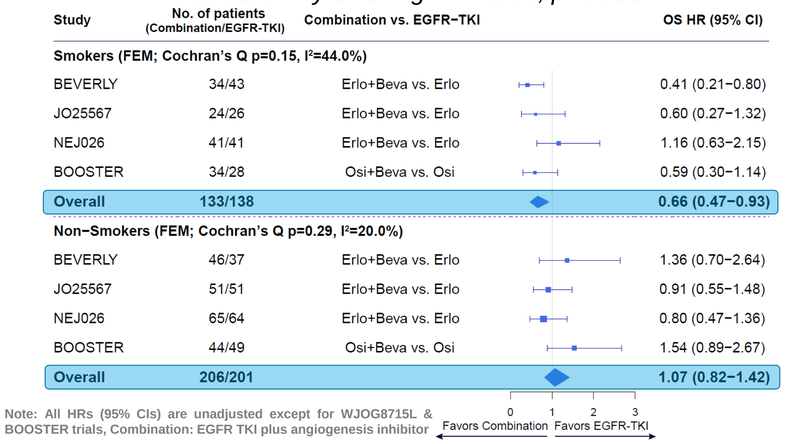


Figure 3: Forest plot for OS

Interaction by smoking: HR=0.62, p=0.030



Note: All HRs (95% CIs) are unadjusted except for WJOG8715L & BOOSTER trials, Combination: EGFR TKI plus angiogenesis inhibitor

Conclusions

- In advanced EGFR-NSCLC patients, the addition of an angiogenesis inhibitor to EGFR TKI therapy was found to provide a statistically significant PFS and OS benefit only in smokers.
- Whether this might be due to a specific co-mutational pattern produced by tobacco exposure remains to be determined. The biological basis for this observation should be pursued.

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***Urania Dafni** reports honorarium as Member of the Tumor Agnostic Evidence Generation working Group of Roche, outside the submitted work*