Alectinib for the treatment of pretreated RET-rearranged advanced NSCLC: results of the ETOP ALERT-lung trial

Felip, E.; Smit, E.F.; Molina-Vila, M.A.; Dafni, U.; Massuti, B.; Berghmans, T.; ... ; ETOP 12-17 ALERT-Lung Collaborator

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Alectinib for the treatment of pretreated RET-rearranged advanced NSCLC: Results of the ETOP ALERT-lung trial

Enriqueta Felip [a], Egbert F. Smit [b], Miguel A. Molina-Vila [c], Urania Dafni [d,e], Bartomeu Massuti [f], Thierry Berghmans [g], Filippo de Marinis [h], Francesco Passiglia [i], Anne-Marie C. Dingemans [j], Manuel Cobo [k], Santiago Viteri [l], Christian Britschgi [m], Sinead Cuffe [n,o], Mariano Provencio [p], Sabine Merkelbach-Bruse [q], Charitini Andriakopoulou [e], Roswitha Kammler [r], Barbara Ruepp [r], Heidi Roschitzki-Voser [r], Solange Peters [s], Jürgen Wolf [t], Rolf Stahel [r,*], on behalf of the ETOP 12-17 ALERT-lung Collaborators

[a] *Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[b] *Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[c] *Laboratory of Oncology, Pangaea Oncology, Dexeus University Hospital, Barcelona, Spain*
[d] *National and Kapodistrian University of Athens, Athens, Greece*
[e] *Frontier Science Foundation Hellas, Athens, Greece*
[f] *Medical Oncology Department, Hospital General Universitario Alicante, Alicante, Spain*
[g] *Institute Jules Bordet, Brussels, Belgium*
[h] *Thoracic Oncology Division, European Institute of Oncology IRCCS, Milan, Italy*
[i] *Department of Oncology, University of Turin, S. Luigi Hospital, Orbassano, Turin, Italy*
[j] *Department of Pulmonology, Maastricht University Medical Center, Maastricht, the Netherlands & Department of Pulmonology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands*
[k] *Unidad Gestion Intercentros of Medical Oncology. Regional and Virgen de la Victoria University Hospitals (IBIMA), Málaga, Spain*
[l] *Instituto Oncológico Dr Rosell, Hospital Universitario Dexeus. Grupo QuironSalud, Barcelona, Spain*
[m] *Department of Medical Oncology and Hematology, University Hospital Zurich, Comprehensive Cancer Center Zurich, Zurich, Switzerland*
[n] *Department of Medical Oncology, St. James's Hospital, Dublin, Ireland*
[o] *Cancer Trials Ireland, Dublin, Ireland*
[p] *Hospital Puerta de Hierro, Majadahonda Medical Oncology Service, Madrid, Spain*
[q] *University of Cologne, Faculty of Medicine and University Hospital Cologne, Institute of Pathology, Cologne, Germany*
[r] *ETOP IBCSG Partners Foundation, Coordinating Center, Bern, Switzerland*
[s] *Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland*
[t] *Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany*

A B S T R A C T

Background: Alectinib, a highly selective next generation ALK-inhibitor, has exhibited potent anti-tumour activity in RET-rearranged NSCLC in the preclinical stage.
Methods: ALERT-lung is a single-arm, phase II trial evaluating the activity of alectinib for the treatment of pretreated RET-rearranged advanced NSCLC. Alectinib was administered orally, 600 mg, twice per day until progression, refusal or unacceptable toxicity (treatment could continue beyond progression, if patient was deriving clinical benefit). Patient recruitment closed prematurely due to discouraging results for alectinib in a phase I/II study in the same indication.
Results: All 14 patients who enrolled until the premature accrual closure, received at lease one dose of alectinib. Among them, median age was 61 years, majority (71 %) was female, never smokers, of ECOG PS 1.
No objective response (complete or partial response) was recorded. Of the 13 evaluable patients, three (23 %) achieved and maintained disease stabilisation for 24 weeks. Up to 31 March 2021 (median follow-up 15.9 months), 12 PFS-events (92 %) were observed, with median PFS of 3.7 months (95 % C.I.: 1.8 – 7.3 months). Overall, three deaths (23 %) were reported.
Seven patients (50 %) experienced grade $\geq$ 3 adverse events, while three discontinued treatment due to erythema multiforme of grade 3, related to alectinib. No treatment-related serious adverse event was reported.
Conclusions: Accrual into our trial was terminated early in response to other reports of limited activity of alectinib in patients with RET-fusion NSCLC and the emergence of more potent selective RET-inhibitors. Also in our trial, alectinib did not show the expected potential for anti-tumour activity in NSCLC.

* Corresponding author.
E-mail address: Rolf.Stahel@etop.ibcsg.org (R. Stahel).

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1. Introduction

RET-fusions in non-small cell lung cancer (NSCLC) were first detected in 2012. The most frequent fusion partner of the *RET*-gene in lung cancer is *KIF5B*. Overall, 48 fusion partners have been identified [1]. RET-fusions can be detected in 1–2 % of lung adenocarcinomas [2].

Earlier trials in patients with RET-fusion NSCLC involving multi-targeted tyrosine kinase inhibitors revealed promising results, with response rates between 16 % and 28 % [3–5]. Alectinib is a highly selective second-generation ALK-inhibitor. In preclinical *in vitro* assays, alectinib selectively inhibited ALK, but also RET. In 2016, in a clinical series of four patients with RET-fusion NSCLC, two responded to alectinib [6].

The aim of our trial was to determine prospectively the tumour response to alectinib in patients with RET-rearranged NSCLC.

2. Materials and methods

2.1. Patients

Eligible patients had histologically or cytologically-documented, RET-rearranged advanced NSCLC at least one prior platinum-based systemic regimen, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, radiologically evaluable disease and adequate organ function. Patients with prior RET-targeted therapy, EGFR-mutations, ROS- or ALK-rearrangements, active CNS metastases, carcinomatous meningitis, symptomatic bradycardia or known HIV-positivity were ineligible.

2.2. Trial design, treatment and safety

ALERT-lung, a single-arm multicentre phase II trial, to assess the clinical efficacy of alectinib in RET-rearranged NSCLC. Patients received 600 mg alectinib orally, twice per day (1,200 mg per day) until progression (PD), refusal or unacceptable toxicity. Treatment beyond PD was allowed for as long as patients derived clinical benefit.

Safety data were reviewed bi-annually by the ETOP Independent Data Monitoring Committee (IDMC).

2.3. Endpoints and assessment

The primary endpoint was objective response rate (ORR) per investigator assessment, defined as the rate of patients achieving either complete or partial response (CR or PR) as best response to alectinib according to RECIST v1.1, evaluated from treatment start until the end of clinical follow-up. Tumour assessment was performed at baseline (within 6 weeks prior to enrolment) and subsequently every 8 weeks (±4 days) after the first dose of alectinib until disease progression. Imaging was conducted by contrast-enhanced computed tomography of the thorax and the upper abdomen. Disease control rate (DCR) at 24 weeks, a secondary endpoint, was defined as the rate of patients who achieved either CR, PR or stable disease (SD) (or non-CR/non-PD for patient with non-measurable disease at inclusion). SD had to remain for at least 24 weeks. Other secondary endpoints were progression-free survival (PFS), defined as the time from enrolment to documented progression or death (if progression was not documented); overall survival (OS), defined as the time from enrolment to death from any cause; and safety and tolerability according to CTCAE version 4.0. In the frame of translational analysis, NGS and gene expression analysis (nCounter®) of tissue and plasma samples were performed.

2.4. Statistical analysis

The trial was powered to detect an ORR of ≥ 35 %, while a rate of 15 % was considered to be low, using the exact test for single proportion, at a one-sided significance level of 0.015. A power of 82 % would be achieved with a planned sample size of 44 patients (41 evaluable, allowing for an attrition number of three patients).

ORR and DCR were evaluated along with corresponding 95 % exact binomial confidence intervals. Time-to-event endpoints were analysed with the Kaplan-Meier method, and their estimates are provided along with their associated 95 % log–log confidence intervals.

All statistical analyses were performed using SAS version 9.4.

3. Analysis populations

The primary endpoint of ORR and all secondary efficacy endpoints (i.e., DCR, PFS and OS) were assessed in the cohort of evaluable patients (efficacy cohort), defined as all patients enrolled, excluding patients who were found not to be evaluable (in retrospective review), patients who never started treatment, and patients who were lost to follow-up before their first tumour assessment by RECIST v1.1. Safety and tolerability were assessed in the safety population (i.e., patients who received at least one dose of alectinib).

3.1. Early accrual closure

With the last patient enrolled in April 2020, accrual into the ALERT-lung trial was closed prematurely as of March 2021. The decision not to continue accrual was taken by the trial Steering Committee and endorsed by the ETOP IDMC, in response to reports of limited activity for alectinib in this patient population and the emergence of more potent RET-inhibitors. Patients were allowed to continue treatment for as long as they derived clinical benefit. Safety and follow-up information is updated until 31 March 2021.

4. Results

4.1. Patients

Between November 2018 until April 2020, 14 patients were enrolled from nine centres in the Netherlands, Spain, Italy and Belgium. Median age was 61 years, majority was female (71.4 %), of ECOG PS 1 (71.4 %), never smokers (71.4 %), and of disease stage IVa (78.6 %) (Table 1). All patients had previously received platinum-based chemotherapy and six also immune-checkpoint inhibitors. As per gene expression analysis, most common RET-fusion was KIF5B-RET (in five patients), followed by CCDC6-RET (in two patients). NGS results are summarised in Supplementary Table 1.

4.2. Follow-up and treatment administration

All 14 patients received at least one dose of alectinib. Median follow-up time was 15.9 months [interquartile range (IQR): 13.2 – 19.9 months]. At the time of data cut-off (31 March 2021), 10 patients (71.4 %) were still on follow-up, while all patients stopped alectinib treatment (administration of last dose in April 2020). Median time-to-treatment failure was 3.7 months (95 % C.I.: 1.1 – 4.5 months). Overall, eight patients (57.1 %) discontinued treatment due to disease progression, three (21.4 %) due to toxicity (erythema multiforme in all cases, related to alectinib), two (14.3 %) due to death, and one was lost to follow-up (Supplementary Fig. 1). This patient was lost to follow-up before any tumour assessment and thus not included in the efficacy cohort. Two patients continued alectinib treatment beyond progression since they derived clinical benefit. Both patients discontinued treatment 4.6 and 1.8 months after first PD due to further disease progression. After alectinib discontinuation, majority of patients received further lines of treatment; platinum-based chemotherapy or RET-inhibitors (selpercatinib, BLU-667 or BOS172738), some in the context of other trials.

Table 1
Baseline characteristics.

	All patients (N = 14)
Age at enrolment	
Median (Range)	61 (38–81)
Sex, n (%)	
Female	10 (71.4)
Male	4 (28.6)
Ethnicity, n (%)	
Caucasian	14 (100.0)
Smoking status, n (%)	
Current	1 (7.1)
Former (≥100 cigarettes in the past during the whole life)	3 (21.4)
Never (0–99 cigarettes during the whole life)	10 (71.4)
ECOG PS, n (%)	
0	4 (28.6)
1	10 (71.4)
Stage, n (%)	
IVa	11 (78.6)
IVb	3 (21.4)
RET fusion type (according to n Counter method), n (%)	
KIF5B-RET (ex15-ex12)	5 (35.7)
CCDC6-RET (ex1-ex12)	2 (14.3)
Not detected	6 (42.9)
Unknown	1 (7.1)

4.3. Efficacy

None of the 13 evaluable patients achieved partial or complete response; thus, the primary endpoint of ORR was 0 %. Based on conditional power calculations under the alternative hypothesis of 35 % ORR, even if the trial had proceeded to completion, the probability of success (i.e., observing 12 responses among the next 28 evaluable patients) would be less than 25 % (as low as 0 % under the observed result).

Nine (69.2 %) patients achieved stable disease as best response. One patient with non-measurable disease at baseline had persistence of one or more non-target lesions (non-CR/non-PD), two patients (15.4 %) had progressive disease, one patient died before any tumour assessment (Supplementary Fig. 2). Supplementary Figure 3 constitutes a longitudinal depiction of tumour size (sum of target lesion's diameters) over time, relative to the baseline measurement for each patient, according to his/her best response to alectinib.

Three patients (23.1 %) achieved disease control at 24 weeks, with the disease control rate being 23.1 % (95 % C.I.: 5.0 % – 53.8 %). Twelve PFS-events (92.3 %) were recorded in the efficacy population. Median PFS was 3.7 months (95 % C.I.: 1.8 – 7.3 months), while the 6-month PFS rate was 30.8 % (95 % C.I.: 9.5 % – 55.4 %) (Figs. 1 & 2). Three deaths were reported (23.1 %). The 12-month OS rate was 92.3 % (95 % C.I.: 56.6 % – 98.9 %), while at data cut-off, median OS-time was not reached. Two patients died due to progression and one patient experienced sudden death not-specified (NOS), not related to alectinib.

4.4. Safety and tolerability

All patients experienced at least one adverse event (AE) of any grade, among 12 (85.7 %) with a treatment-related AE. Seven patients (50.0 %) experienced at least one AE of grade ≥ 3, irrespective of relation to the alectinib. Three patients (21.4 %) discontinued treatment due to erythema multiforme grade 3 the only treatment-related AEs of grade ≥ 3. Four patients (28.6 %) experienced at least one serious AE (SAE), unrelated to alectinib. Treatment-related AEs occurring in ≥ 10 % of patients are shown in Table 2.

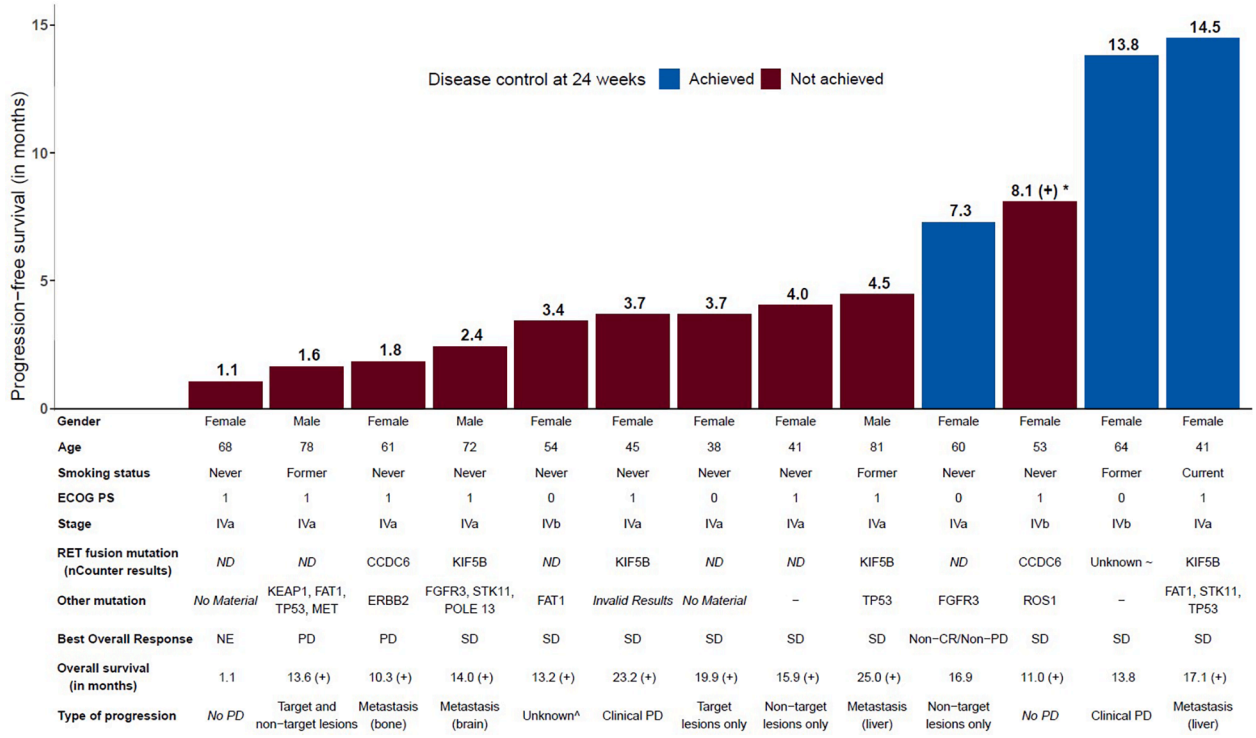

Fig. 1. Progression-free survival (efficacy cohort) with associated patient, tumour and response characteristics. ND: Not detected, KIF5B: KIF5B-RET (ex15-ex12), CCDC6: CCDC6-RET (ex1-ex12), NE: Not evaluable, SD: Stable disease, PD: Progressive disease, Non-CR/Non-PD: Non-Complete response/Non-Progressive disease, + Censored time, * Patient had one tumour assessment at 2 months showing SD and all her subsequent assessments were NE. ~ A RET fusion was detected in tissue, but the type of fusion could not be determined (it wasn't any of the common fusions). Probably patient has a rare RET fusion that might not be clinically relevant. ^ CT scan done at another hospital showing progression (no further info available).

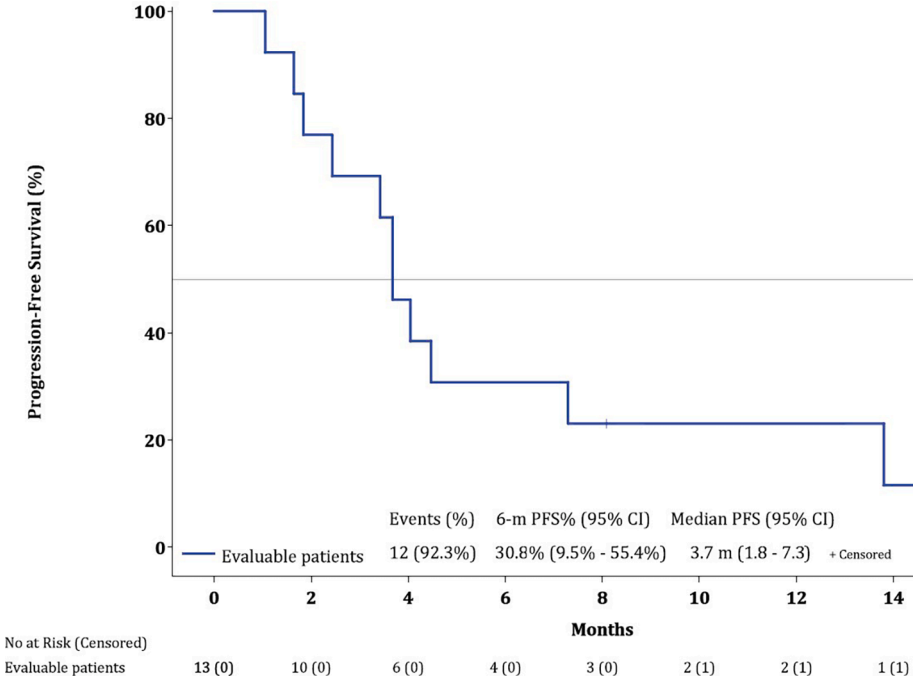

Fig. 2. Progression-free survival (efficacy cohort).

Table 2
Safety overview and adverse events.

	n (%)
Safety cohort	14
Patients experienced:	
Any AE	14 (100.0)
Any AE of grade ≥ 3	7 (50.0)
Any treatment-related AE	12 (85.7)
Any treatment-related AE of grade ≥ 3	3 (21.4)
Any treatment-related AE leading to treatment discontinuation	3 (21.4)
Any treatment-related AE leading to death	–
Any SAE	4 (28.6)
Any SAE leading to death	1 (7.1)
Any treatment-related SAE	–
Treatment-related AEs occurring in ≥ 10 % of patients	
Erythema multiforme	3 (21.4)
Dry skin	3 (21.4)
Fatigue	3 (21.4)
Fever	2 (14.3)
Chills	2 (14.3)
Pain	2 (14.3)
Aspartate aminotransferase increased	2 (14.3)
CPK increased	2 (14.3)
Constipation	2 (14.3)
Mucositis oral	2 (14.3)

5. Discussion

Accrual into our trial was closed prematurely in response to reports for other trials of limited activity of alectinib in patients with RET-fusion NSCLC as well as the emergence of more potent selective RET-inhibitors. Disease stabilisation occurred in 69 % of the 13 evaluable patients but no objective responses (primary endpoint) were observed. Even if the trial had proceeded to accrual completion, the power of detecting a promising ORR would have been very low (less than 25 %). A similar study from Japan reported one objective response out of 34 patients and stable disease in 48 % of patients treated with alectinib [7]. Earlier clinical observations suggested a potential for escalating the alectinib dose in patients with RET-rearranged NSCLC [6]. Whether a too low alectinib dose was responsible for in the lack of anti-tumour activity in these trials remains an open question. In the ALERT-lung trial we used the standard dose of 600 mg twice daily, while the Japanese trial used a slightly reduced dose of 450 mg twice daily. In the light of the emerging of more promising RET-inhibitors, we have refrained from amending the protocol to escalate the alectinib dose.

The high rate of patients who developed erythema multiforme while on treatment with alectinib is unusual and to our knowledge has not been reported before. The fact that this adverse event only occurred in patients who received previous anti-PD-1 therapy suggests a potential causality to the previous immune-checkpoint inhibitor therapy.

Meanwhile, patients with RET-rearranged NSCLC now the option to receive potent and specific RET-inhibitors either as first- or second-line therapy. Selpercatinib has been approved by the US Food and Drug Administration and the European Medicines Agency based on a phase I/II trial, demonstrating a response rate of 54 % after platinum-based chemotherapy and 85 % in treatment-naïve patients [8]. Pralsetinib has also been approved by the same authorities based on a phase I/II trial, demonstrating a response rate of 61 % after platinum pretreatment and of 70 % in treatment-naïve patients [9].

Credit authorship contribution statement

Enriqueta Felip: Conceptualization, Methodology, Supervision. **Egbert F. Smit:** Conceptualization, Methodology, Supervision. **Urania Dafni:** Conceptualization, Methodology. **Roswitha Kammler:** Project administration. **Barbara Ruepp:** Project administration. **Heidi Roschitzki-Voser:** Project administration. **Solange Peters:** Conceptualization, Methodology, Supervision. **Jürgen Wolf:** Conceptualization, Methodology. **Rolf Stahel:** Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Enriqueta Felip reports grants for oncology innovation (GOI) from Merck Healthcare KGAa and Fundación Merck Salud, consulting fees from Amgen, Astra Zeneca, Bristol Myers Squibb, Daichii Sankyo, Eli Lilly, F. Hoffmann-La Roche, Glaxo Smith Kline, Janssen, Merck Serono,

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Dingemans reports grants or contracts from Amgen, Dutch Cancer Society, and HANART, consulting fees from Amgen, Bayer, Boehringer Ingelheim, Sanofi, and Roche, payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen, Pfizer, AstraZeneca, Lilly, and Takeda, reports participation on a Data Safety Monitoring Board or Advisory Board for Takeda and Roche, leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid as chair of EORTC LCG (unapaid). Santiago Viteri reports payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from MSD, BMS, TAKEDA, CURIO, and ROCHE, payments for expert testimony from REDDY PHARMA IBERIA, support for attending meetings and/or travel from OSE IMMUNOTHERAPEUTHICS, MSD, TAKEDA, and MERCK, reports participation on a data safety monitoring board or advisory board for MERCK, JANSSEN, PUMA, ASTRA ZENECA, BMS, TAKEDA, and ROCHE. Christian Britschgi reports consulting fees from Astra Zeneca, Pfizer, Roche, Takeda, Janssen-Cilag, Boehringer-Ingelheim, support for attending meetings and/or travel from AstraZeneca and Takeda. Sinead Cuffe reports support for attending meetings and/or travel from MSD, BMS, and Pfizer. 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Jürgen Wolf reports participation on advisory boards for Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Ignyta, Janssen, Lilly, Loxo, MSD, Novartis, Pfizer, Roche, Seattle Genetics, and Takeda, reports lecture fees from Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Ignyta, Janssen, Lilly, Loxo, MSD, Novartis, Pfizer, Roche, Seattle Genetics, and Takeda, reports research support to institution from BMS, Janssen Pharmaceutica, Novartis, Pfizer. Rolf A. Stahel reports grants or contracts from AstraZeneca, BMS, Daiichi Sankyo, Celgene, Ipsen, Janssen, Mirati, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. 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Appendix A

ETOP 12-17 ALERT-lung Collaborators.

ALERT-lung Steering Committee: Rolf Stahel, Enriqueta Felip, Jürgen Wolf, Egbert F. Smit, Solange Peters, Urania Dafni, Anita Hiltbrunner, Barbara Ruepp, Heidi Roschitzki-Voser, Christian Britschgi, Mariano Provencio, Sinead Cuffe.

ETOP IBCSG Partners Foundation Coordinating Center, Bern, Switzerland: Anita Hiltbrunner, Adriana Gasca-Ruchti, Nino Giacomelli, Rosita Kammler, Nesa Marti, Lionel Nobs, Mariana Pardo-Contreras, Rita Pfister, Anne-Christine Piguet, Sabrina Ribeli-Hofmann, Virginia Rodriguez Martinez, Heidi Roschitzki-Voser, Judith Schroeder, Susanne Roux, Barbara Ruepp, Magdalena Sanchez-Hohl, Mirjam Schneider, Robin Schweri, Sandra Troesch, Isabel Zigomo, Uli Kodjadjiku, Anne Carrer.

European Thoracic Oncology Platform Statistical Office, Frontier Science Foundation-Hellas, Athens, Greece: Urania Dafni, Zoi Tsourti, Panagiota Zygoura, Marie Kassapian, Katerina Vervita, Georgia Dimopoulou, Charitini Andriakopoulou, Androniki Stavrou.

ALERT-lung participating groups:

Spanish Lung Cancer Group (SLCG): Maria Fernandez, Eva Pereira, Anna Hernández, Aina Mur.

Cancer Trials Ireland: Lisa Tucker, Tara Byrne.

ALERT-lung participating centres:

Spain (under the SLCG umbrella).

Hospital Universitario Dexeus, Grupo QuironSalud Barcelona, Principal Investigator: Santiago Viteri.

Hospital Regional Universitario Carlos Haya, Málaga, Principal Investigator: Manuel Cobo Dols.

Hospital Universitario a Coruña, Coruña, Principal Investigator: Rosario Garcia-Campelo.

Hospital Universitario 12 de Octubre, Madrid, Principal Investigator: Santiago Ponce.

Vall d'Hebron University Hospital, Barcelona, Principal Investigator: Enriqueta Felip.

Hospital Universitari Sant Pau, Barcelona, Principal Investigator: Ivana Sullivan.

Hospital Universitario General de Alicante, Alicante, Principal Investigator: Bartomeu Massuti.

Hospital Puerta de Hierro, Madrid, Principal Investigator: Mariano Provencio.

Switzerland.

University Hospital Zurich, Zurich, Principal Investigator: Christian Britschgi.

Fribourg Cantonal Hospital, Fribourg, Principal Investigator: Daniel Betticher.

Geneva University Hospital, Geneva, Principal Investigator: Alfredo Addeo.

Italy.

University Hospital of Turin, Turin, Principal Investigator: Silvia Novello.

Istituto Europeo di Oncologia (IEO), IRCCS, Milan, Principal Investigator: Filippo de Marinis.

Universita di Verona - Department of Medicine, Verona, Principal Investigator: Sara Pilotto.

IRCCS Instituto Tumori Giovanni Paolo II, Bari, Principal Investigator: Domenico Galetta.

The Netherlands.

The Netherlands Cancer Institute Amsterdam, Amsterdam, Principal Investigator: Egbert Smit.

University Medical Center Maastricht, Maastricht, Principal Investigator: Anne-Marie Dingemans.

Ireland (under the Cancer Trials Ireland umbrella).

St. James Hospital, Dublin, Principal Investigator: Sinead Cuffe.

Belgium.

Institut Jules Bordet, Brussels, Principal Investigator: Thierry Berghmans.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.08.008.

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