AGENCIA DE EVALUACIÓN
DE TECNOLOGÍAS SANITARIAS
DE ANDALUCÍA (AETSA)

Alectinib en primera línea de tratamiento en pacientes adultos con carcinoma de pulmón no microcítico avanzado ALK positivo

Informe de evaluación de medicamentos

Informe adoptado de EUnetHTA

Alectinib as monotherapy for the first-line treatment of adult patients with ALK-positive advanced non-small cell lung cancer

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Agencia de Evaluación de Tecnologías Sanitarias de Andalucía **(AETSA)**

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1. Carcinoma pulmonar de células no pequeñas 2. Tratamiento farmacológico

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EUnetHTA adopted HTA report

Agencia de Evaluación de Tecnologías Sanitarias de Andalucía

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La Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) participa como miembro activo en la *Joint Action* 3 de la *European Network for Health Technology Assessment* (EUnetHTA). AETSA asume el compromiso de considerar la implementación a nivel nacional y/o regional de los informes elaborados en el marco de este proyecto.

En la "Guía para la elaboración y adaptación de informes rápidos de evaluación de tecnologías sanitarias"[1], elaborada por la Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud (RedETS), se indica que uno de los objetivos de la colaboración EUnetHTA desde su inicio ha sido promover que la evaluación de tecnologías sanitarias desarrollada por cada una de las agencias que la integran, y los informes que se obtengan de la actividad conjunta a nivel europeo, sean utilizados al máximo en todos los entornos posibles, evitando duplicidades en la evaluación y haciendo la actividad de ETS lo más eficiente posible.

En este contexto de reutilización, el término *uptake* (que traducimos como implementación) hace referencia a la aplicación al ámbito nacional, regional o local de cualquier producto procedente de otra agencia de evaluación de tecnologías sanitarias. Según se describe en la web de EUnetHTA (http://www.eunethta.eu/national-uptake), la implementación puede llevarse a cabo de diferentes formas, entre ellas, la adopción (*adopting*) que consiste en el uso de un informe de ETS sin realizarle ningún cambio a su contenido, excepto la posible traducción al idioma nacional, y que es la forma de implementación seleccionada en este caso.

AETSA ha colaborado en el desarrollo del presente informe de EUnetHTA como revisor. Este informe adoptado presenta, en primer lugar, una traducción del resumen del informe original, seguido del documento íntegro de EUnetHTA, que se encuentra disponible en la web de la red europea. En dicha web también están disponibles el protocolo del proyecto, los comentarios del laboratorio titular de la autorización de comercialización y las respuestas de los autores a los comentarios[2].

Este informe de evaluación proporciona una revisión de la evidencia de un fármaco comercializado con anterioridad, para el que se aprueba una nueva indicación de uso. Su adopción tiene como objetivo servir como herramienta de ayuda a profesionales y grupos implicados en la evaluación y posicionamiento terapéuticos de fármacos de reciente aprobación a nivel nacional.

1. Puñal Roibóo J, Baños Álvarez E, Varela Lema L, Castillo Muñoz MA, Atienza Merino G, Ubago Pérez R, Triñanes Pego Y, Molina López T y López García M en representación del Grupo de trabajo de la Guía para la elaboración y adaptación de informes rápidos de evaluación de tecnologías sanitarias. Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del SNS. Agencia Gallega para la Gestión del Conocimiento en Salud. Unidad de Asesoramiento Científico-técnico, avalia-t; Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2016.

2. Dental and Pharmaceutical Benefits Agency (TLV), Main Association of Austrian Social Security Institutions (HVB), Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ). Rapid assessment on pharmaceutical technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. Alectinib as monotherapy for the first-line treatment of adult patients with ALK-positive advanced non-small cell lung cancer. EUnetHTA Project ID: PTJA03. 2017. Disponible en: http://eunethta.eu/outputs/wp4-ptja03-alectinib-alecensa-monotherapy-first-line-treatment-adult-patients-alk-positive-a

Resumen

Introducción

El objetivo es evaluar la eficacia y seguridad relativas de alectinib, en comparación con crizotinib y ceritinib, en el tratamiento de primera línea en pacientes adultos con cáncer de pulmón no microcítico (CPNM) avanzado, positivo para la quinasa del linfoma anaplásico (ALK).

Descripción de la tecnología y los comparadores

Alectinib es un inhibidor altamente selectivo y potente de la actividad de la tirosina quinasa ALK que se administra por vía oral. Está indicado en monoterapia para pacientes adultos con CPNM avanzado ALK positivo como tratamiento de primera línea y también en pacientes previamente tratados con crizotinib. Alectinib ha demostrado ser activo en las formas mutadas de ALK, incluidas las mutaciones responsables de la resistencia a crizotinib, y es capaz de distribuirse y ser retenido en el Sistema Nervioso Central (SNC).

Crizotinib y ceritinib también están autorizados como tratamientos de primera línea para el CPNM avanzado ALK positivo en la Unión Europea (UE). La guía europea publicada en 2016 recomienda crizotinib como tratamiento estándar, ceritinib no aparece en la guía, ya que ha sido recientemente autorizado para esta población. Ambos fármacos se consideran como comparadores apropiados para alectinib en el tratamiento de primera línea. Sin embargo, el beneficio de alectinib se asocia con una supervivencia libre de progresión (SLP) significativamente más larga, independientemente de si los pacientes tenían metástasis en el SNC al inicio del estudio; eficacia superior a nivel del SNC (reduciendo el número de pacientes con metástasis nuevas o en progresión en el SNC a los 12 meses); menor incidencia de eventos adversos (EA) y mayor tolerabilidad indicada por los pacientes.

La presencia de defectos genéticos que afectan a ALK (estado ALK positivo) debe confirmarse antes del inicio del tratamiento mediante métodos apropiados.

Problema de salud

El cáncer de pulmón ha sido el cáncer más frecuente durante varias décadas y también es la causa más frecuente de mortalidad asociada a cáncer en todo el mundo. El CPNM es el tipo más frecuente de cáncer de pulmón, aunque el análisis molecular permite una mayor subdivisión de los tipos de cáncer de pulmón. El CPNM ALK positivo es más frecuente en personas que nunca han fumado, en un subtipo histológico específico (es decir, adenocarcinomas) y en pacientes más jóvenes, con una edad media en el momento del diagnóstico de 52-58 años.

Generalmente las neoplasias de pulmón se diagnostican en una etapa tardía debido a que son asintomáticas durante períodos prolongados. Por lo tanto, la esperanza de vida de los pacientes con CPNM avanzado o metastásico es baja. La supervivencia a los 5 años después del diagnóstico es inferior al 5%, y generalmente oscila entre 8 y 10 meses.

Para pacientes con CPNM ALK positivo, existen terapias específicas dirigidas que actúan inhibiendo la enzima ALK. Actualmente, el tratamiento con crizotinib es la terapia estándar en Europa, aunque el desarrollo de metástasis cerebrales es aún frecuente. En 2012, en la UE, se estimaron aproximadamente 313,000 casos nuevos y 270,000 muertes relacionadas con el cáncer de pulmón. De esos pacientes, entre 11,000 y 12,000 serían candidatos a recibir, como

tratamiento de inicio, terapia específica frente a ALK.

Metodología

El dossier del laboratorio titular de la autorización de comercialización fue utilizado como punto de partida.

Para los dominios de eficacia y seguridad, el titular de la autorización de comercialización realizó una búsqueda sistemática de la literatura de acuerdo con la estrategia de búsqueda predefinida, en febrero de 2017, en las principales bases de datos *(the Cochrane Central Register of Controlled Trials [CENTRAL], the Database of Abstracts of Reviews of Effects [DARE], the Cochrane Database of Systematic Reviews [CDSR], MEDLINE, Embase, MEDLINE in-process* y publicaciones electrónicas previas a su publicación a través de PubMed). La búsqueda fue evaluada críticamente por los autores de este informe de evaluación. La estrategia de búsqueda para MEDLINE fue reproducida por los autores en PubMed. En octubre de 2017 se actualizó la búsqueda bibliográfica: no se identificó ningún ensayo clínico aleatorizado (ECA) adicional relevante.

También se realizó una búsqueda manual de resúmenes de congresos y de las principales reuniones sobre oncología y cáncer de pulmón abarcando el periodo 2014-2016, de las listas de referencias de las publicaciones incluidas y entre las referencias de revisiones sistemáticas y metanálisis relevantes posteriores al 2012.

Adicionalmente, se realizaron búsquedas en los siguientes registros de ensayos clínicos en enero de 2017: clinicalTrials.gov, en registros de la OMS (metaregistro de la *International Clinical Trials Registry Platform*) y en el registro europeo *EU Clinical Trials Register*.

En diciembre de 2017, los autores actualizaron la búsqueda de guías de práctica clínica en las siguientes bases: *Guidelines International Network, National Guideline Clearinghouse,* y *TRIP Database,* y además realizaron una búsqueda manual.

Los dominios Problema de salud y el uso actual de la tecnología y Descripción y características técnicas de la tecnología se resumieron descriptivamente. Los datos utilizados para los dominios de Eficacia y Seguridad se extrajeron del dossier presentado por el laboratorio tras la verificación por los autores. El riesgo de sesgo a nivel de estudio y a nivel de las variables de resultado para los ECA fue evaluado de forma independiente por los coautores mediante la herramienta de la *Cochrane* y la calidad de la evidencia, según GRADE. Además, el laboratorio realizó una comparación indirecta utilizando el método de Bucher y un metanálisis en red. Los autores evaluaron críticamente estas comparaciones indirectas utilizando un documento de soporte técnico de la *Decision Support Unit* del *National Institute for Health and Care Excellence* (NICE).

Un paciente, diagnosticado recientemente con CPNM ALK positivo y tratado durante cuatro semanas con crizotinib, proporcionó su valoración sobre el impacto de la patología y sobre las variables finales que consideraba más importantes, mediante una hora de entrevista telefónica.

Resultados

Evidencia disponible

La evaluación de la eficacia clínica y seguridad se basa principalmente en tres ECA fase III:

• ALEX (alectinib *vs.* crizotinib),

• ASCEND-4 (ceritinib *vs*. quimioterapia) y

• PROFILE 1014 (crizotinib *vs*. quimioterapia).

El estudio ALEX proporciona una comparación directa entre alectinib y crizotinib, mientras que los resultados de ASCEND-4 y PROFILE 1014 se usan en un metanálisis en red, que también incluyó los resultados del ECA ALEX, para proporcionar una comparación con ceritinib. Además, se realizó un análisis de sensibilidad que incluyó los resultados del estudio PROFILE 1029 (crizotinib *vs*. quimioterapia).

Eficacia clínica

Para la evaluación de la eficacia clínica de alectinib como tratamiento de primera línea de CPNM avanzado ALK positivo se usaron comparaciones directas e indirectas. Los comparadores más relevantes identificados fueron crizotinib y ceritinib, ambos autorizados para la misma indicación.

Para la comparación entre alectinib y crizotinib, se dispone de los datos de comparación directa del estudio ALEX. En el caso de alectinib y ceritinib no hay comparaciones directas, pero se realizó una comparación indirecta a través de crizotinib y regímenes de quimioterapia utilizando los estudios ALEX, ASCEND-4 y PROFILE 1014. Sin embargo, hay que tener en cuenta que en el estudio ASCEND-4, se administraron cuatro ciclos de pemetrexed además de la terapia con cisplatino o carboplatino, seguido de mantenimiento con pemetrexed, mientras que en el estudio PROFILE 1014 se permitieron hasta seis ciclos del mismo esquema, y no se administró terapia de mantenimiento con pemetrexed. También existen diferencias en los porcentajes de pacientes con metástasis en el SNC (factor pronóstico importante) entre los estudios incluidos en el metanálisis en red.

Debido a las incertidumbres en relación a las asunciones de heterogeneidad en los resultados del metanálisis en red, dichos resultados se consideran con precaución.

Supervivencia global

Alectinib vs. crizotinib (ALEX):
En el análisis de datos en la fecha de corte, el 23 % de los pacientes en el grupo de alectinib y el 27 % de los pacientes con crizotinib habían fallecido. La tasa de supervivencia al año fue del 84,3 % y 82,5 %, respectivamente, HR: 0,76 (IC 95 %: 0,48 - 1,20, p = 0,2). La mediana de supervivencia global (SG) no se alcanzó en ninguno de los grupos de tratamiento. El análisis de supervivencia se planificó para cuando se hubieran producido el 50 % de los eventos.

Alectinib vs. ceritinib (metanálisis en red):
No se observaron diferencias estadísticamente significativas entre alectinib y ceritinib en el análisis de la SG mediante un análisis no ajustado, HR: 0,85 (intervalo credibilidad al 95 %, ICr 95 %: 0,41 - 1,73).

Progresión de la enfermedad

Alectinib vs. crizotinib (ALEX):
El estudió alcanzó su objetivo principal en el análisis primario, demostrando un aumento estadísticamente significativo en la SLP evaluada por el investigador. Considerando toda la población, no se alcanzó la mediana de SLP (evaluada por el investigador) para alectinib (IC 95

%: 17,7 meses - no estimable) *vs.* 11,1 meses para crizotinib (IC 95 %: 9,1 - 13,1 meses), HR: 0,47; IC 95 %: 0,34 - 0,65, p <0,0001.

La SLP evaluada por un comité independiente también fue significativamente más prolongada con alectinib que con crizotinib [mediana de SLP de 25,7 meses (IC 95 %: 19,9 meses - no estimable) *vs.* 10,4 meses (IC 95 %: 7,7 – 14,6 meses) HR: 0,50 (IC 95 %: 0,36 - 0,70, p <0,001)].

El tiempo transcurrido hasta la progresión a nivel del SNC fue significativamente más prolongado con alectinib que con crizotinib en la población por intención de tratar [(HR: 0,16; IC 95 %: 0,10 - 0,28; p <0,001); 18 pacientes (12 %) en el grupo de alectinib tuvieron un evento de progresión a nivel del SNC, en comparación con 68 pacientes (45 %) en el grupo de crizotinib].

En general, el efecto del tratamiento fue consistente en todos los subgrupos. El beneficio en SLP fue consistente para pacientes con metástasis basales a nivel del SNC [(HR: 0,40; IC 95 %: 0,25 a 0,64); mediana de SLP para alectinib no es estimable (IC 95 %: 9,2 meses - no estimable) *vs.* mediana de SLP para crizotinib 7,4 meses (IC 95 %, 6,6 - 9,6 meses)] y para pacientes sin metástasis basales a nivel del SNC [(HR: 0,51; IC 95 %: 0,33 - 0,80); mediana de SLP para alectinib no es estimable (IC 95%, NE - NE), mediana de SLP para crizotinib 14,8 meses, (IC 95 %: 10,8 – 20,3 meses)]. Estos resultados indican el beneficio de alectinib sobre crizotinib en ambos subgrupos (información procedente del dossier del laboratorio).

La eficacia relativa en términos de SLP pareció inferior en los subgrupos de fumadores activos y en pacientes con un ECOG de 2. No obstante, el pequeño número de pacientes en estos subgrupos dificulta el establecimiento de conclusiones sólidas.

Alectinib vs. ceritinib (metanálisis en red):

Se observó una SLP superior de forma estadísticamente significativa para alectinib frente a ceritinib en el metanálisis en red, HR: 0,41 (ICr 95 %: 0,25 - 0,67). Este hallazgo fue consistente en el subgrupo de pacientes con metástasis en el SNC al inicio del estudio, HR: 0,30 (ICr 95 %: 0,13 - 0,71). Los resultados deben interpretarse con cautela debido a la incertidumbre existente.

Calidad de vida relacionada con la salud

Se observó una tendencia a favor de alectinib frente a crizotinib en términos de estado de salud global informado por el paciente / calidad de vida relacionada con la salud (CVRS) (HR: 0,72; IC 95 %: 0,38 - 1,39). En general, los pacientes en el grupo de alectinib describieron una mejoría clínicamente significativa en la CVRS y mejoría en múltiples síntomas de cáncer de pulmón durante un tiempo más prolongado que los pacientes en el grupo con crizotinib. Sin embargo, las diferencias no fueron estadísticamente significativas.

Por otra parte, no hay información disponible sobre la CVRS para alectinib *vs.* ceritinib.

Seguridad

Los resultados de seguridad se basan en el ECA ALEX y en los estudios incluidos en el metanálisis en red. Además, las frecuencias de EA de los tres fármacos considerados se presentaron a partir de los resúmenes de las características del producto (fichas técnicas) de alectinib, crizotinib y ceritinib. Se refleja el perfil de seguridad establecido por la Agencia Europea de Medicamentos (EMA), basándose en todos los estudios relevantes con las dosis aprobadas.

Los EA más frecuentes (≥ 20 %) para alectinib fueron estreñimiento (35 %), edema (30 %, incluyendo edema periférico, edema generalizado, edema del párpado, edema periorbitario, edema facial y edema localizado) y mialgia (28 %; incluyendo mialgia y dolor musculoesquelético).

En una comparación indirecta no ajustada o *naïve* de las frecuencias de EA indicadas en las fichas técnicas, y sin considerar la duración mediana del tratamiento (que fue superior para alectinib), las frecuencias de EA fueron inferiores para alectinib en comparación con crizotinib y ceritinib para la diarrea (16 %, 54 % y 82 %, respectivamente), vómitos (11 %, 51 % y 63 %, respectivamente), náuseas (19 %, 57 % y 75 %, respectivamente) y fatiga (no identificada como EA, 30 % y 48 %, respectivamente). Estos EA afectaron a la tolerabilidad y la calidad de vida de los pacientes.

Otros eventos adversos que pueden afectar a la calidad de vida fueron, por ejemplo, los edemas, que no se identificaron como una EA para ceritinib, pero que fueron frecuentes con alectinib (30 %) y crizotinib (47 %); y mialgia, que se informó solo en alectinib (28 %).

La neumonitis / enfermedad pulmonar intersticial también fue menos frecuente con alectinib que con crizotinib y ceritinib (0,7 %, 3 % y 2 %, respectivamente).

Los tres agentes causaron anemia (15 % - 17 %). Crizotinib también causó neutropenia (22 %). Sin embargo, no se identificaron infecciones como EA para crizotinib.

Los trastornos visuales fueron similares para alectinib y ceritinib, con una tasa del 7 % - 9 %, mientras que la tasa fue marcadamente superior para crizotinib (63 %).

La obtención de resultados anormales de pruebas de laboratorio a nivel hepático fue menos frecuentes con alectinib.

Las frecuencias de EA hepáticos graves fueron altamente similares en todos los fármacos; daño hepático inducido por fármacos 0,7 % (alectinib), insuficiencia hepática <1 % (crizotinib) y hepatotoxicidad 1,1 % (ceritinib).

La bradicardia fue menos frecuente con ceritinib (2 %) en comparación con alectinib (9 %) y crizotinib (13 %). A diferencia de alectinib, tanto crizotinib como ceritinib están asociados con la prolongación del intervalo QT (4 % y 10 %, respectivamente). Esto puede tener consecuencias potencialmente graves, incluida la muerte súbita. No obstante, esos resultados son muy infrecuentes. El riesgo de prolongación del intervalo QT afecta al tratamiento de los pacientes y algunos pacientes pueden requerir mayor monitorización.

Se observó rash en el 18%, 13 % y 20 % de los pacientes tratados con alectinib, crizotinib y ceritinib, respectivamente.

La fotosensibilidad se identificó como EA para alectinib (9 %), aunque no para los otros dos inhibidores de ALK.

Las tasas de EA que llevaron a la interrupción del tratamiento fueron del 11 %, 13 % y 11 %, respectivamente.

Las tasas de EA que condujeron a la interrupción de la dosis administrada fueron del 19 %, 25 % y 69 %, respectivamente. El metanálisis en red indica menos EA de grado 3 o 4 con alectinib que con ceritinib, y la ausencia de diferencias significativas para las interrupciones de tratamiento debidas a EA.

Aspectos éticos, organizacionales, sociales y legales

No se identificaron cuestiones específicas relacionadas con aspectos éticos, organizativos, sociales o legales tras la aplicación de la lista de verificación del *Rapid REA*.

Participación de pacientes

Un paciente participó en este informe de evaluación. Este hizo hincapié en que los aspectos más importantes para los pacientes en relación con un nuevo medicamento para el tratamiento del CPNM son la prolongación de la supervivencia, menos EA y ausencia de consecuencias económicas.

Evidencia futura

Los resultados de SG del ECA ALEX serán proporcionados cuando se alcance una tasa de eventos del 50%.

Financiación

El estado de financiación de alectinib, como primera línea en monoterapia se decidirá a nivel nacional, en los diferentes países de la UE, tras la extensión de la autorización de comercialización.

Discusión

Las limitaciones más importantes en este informe de evaluación son la inmadurez de los resultados de SG en la comparación directa de alectinib y crizotinib, y la elevada incertidumbre en los resultados de la comparación indirecta entre alectinib y ceritinib.

Con alectinib se obtuvo un aumento estadísticamente significativo y sustancial en la SLP en comparación con crizotinib en el estudio ALEX. La mediana de SLP determinada por el investigador no se alcanzó en el grupo de alectinib en el análisis realizado en el momento de corte. No obstante, en la SLP determinada por el comité independiente se observó una diferencia entre las medianas de 15,3 meses (25,7 *vs*. 10,4 meses, respectivamente).

En relación a otras variables, también se demostró la superioridad de alectinib frente a crizotinib en la variable secundaria tiempo hasta la progresión a nivel del SNC. Esto tiene una gran relevancia clínica, ya que las metástasis en el SNC y la progresión afectan tanto a los síntomas, como a la calidad de vida, y al pronóstico de los pacientes.

La tasa de respuesta global fue numéricamente mayor con alectinib (83 % *vs*. 76 %). No obstante, no se observaron diferencias estadísticamente significativas. Sin embargo, la duración de la respuesta fue significativamente mayor para alectinib (mediana aún no alcanzada *vs*. 11,1 meses en el grupo de crizotinib, p <0,0001).

En la comparación directa de alectinib y crizotinib, la calidad de la evidencia es elevada para la mayoría de las variables de resultado (SLP, tasa de respuesta y tiempo hasta la progresión a nivel del SNC); moderada para los principales resultados de seguridad; y muy baja para la calidad de vida (tiempo hasta el deterioro en la escala EORTC QLQ-30). Esta última variable se asocia con un alto riesgo de sesgo debido al diseño abierto del ECA y al reducido número de cuestionarios completados en el momento basal. Por otra parte, los resultados de SLP evaluada por el investigador fueron consistentes con los resultados de los revisores independientes cegados, lo que sugiere ausencia de sesgo en las evaluaciones realizadas por los investigadores.

Dado que la población en el estudio ALEX se corresponde esencialmente con la población con CPNM ALK positiva, se puede asumir que la evidencia disponible es aplicable a

la práctica clínica.

En la comparación indirecta de alectinib y ceritinib, los resultados se derivaron de un metanálisis en red de efectos fijos. Debido al número limitado de estudios, no se realizó un ajuste de las características de los pacientes a nivel de estudio.

Hubo el mismo porcentaje de EA de cualquier grado para alectinib y crizotinib (97 %) en el ECA fase III ALEX. Los EA graves ocurrieron con una frecuencia similar en los pacientes en ambos grupos de tratamiento (29 % con crizotinib y 28 % con alectinib).

En el ECA ALEX, la incidencia de EA que condujeron a la interrupción del tratamiento fue similar entre alectinib y crizotinib (11 % *vs*.13 %). Los pacientes con alectinib tuvieron una mayor exposición al tratamiento (17,9 meses vs. 10,7 meses); la incidencia de interrupciones del tratamiento y reducciones de dosis fue numéricamente inferior, y la frecuencia acumulativa de EA de grado 3 o superior más baja (41 % *vs*. 50 %).

Los únicos EA graves que se produjeron con una incidencia mayor en el grupo de alectinib fueron insuficiencia renal aguda (3 % *vs*. 0 %) e infección pulmonar (2 % *vs*. 0 %). Para EA de cualquier grado, la frecuencia de mialgia (16 % *vs*. 2 %) y anemia (20 % *vs*. 5 %) fue superior para alectinib *vs*. crizotinib.

Alectinib parece tener un perfil de seguridad más favorable que crizotinib en relación a los EA no graves que afectan a la calidad de vida, como náuseas, diarrea y vómitos. Lo que se ve respaldado por una menor frecuencia de interrupciones de tratamiento y reducciones de dosis.

Las comparaciones indirectas entre alectinib y ceritinib se realizaron usando un metanálisis en red y comparaciones no ajustadas o *naïve* de las frecuencias de EA. Ambos análisis indicaron un perfil general de seguridad superior para alectinib *vs*. ceritinib, con la excepción de algunos EA no graves. Debido al alto grado de incertidumbre inherente en cualquier comparación indirecta, no es posible una conclusión sólida. En base a la evidencia disponible, sería razonable asumir que el perfil de seguridad de alectinib no es peor que el de ceritinib.

El paciente involucrado en este informe de evaluación enfatizó que los aspectos más importantes relacionados con el tratamiento del CPNM son el aumento de la supervivencia con un nuevo medicamento, menos EA y la ausencia de implicaciones económicas para los pacientes. Como limitación hay que resaltar que esta información proviene de un único paciente y que no se involucró en este informe rápido a ninguna organización de pacientes. Por lo tanto, falta una visión más amplia de la perspectiva de los pacientes, específicamente la de los pacientes con síntomas pulmonares específicos y con mayor duración de tratamiento con crizotinib. Estos aspectos podrían impactar en las experiencias del paciente con la enfermedad, tratamiento y las respuestas relacionadas con preguntas específicas.

Conclusiones

En la comparación directa, evidencia de elevada calidad, alectinib demostró un aumento sustancial y estadísticamente significativo en la SLP. También se asoció con un aumento estadísticamente significativo del tiempo hasta la progresión a nivel del SNC en comparación con crizotinib. Esto tiene gran relevancia clínica, ya que las metástasis en el SNC y la progresión afectan tanto a los síntomas, como a la calidad de vida y al pronóstico de los pacientes. Los datos de SG son inmaduros y, por lo tanto, impiden el establecimiento de conclusiones sólidas.

En la comparación indirecta, alectinib obtiene mejores resultados frente a ceritinib en términos de SLP. No obstante, debido a la incertidumbre en cuanto a la adecuación de la comparación, este resultado se debe considerar con cautela.

En relación al perfil de seguridad, en la comparación directa, los EA graves y los EA que

condujeron a la interrupción del tratamiento se produjeron con frecuencias similares tanto para alectinib como para crizotinib. Alectinib parece tener un perfil de seguridad más favorable en comparación con crizotinib en relación a los EA no graves que tienden a afectar la calidad de vida, así como los EA de grado ≥3. Estos resultados son respaldados por menor interrupción de tratamiento y reducciones de dosis observadas para alectinib en la comparación directa con crizotinib. Los porcentajes de diarrea, vómitos y náuseas fueron marcadamente inferiores para alectinib. La mialgia y la anemia de cualquier grado se presentaron con mayor frecuencia en alectinib que crizotinib.

Si bien las conclusiones sobre la seguridad relativa de alectinib en comparación con ceritinib deben tomarse con precaución, tanto los resultados del metanálisis en red como la comparación *naïve* de los perfiles de EA indican un perfil de seguridad general más favorable para alectinib.

Los pacientes que recibieron alectinib tuvieron una mejoría clínicamente significativa en términos de calidad de vida mantenida durante más tiempo en comparación con los pacientes que recibieron crizotinib. En general, se observó una tendencia a favor de alectinib, pero la diferencia no fue estadísticamente significativa.

Como solo se entrevistó a un paciente, no se pueden extraer conclusiones generales en este aspecto.

EUnetHTA Joint Action 3 WP4

Rapid assessment of pharmaceutical technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

ALECTINIB AS MONOTHERAPY FOR THE FIRST-LINE TREATMENT OF ADULT PATIENTS WITH *ALK*-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

Project ID: PTJA03

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Disclaimer

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All authors and dedicated reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA declaration of interest and confidentiality undertaking form.

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LIST OF ABBREVIATIONS

AAZ	Agency for Quality and Accreditation in Health Care and Social Welfare
ADR	adverse drug reaction
AE	adverse event
AIC	Akaike's information criterion
ALK	anaplastic lymphoma kinase
AUC	area under the curve
BIC	Bayesian information criterion
Bucher IC	Bucher indirect comparison
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CrI	credible interval
CT	computed tomography
DARE	Database of Abstracts of Reviews of Effects
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridisation
HR	hazard ratio
HRQoL	health-related quality of life
HVB	Hauptverband der österreichischen Sozialversicherungsträger
IHC	immunohistochemistry
IRC	independent review committee
ITT	intent to treat
MAH	marketing authorisation holder
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
PR	partial response
RCT	randomised controlled trial

REA	Relative Effectiveness Assessment
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1
SmPC	summary of product characteristics
TKI	tyrosine kinase inhibitor
TLV	Tandvårds- och läkemedelsförmånsverket, Dental and Pharmaceutical Benefits Agency
TNM	tumour, node, metastasis
WBRT	whole-brain radiation therapy
WHO	World Health Organization

SUMMARY OF RELATIVE EFFECTIVENESS OF ALECENSA (ALECTINIB)

Scope

The scope can be found here: Scope.

Introduction

The objective is to assess the relative effectiveness and safety of alectinib as first-line monotherapy for adult patients with *ALK*-positive advanced non-small cell lung cancer (NSCLC) in comparison with crizotinib and ceritinib.

Description of technology and comparators

Alectinib (Alecensa®) is a potent, highly selective, central nervous system (CNS)-active inhibitor of anaplastic lymphoma kinase (ALK) which is taken orally. As monotherapy, it is indicated for the first-line treatment of adult patients with *ALK*-positive advanced NSCLC and also for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib [B0001, A0020]. Alectinib demonstrated activity against mutant forms of ALK, including mutations responsible for resistance to crizotinib, and is able to distribute itself into and be retained within the CNS [B0001].

Crizotinib and ceritinib are also approved as first-line monotherapy for *ALK*-positive advanced NSCLC in the European Union (EU). Because ceritinib has been authorised only recently in this setting, European guideline published in 2016 currently recommend crizotinib as the standard of care. Both compounds are considered as appropriate comparators for alectinib in the first-line treatment indication, however [B0001, A0020].

The claimed benefit of alectinib is related to a significantly longer progression-free survival (PFS), irrespective of whether patients had CNS metastases at the baseline; superior efficacy in the CNS (reducing the number of patients with new or progressive CNS metastases at 12 months); lower incidence of adverse events (AEs) and greater tolerability reported by patients [B0002].

The presence of genetic defects affecting ALK (‘*ALK*-positive’ status) has to be confirmed in advance by appropriate methods [B0008].

Health problem

Lung cancer has been the most common cancer overall for several decades and is also the most common cause of cancer-related death worldwide. NSCLC is the most frequent type of lung cancer, but molecular analysis allows further subdivision of lung cancer. *ALK*-positive NSCLC is more frequent in never smokers, in a specific histologic subtype (i.e., adenocarcinomas) and in younger patients (mean age at diagnosis 52–58 years) [A0002].

Since lung cancers are asymptomatic for long periods, they are usually diagnosed at a late stage. Therefore life expectancy of patients with advanced or metastasised NSCLC is low. Less than 5% of these patients are alive 5 years after diagnosis, and they usually survive for only about 8–10 months [A0004].

For patients with *ALK*-positive NSCLC, specific therapies targeting ALK are available. Currently, crizotinib therapy is the standard of care in Europe, but development of brain metastases is still commonly observed [A0025]. In the European Union, about 313,000 new cases and 270,000 lung cancer-related deaths were estimated in 2012. Of the patients involved, about 11,000–12,000 would be eligible to receive specific ALK-targeted therapy as initial therapy [A0023].

Methods

The completed part of the EUnetHTA submission file from the manufacturer was used as the starting point.

For the effectiveness and safety domains, a systematic literature search, according to the predefined search strategy, was performed by the marketing authorisation holder (MAH) in February 2017 in key clinical electronic databases (the Cochrane Central Register of Controlled Trials [CENTRAL], the Database of Abstracts of Reviews of Effects [DARE], the Cochrane Database of Systematic Reviews [CDSR], MEDLINE, Embase, MEDLINE in-process and electronic publications ahead of print through PubMed) and was critically assessed by the authors of this assessment. The search strategy relevant for MEDLINE was reproduced by the authors of

this assessment for PubMed. The update of the literature search was conducted in October 2017: no other relevant randomised controlled trial (RCT) was identified.

A hand search was also performed on conference proceedings for major oncology and lung cancer meetings (2014–2016) and reference lists of included publications and of relevant systematic reviews and meta-analyses from 2012 onwards. The following clinical trial registries were searched in January 2017: ClinicalTrials.gov (http://www.clinicaltrials.gov/), World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

A separate guideline update search (Guidelines International Network, National Guideline Clearinghouse, TRIP Database and hand search) was performed by the authors in December 2017.

The health problem and current use of the technology domain and the description and technical characteristics of technology domain were only summarised descriptively. Data used for the effectiveness and safety domains were extracted from the file submitted by the MAH and verified by the authors. The risk of bias at the study level and the outcome level for the RCTs was independently assessed by the co-authors according to the Cochrane Risk of Bias tool and the quality of evidence according to GRADE. In addition, an indirect comparison using the Bucher method and a network meta-analysis (NMA) were performed by the MAH and critically appraised by the authors using a technical support document from the Decision Support Unit of the National Institute for Health and Care Excellence [1] (Appendix 6. Indirect comparisons – statistical aspects).

One individual patient who was recently diagnosed with *ALK*-positive NSCLC and being treated for four weeks with crizotinib was willing to provide relevant input on the impact of the condition and on the most important endpoints through a one hour telephone interview.

Results

Available evidence

The assessment of clinical effectiveness and safety is based primarily on three phase III randomised active-controlled trials:

- ALEX (alectinib vs. crizotinib),
- ASCEND-4 (ceritinib vs. chemotherapy) and
- PROFILE 1014 (crizotinib vs. chemotherapy).

The ALEX study thus provides a direct comparison between alectinib and crizotinib, while the results from ASCEND-4 and PROFILE 1014 are used in an NMA that also included results from ALEX to provide a comparison against the other comparator, ceritinib. In addition, a sensitivity analysis was performed that included results from PROFILE 1029 (crizotinib vs. chemotherapy).

Clinical effectiveness

For the assessment of clinical effectiveness of alectinib as first-line treatment of *ALK*-positive advanced NSCLC, both direct and indirect comparisons were used. Crizotinib and ceritinib, both approved for the first-line treatment of *ALK*-positive advanced NSCLC, were identified as the most relevant comparators.

For the comparison between alectinib and crizotinib, direct head-to-head data from the clinical study ALEX are available. For alectinib and ceritinib, there are no direct comparisons, but an indirect comparison was performed via crizotinib and chemotherapy regimens through the studies ALEX, ASCEND-4 and PROFILE 1014. It is noted, however, that in ASCEND-4, 4 cycles of pemetrexed plus cisplatin or carboplatin therapy, followed by maintenance pemetrexed therapy, were used; while in PROFILE 1014 up to 6 cycles of the same regimen were allowed, but there was no maintenance therapy with pemetrexed. Differences in the proportion of patients with CNS metastasis, an important prognostic factor, also exist between the studies included in the NMA.

Because of the uncertainties involved and possible dependencies regarding the heterogeneity assumptions on the results in the NMA, these results are considered with caution.

Overall survival [D0001]

Alectinib versus crizotinib (ALEX):

At the data cutoff point, 23% of patients in the alectinib arm and 27% of patients in the crizotinib arm had died, with a 1-year survival rate of 84.3% and 82.5%, respectively, with a hazard ratio (HR) of 0.76 (95% confidence interval, CI, 0.48, 1.20, *p*=0.2). Median overall survival (OS) was not reached in either treatment arm. Survival analysis has been planned after 50% of events have occurred [2].

Alectinib versus ceritinib (NMA):

No statistically significant differences between alectinib and ceritinib were observed in the unadjusted NMA OS analysis; HR 0.85 (95% Credible interval, CrI, 0.41, 1.73).

Disease progression [D0006]

Alectinib versus crizotinib (ALEX):

The trial met its primary endpoint at the primary analysis, demonstrating a statistically significant increase in progression-free survival (PFS) by investigator assessment. In the entire population the median PFS (investigator assessed) for alectinib was not reached (95% CI, 17.7 months to not estimable) versus 11.1 months for crizotinib (95% CI, 9.1, 13.1 months); HR 0.47 (95% CI, 0.34, 0.65, *p*<0.0001).

Independent review committee (IRC)-assessed PFS was also significantly longer with alectinib than with crizotinib (median PFS 25.7 months (95% CI, 19.9 months, not estimable] vs. 10.4 months (95% CI, 7.7, 14.6 months); HR for disease progression or death 0.50 (95% CI, 0.36, 0.70, *p*<0.001) [1].

The time to CNS progression was significantly longer with alectinib than with crizotinib in the intention-to-treat population (cause-specific HR 0.16, (95% CI, 0.10, 0.28), *p*<0.001); 18 patients (12%) in the alectinib group had an event of CNS progression, as compared with 68 patients (45%) in the crizotinib group.

The treatment effect was generally consistent across the subgroups. The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, (95% CI, 0.25, 0.64); median PFS for alectinib not estimable (95% CI, 9.2 months to not estimable); median PFS for crizotinib 7.4 months (95% CI, 6.6, 9.6 months) and for patients without CNS metastases at the baseline (HR 0.51, (95% CI, 0.33, 0.80); median PFS for alectinib not estimable, (95% CI, not estimable to not estimable); median PFS for crizotinib 14.8 months, (95% CI, 10.8, 20.3 months), indicating benefit of alectinib over crizotinib in both subgroups (MAH submission).

The relative PFS benefit appeared lower in the subgroups of active smokers and patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2, although the small numbers of patients in these subgroups preclude any firm conclusions [1].

Alectinib versus ceritinib (NMA):

Statistically significantly longer PFS in terms of 95% credible intervals (CrI) was observed for alectinib versus ceritinib in the NMA, HR 0.41 (95% CrI, 0.25, 0.67). This finding was consistent in the subgroup of patients with CNS metastases at the baseline, NMA HR 0.30 (95% CrI, 0.13, 0.71). The results should be interpreted with caution because of the uncertainties involved.

Health-related quality of life [D0012, D0013]

Quality of life

A trend favouring alectinib over crizotinib was observed for patient-reported global health status/health-related quality of life (HRQoL) (HR 0.72, 95% CI, 0.38,1.39). Overall, patients in the alectinib arm reported clinically meaningful improvement in HRQoL and improvement in multiple lung cancer symptoms for a longer duration of time than patients in the crizotinib arm, but the differences were not statistically significant.

No information was available on HRQoL from the NMA for alectinib versus ceritinib.

Safety [C0008]

The safety results are based on the ALEX trial and the studies included in the NMA. In addition, adverse drug reaction (ADR) frequencies are presented from the summaries of product characteristics (SmPCs) of Alecensa, Xalkori (crizotinib) and Zykadia (ceritinib). The SmPC frequencies reflect the European Medicines Agency (EMA) established safety profile and are based on all relevant studies at the approved dose. The most common (≥20%) ADRs for alectinib were constipation (35%), oedema (30%; including peripheral oedema, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedema) and myalgia (28%; including myalgia and musculoskeletal pain).

In a naïve comparison of the ADR frequencies in the SmPCs, and without consideration of the longer median treatment length for alectinib, the frequencies were lower for alectinib than for crizotinib and ceritinib for diarrhoea (16%, 54% and 82%, respectively), vomiting (11%, 51% and 63%, respectively), nausea (19%, 57% and 75%, respectively), and fatigue (not identified as ADR, 30% and 48%, respectively). These are ADRs that impact tolerability and everyday quality of life.

Other reactions that may impact quality of life include, for example, oedema, which was not identified as an ADR for ceritinib, but was common with alectinib (30%) and crizotinib (47%), and myalgia, which was reported only for alectinib (28%).

Pneumonitis/interstitial lung disease was also less frequent with alectinib than with crizotinib and ceritinib (0.7%, 3% and 2%, respectively).

All three agents caused anaemia (15%–17%), while crizotinib also caused neutropenia (22%). No infections were identified as ADRs for crizotinib, however.

Vision disorders were similar for alectinib and ceritinib at a rate of 7%–9%, but the rate was markedly higher for crizotinib (63%).

Abnormal liver laboratory results appeared least common with alectinib, while acknowledging that a comparison based on the varying items in the SmPCs is difficult.

The frequencies of severe liver reactions were largely similar across the drugs (drug-induced liver injury 0.7% (alectinib), hepatic failure <1% (crizotinib) and hepatotoxicity 1.1% (ceritinib).

Bradycardia was less common with ceritinib (2%) compared with alectinib (9%) and crizotinib (13%). Unlike alectinib, both crizotinib and ceritinib are associated with QT interval prolongation (4% and 10%, respectively). This can have potentially serious consequences, including sudden death, but such outcomes are very rare. The risk of QT interval prolongation affects the handling of patients and may require more monitoring of some patients.

Rash occurred in 18% of patients treated with alectinib, 13% of patients treated with crizotinib and 20% of patients treated with ceritinib.

Photosensitivity was identified as an ADR for alectinib (9%), but not for the other two ALK inhibitors.

The rates of AEs leading to treatment discontinuation were 11%, 13% and 11% respectively.

The rates of AEs leading to dose interruption were 19%, 25% and 69% respectively. The NMA indicates the presence of significantly fewer grade 3 or 4 AEs with alectinib than with ceritinib, and no significant differences were observed for discontinuations due to AEs.

Ethical, organisational, patient and social and legal aspects

No specific aspects concerning ethical, organisational, patient and social, or legal aspects were identified from the Rapid REA Checklist.

Patient involvement

One patient who was involved in this assessment, emphasised that the most important issues concerning treatment for NSCLC are life-extension by a new drug, fewer side effects and no financial implications for patients.

Upcoming evidence

OS results from the ALEX trial will be reported at the 50% event rate.

Reimbursement

The reimbursement status of alectinib, as first-line monotherapy, in different EU countries will be decided at the national level after extended marketing authorisation.

Table 0.1. Summary of findings for alectinib, primary analysis 9 February 2017

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (number of studies)	Quality	Comments
	Risk with alectinib	Risk with crizotinib				
OS	1-year survival rate 84.3%	1-year survival rate 82.5%	HR 0.76 (0.48, 1.20); p=0.24	303 (1)	Low	Immature data (interim analysis). At the data cutoff point 23% of patients in the alectinib arm and 27% of patients in the crizotinib arm had died, with a 1-year survival rate of 84.3% and 82.5%, respectively. Median OS was not reached in either treatment arm. Survival analysis has been planned after 50% of events have occurred
PFS	Median: NE (17.7 months to NE)	Median: 11.1 months (9.1–13.1 months)	HR 0.47 (0.34, 0.65); p<0.0001	303 (1)	High	Of note, investigator assessed PFS was consistent with independently assessed PFS.
ORR	75.5% (67.8%–82.1%)	82.9% (76.0%–88.5%)	—	303 (1)	High	—
Time to CNS progression	Rate of events of CNS progression: 18 (of 152, 12%)	Rate of events of CNS progression: 68 (of 151, 45%)	Cause-specific HR: 0.16 (0.10, 0.28); p<0.0001	303 (1)	High	—
Total proportion of patients with ≥1 AE	97%	97%	—	303 (1)	Moderate	Open label
Total proportion of patients with serious AE	28%	29%	—	303 (1)	Moderate	Open label
Time to deterioration in EORTC QLQ-C30 global health score	—	—	HR 0.72 (0.38, 1.39); p =0.326	197 (1)	Very low	Low numbers of completed questionnaires at the baseline ; open label

Abbreviations: AE=adverse event; CI=confidence interval; CNS=central nervous system; EORTC=European Organisation for Research and Treatment of Cancer; HR=hazard ratio; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Discussion

The most important limitations in this assessment are the immature OS data in the direct comparison of alectinib and the comparator crizotinib, and the high uncertainty in the indirect comparison of alectinib with ceritinib.

Alectinib resulted in a substantial statistically significant increase in PFS compared with crizotinib in the ALEX study. While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs 10.4 months, respectively).

Concerning further endpoints, the secondary endpoint time to CNS progression also demonstrated superiority of alectinib over crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients. The ORR was numerically higher with alectinib (83% vs 76%) although not statistically significantly different. However, the duration of response was significantly longer for alectinib with the majority of responses ongoing (median not yet reached vs 11.1 months in the crizotinib arm, $p<0.0001$).

In the direct comparison of alectinib and the comparator crizotinib, the quality of evidence is high for the majority of outcomes (PFS, ORR, Time to CNS progression), moderate for major safety outcomes and very low for the outcome related to QoL (i.e. time to deterioration in EORTC QLQ-30 global health score). The latter is associated with a high risk of bias due to the open-label design and low baseline values of completed questionnaires at the baseline. The primary investigator-assessed PFS results were consistent with those of the blinded independent reviewers, suggesting a lack of bias in investigator assessments.

Since the population in the ALEX study essentially corresponds to the *ALK*-positive NSCLC population, it can be assumed that the available evidence is applicable.

In the indirect comparison of alectinib and the comparator ceritinib, the results were derived from the fixed effects NMA model. Due to the limited number of studies, no adjustment of patient characteristics was made at the study level.

The same numbers of AEs of any grade were reported for both alectinib and crizotinib (97%) in the randomized phase III ALEX trial. Serious AEs occurred at a similar frequency in patients in both treatment arms (29% with crizotinib, 28% with alectinib).

In the ALEX trial the incidence of AEs leading to treatment discontinuation was similar with alectinib compared with crizotinib (11% vs. 13%). The patients in the alectinib arm had longer exposure to treatment (17.9 months vs. 10.7 months for crizotinib) but a numerically lower incidence of treatment interruptions and dose reductions and a lower cumulative frequency of grade 3 or higher AEs (41% vs. 50% in the crizotinib arm).

The only serious AEs which occurred at a higher (≥2% difference) incidence in the alectinib arm were acute kidney injury (3% with alectinib vs. 0% with crizotinib) and lung infection (2% vs. 0%). For any grade AEs, myalgia was reported more frequently for alectinib than crizotinib (16% vs. 2%) and anaemia (20% vs. 5%).

Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious AEs that tend to affect quality of life, such as nausea, diarrhoea and vomiting. This impression is also supported by lower observed frequencies of treatment interruptions and dose reductions.

Indirect comparisons between alectinib and ceritinib were performed using an NMA and a naïve comparison of the established AE frequencies as per the SmPCs, respectively. Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-serious AEs. Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Based on the available data, it might be considered reasonable to assume that the overall burden of toxicity from alectinib is at least not worse than that of ceritinib.

The patient involved emphasised that the most important issues concerning treatment for NSCLC are life-extension by a new drug, fewer side effects and no financial implications for patients. Limitations are that only one patient and not a patient organisation was involved in this rapid REA. Thus, a broader patient view is missing, specifically that of patients with specific lung symptoms and with a longer treatment duration with crizotinib. This might have impacted on patient's experiences with the condition, treatment and answers related to specific questions.

Conclusion

From direct comparison, based on high quality of evidence, alectinib demonstrated a substantial and statistically significant increase in PFS. It is also associated with a statistically significant longer time to CNS progression compared to crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients. The OS data are immature and therefore preclude firm conclusions.

From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS, but because of uncertainties regarding the adequacy of the comparison, this observed result has to be regarded as unsure.

From direct comparison, the serious adverse events and adverse events leading to treatment discontinuation occurred at similar frequencies for both alectinib and crizotinib. Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious adverse events that tend to affect quality of life, as well as severe (grade ≥3) events. This notion is supported by the lower frequencies of treatment interruptions and dose reductions observed for alectinib in the direct comparison to crizotinib. Thus markedly lower frequencies for alectinib were reported for diarrhoea, vomiting and nausea. For any grade adverse event, myalgia and anaemia were reported more frequently for alectinib than crizotinib.

While conclusions on relative safety compared with ceritinib should be made with caution, both the NMA and the comparison of the established AE profiles in the SmPCs indicate an overall superior safety profile of alectinib.

Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. Overall a trend favouring alectinib was observed in HRQoL, but the difference was not statistically significant.

As only one patient was interviewed, no general conclusions can be drawn.

1 SCOPE

Table 1.1. Scope according to population, intervention, comparison, outcomes and study design analysis

Description	Project scope
Population	• First-line treatment of adult patients with *ALK*-positive advanced NSCLC • ICD-10: C34.xx • MeSH terms: carcinoma, non-small-cell lung (C04.588.894.797.520.109.220.249; C08.381.540.140.500; C08.785.520.100.220.500) • A validated ALK assay is necessary for the selection of *ALK*-positive NSCLC patients. *ALK*-positive NSCLC status should be established before initiation of alectinib therapy • Subgroup analysis: patients with brain metastases at the baseline
Intervention	• The recommended dose of alectinib is 600 mg (four 150-mg capsules) taken twice daily with food (total daily dose of 1200 mg). Treatment with alectinib should be continued until there is disease progression or unacceptable toxicity • Alectinib is a highly selective and potent ALK and RET tyrosine kinase inhibitor
Comparison	• Crizotinib (direct comparison), 250 mg twice daily (total daily dose 500 mg), is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase and its oncogenic variants (i.e., *ALK* fusion events and selected *ALK* mutations). • Ceritinib (indirect comparison, NMA), 750 mg once daily, is an orally highly selective and potent ALK inhibitor • According to approved first-line indications • Since direct study data for alectinib vs. ceritinib are missing, an indirect comparison is needed – NMA • Rationale: Comparators have been chosen on the basis of information from the manufacturer submission file, relevant EPARs [3] [4] and SmPCs [5-7], clinical guidelines [8] [9] and EUnetHTA guidelines [10].
Outcomes[1]	• Effectiveness domain Primary endpoint: overall survival, progression-free survival Secondary endpoints: time to CNS progression, objective response rate, health-related quality of life, other patient-reported outcomes, CNS objective response rate, CNS duration of response • Safety domain AEs Any AEs, SAE, most frequent AEs and SAEs, death as SAE, discontinuation due to AEs, AE leading to dose reduction, AE of special interest/grade 3 or higher AEs • Rationale: Outcomes are selected on the basis of the recommendations from the clinical guidelines [9, 11] and the EUnetHTA guidelines [12].
Study design	Effectiveness:

[1] It should be noted that the priority in terms of primary and secondary endpoints is the priority with regards to this EUnetHTA assessment and differs from the study plan.

Description	Project scope
	• Randomised controlled trials only Safety: • Randomised controlled trials • Nonrandomised controlled trials (if applicable) • Prospective studies with or without a control group (if applicable) • Post-marketing surveillance data on alectinib-related AEs (if applicable) Organisational, ethical, patient and social and legal aspects (if needed): qualitative and qualitative studies, reports or opinions according to EUnetHTA Core HTA Model 3.0 [13] • Only English language studies will be included

Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; CNS=central nervous system; EPAR=European public assessment report; ICD=International Classification of Diseases; MeSH=Medical Subject Headings; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; RET=rearranged during transfection; SAE=serious adverse event; SmPCs=summaries of product characteristics.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The main author, TLV, was responsible for writing the effectiveness and safety domains, validation of the information provided in the other two domains and performing an extrapolation on OS.

The co-author Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ) was responsible for producing the description and technical characteristics of technology domain and patient involvement, and the co-author Main Association of Austrian Social Security Institutions (HVB) was responsible for the health problem and current use of the technology domain. In addition, they both assessed the risk of bias at the study and outcome level, quality of evidence (GRADE), statistically validated the information provided in the NMA (HVB), and checked the systematic literature search conducted by the MAH (AAZ).

Dedicated reviewers (NICE, Regione Veneto, Andalusian Agency for Health Technology Assessment, and National Institute of Pharmacy and Nutrition) reviewed the draft of the project plan and the draft of the assessment report and commented on the draft of the submission file from the MAH.

2.2 Source of assessment elements

The selection of assessment elements was based on the EUnetHTA Core Model® for Rapid Relative Effectiveness Assessment (4.2) [13].

2.3 Search

The systematic literature search, including update, was performed by the MAH and the findings were included in the submission file. The literature search strategy was checked and validated by the authors of this assessment. The reporting of the search strategy followed the EUnetHTA guidelines and the requirements of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement (slightly modified by the authors of this assessment). The systematic search was performed on 2nd February 2017 in the following electronic databases or conference abstracts:

- From database inception in EMBASE (Excerpta Medica Database; 1974) and MEDLINE (Medical Literature Analysis and Retrieval System Online) up to 23rd January 2017 (until 23rd January 2017 for MEDLINE in-process and electronic publications ahead of print through PubMed)
- From database inception in the Cochrane libraries DARE (until database closure in April 2015), CDSR (until monthly update in January 2017) and CENTRAL (until monthly update in November 2016)
- In the US National Institutes of Health registry und results database, the WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register until 15th January 2017
- Abstracts for the following conferences: American Society of Clinical Oncology Annual June Meeting 2016; European Society for Medical Oncology October 2016 Congress; European Cancer Congress January 2017; International Association for the Study of Lung Cancer World Conference on Lung Cancer December 2016; European Lung Cancer Conference April 2016; British Thoracic Oncology Group conferences January 2015, 2016, and 2017.

The update of the literature search was conducted on 3rd October 2017 to identify new studies that had been indexed since the original search. No other relevant RCT was identified.

The Patient or Population, Intervention, Comparison, Outcomes and Study design (PICOS) approach was used to define the search strategy (see literature search inclusion and exclusion criteria in Appendix 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED). All details on the search strategy can be found in Appendix 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED.

Our two objections to the search strategy are related to the simultaneous search of more than one database (one search strategy was used for EMBASE and MEDLINE, as well as one search strategy for three databases from Cochrane Library) and to fact that in the search strategy for EMBASE and MEDLINE, search terms related to EMTREE Thesaurus were used only. Because of that, the search strategy relevant for MEDLINE was performed and reproduced on PubMed by the authors of this assessment, on the 12th of December 2017. The search results corresponded to those presented by MAH.

The following clinical trial registries were searched in January 2017: ClinicalTrials.gov (http://www.clinicaltrials.gov/), WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

A separate Guideline (GL) update search (G-I-N, National Guidelines Clearinghouse, TRIP-Database and hand search) was performed by the authors in December 2017.

2.4 Study selection

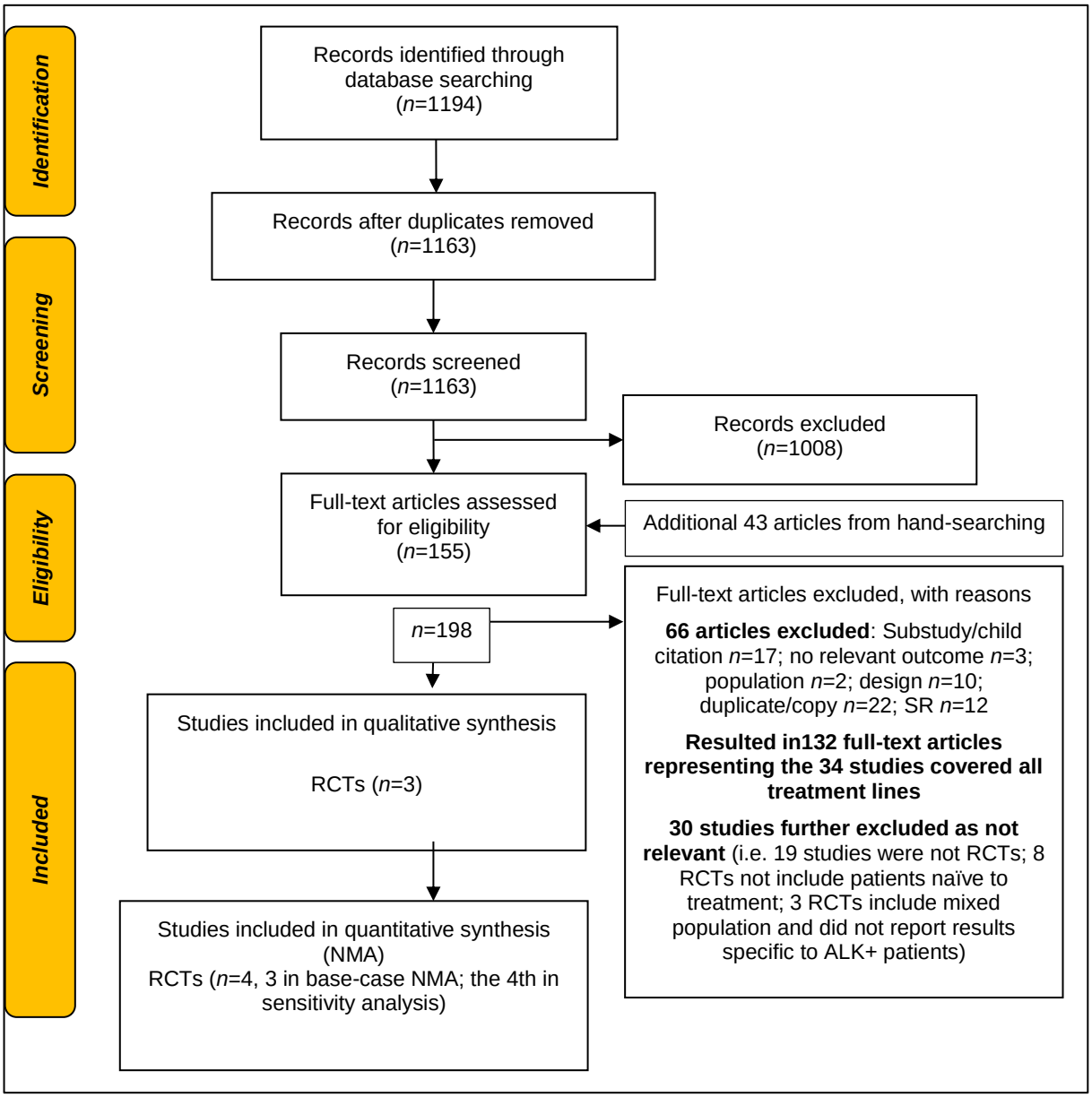


Figure 1.1. Flow chart.

Abbreviations: NMA=network meta-analysis; RCT randomised controlled trial; SR=systematic review.

Figure 1.1 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart. In total, 34 unique studies were identified, which covered all treatment lines for *ALK*-positive advanced or metastatic NSCLC patients (i.e., any combination of chemotherapy-naïve or chemotherapy-experienced or ALK tyrosine kinase inhibitor (TKI) naïve or ALK TKI experienced in any treatment line (advanced or metastatic).

Of the 34 studies, seven RCTs enrolled patients naïve to treatment (both chemotherapy-naïve and crizotinib-naïve) within the advanced/metastatic setting. Of these, three studies included mixed populations (i.e., ALK and non-ALK treatment-naïve patients) and did not report results specific to *ALK*-positive patients; therefore they were not considered further. These studies included CALGB 30406 in the United States [14] (erlotinib vs. erlotinib plus carboplatin/paclitaxel), the study of Zhang et al. 2013 [15] in China (pemetrexed plus cisplatin vs. gemcitabine plus cisplatin) and EURTAC [16] in Spain, France and Italy (erlotinib vs. standard of care).

This resulted in three main trials included in the qualitative synthesis and base-case NMA: ALEX (alectinib vs. crizotinib), PROFILE 1014 (crizotinib vs. chemotherapy), and ASCEND-4 (ceritinib vs. chemotherapy). Four trials were included in the sensitivity analysis of the NMA: ALEX, PROFILE 1014, PROFILE 1029 (crizotinib vs. chemotherapy), and ASCEND-4.

The safety results are based on the ALEX study and the studies included in the NMA. In addition, ADR frequencies are presented from the SmPCs of Alecensa, Xalkori and Zykadia. The SmPC frequencies reflect the EMA established safety profile and are based on all relevant studies at the approved dose. Other RCTs enrolling mixed populations of treatment-naïve and chemotherapy-experienced *ALK*-positive patients were considered but ultimately excluded. These studies included J-ALEX, which was excluded because of the mixed population (i.e., chemotherapy-naïve and chemotherapy experienced patients), the lower dose of alectinib and the Japanese only population, and ALTA-1L (brigatinib vs. crizotinib), which was ongoing.

2.5 Data extraction and analyses

The submission file as well as an NMA produced by the MAH served as the primary documents for this assessment [17]. In addition, all full-text publications referenced in the submission file were provided as an additional information source.

The safety results are based on the ALEX study and the studies included in the NMA. In addition, ADR frequencies are presented from the SmPCs of Alecensa, Xalkori and Zykadia. The SmPC frequencies reflect the EMA established safety profile and are based on all relevant studies at the approved dose. The health problem and current use of the technology domain was cross-checked with the full-text publications provided and with further information sources identified by a hand search. The results were summarised descriptively.

Direct comparison

The efficacy results between alectinib and crizotinib are based on the ALEX study.

Indirect comparison/NMA

As a direct comparison of alectinib versus ceritinib was not available, the MAH performed several methods for indirect comparison. The following two analyses were considered most relevant for this assessment:

- The base case, which included the ALEX, PROFILE 1014 and ASCEND-4 studies.
- A sensitivity analysis, which in addition to the studies included in the base case, also includes the PROFILE 1029 study.

First, an indirect treatment comparison using the Bucher indirect comparison method was performed for the base case and the sensitivity analysis. Second, a Bayesian fixed effects NMA was performed for the base case and the sensitivity analysis. Third, a Bayesian random effects NMA was performed for the sensitivity analysis. The results of the Bucher method are considered

to be nearly identical to the results of the Bayesian fixed effects NMA because of the simple structure of the network. Therefore these results are not shown in this evaluation to avoid duplication.

The Bayesian fixed effects and random effects NMAs were calculated according to Bayesian Markov chain Monte Carlo methods with the software program WinBUGS. Here, vague priors were used for the treatment effect, whereas the standard deviation of the treatment effect estimates is considered to be known. In the Bayesian random effects NMA, a prior, which the MAH considers to be vague, was chosen for the between-study standard deviation within each treatment comparison. In the Bayesian fixed effects NMA, this quantity is implicitly defined to be equal to zero.

In the evaluation of the results of these differing methods, the Bayesian fixed effects NMA was mainly discussed, since in the base case no estimation of the between-study standard deviation was possible. In this case it has to be kept in mind that this particular standard deviation is by assumption equal to zero. The impact of relaxing this assumption can partly be seen in the results of the Bayesian random effects NMA, which simultaneously considers low, moderate and high values of the between-study standard deviation.

A proper sensitivity analysis regarding different informative priors of the between-study standard deviation was requested by the authors but not delivered by the MAH. Therefore in the evaluation of the indirect evidence it is possible to compare only the Bayesian fixed effects NMA with the Bayesian random effects NMA in terms of sensitivity.

An appendix with extrapolation of survival data has been added to the report; see Appendix 1. EXTRAPOLATION OF PFS AND OS/SURVIVAL ANALYSIS. The aim of this section is to discuss different extrapolation models of clinical data over time after the observed data in the clinical trial. No base case will be chosen; this section has been added for discussion.

2.6 Quality rating

The quality rating tool developed by the Cochrane Collaboration (version 5.1.0; March 2011) was used to assess the risk of bias in RCTs [18].

This approach classifies the risk of bias into six different domains:

- Method used to generate the sequence of randomisation (random sequence generation);
- Method used to mask the sequence of allocation to treatment (allocation concealment);
- Measures used to ensure the ‘blindness’ of the study with respect to treatment assignment (blinding of participants, medical personnel and outcome assessors);
- Completeness of the data for each outcome considered (incomplete outcome data);
- Selective description of the results (selective outcome reporting);
- Other sources of bias (e.g., bias due to the early interruption of the study because of the benefits without an appropriate stopping rule, use of a non-validated measurement instrument, incorrect statistical analysis).

For each domain, two independent assessors judged the risk of bias (‘low risk’, ‘high risk’ or ‘unclear’) on the basis of the information retrieved from the full-text publications, the protocols and the submission file. The results of the risk of bias assessment at both the study level and the outcome level are presented in Table A19 and Table A20 in Appendix 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED.

For rating the quality of the evidence, GRADE was applied. The quality of the body of evidence is rated according to four grades:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.

- Moderate: we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

- Low: our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect.

- Very low: we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect. In case of disagreement, a third individual was involved to resolve the differences.

The risk of bias at the study level was applied to all studies included in this assessment for direct and indirect comparisons. The risk of bias at the outcome level was assessed for all outcomes reported in ALEX which had been included in the scope and for the outcomes from the other two trials which had been reported in the NMA. GRADE was applied for direct comparisons with outcomes considered most relevant for this assessment, namely OS, PFS, time to CNS progression, ORR, AEs and health related quality of life (Table A21 in Appendix 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED). Since the PROFILE 1029 has not been fully published yet, the risk of bias was only assessed on study level.

The quality of the NMA was also independently assessed by two individuals according to a technical support document from NICE's Decision Support Unit; in the case of disagreement, a third individual was involved to resolve this disagreement [1] (see Appendix 6. Indirect comparisons – statistical aspects for details).

The external validity of the included trials was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals [12] considering the following elements: population, intervention, comparator, outcomes and setting. The results of the external validity assessment are presented in Table A15.

No quality assessment tool was used for the domains description and technical characteristics of the technology and health problem and current use of technology.

2.7 Patient involvement

An individual patient recently diagnosed with *ALK*-positive NSCLC and being treated with crizotinib was asked to provide input through an one hour telephone interview. Questions posed were related to the impact of the condition; experiences with currently available medicines; expectations of the medicines being assessed; and additional information considered relevant for HTA researchers by the patient.

The template "Patient Group Submission Template for HTA of Medicines" developed by HTAi [19], was significantly modified by the assessment team. Topics and issues from the Patients and Social Domain of the EUnetHTA Core Model 3.0 were included. The adapted document was sent to the patient prior to the interview to allow familiarity with the questions related to above mentioned sections.

The entire interview was recorded and fully transcribed in English. The patient provided orally informed consent. It was agreed to not share the collected data with any third party and all data were stored electronically on encrypted files. No ethical approval was needed. After the interview, the fully anonymized transcription was sent to the patient for an accuracy check and for providing additional data.

2.8 Description of the evidence used

Table 2.1. Main characteristics of studies included

Authors and year (study name)	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain
Peters et al. [1], 2017 (ALEX)	Phase III, open label, randomised	152 alectinib 151 crizotinib	Alectinib vs. crizotinib	PFS (investigator assessed) Key secondary PFS (IRC assessed) Time to CNS progression ORR OS	Effectiveness Safety
Solomon, et al. 2014[20] (PROFILE 1014)	Phase III, open label, randomised	189 crizotinib 175 chemotherapy	Crizotinib vs. chemotherapy	PFS (IRC assessed) or death Key secondary ORR OS	Effectiveness Safety
Soria et al. 2017 [51] (ASCEND-4)	Phase III, open label, randomised	171 ceritinib 169 chemotherapy	Ceritinib vs. chemotherapy	PFS (IRC) or death Key secondary OS	Effectiveness Safety

Abbreviations: IRC=independent review committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

2.9 Deviations from project plan

1. [B0010] "What kind of data/records and/or registry is needed to monitor the use of the alectinib and the comparator" was initially selected as relevant research question in the project plan. During the assessment phase, the authors decided that this question was not relevant and did therefore not include it in the final assessment.

2. In the project plan inclusion of a relevant patient organisation was planned. Despite repeated efforts by the coordinator this was not possible in an early phase of the assessment. An individual patient agreed though to participate in a telephone interview to capture some aspects deemed relevant for patients with ALK-positive NSCLC.

3. According to EUnetHTA procedures and as stated in the project plan, clinical experts as well as payers should be included in the assessment. Unfortunately, neither of these groups could be involved.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What are alectinib and the comparators – crizotinib and ceritinib?
A0020	What are the approved indications of alectinib?
B0002	What is the claimed benefit of alectinib in relation to the comparator(s)?
B0003	What is the phase of development and implementation of alectinib and the comparator(s)?
B0004	Who administers alectinib and the comparator(s) and in what context and level of care are they provided?
B0008	What kind of special premises are needed for alectinib and the comparator (s)?
A0021	What is the reimbursement status of alectinib?

3.2 Results

Features of the technology and comparators

[B0001] – What are alectinib and the comparators – crizotinib and ceritinib?
[A0020] What are the approved indications of alectinib?
[B0002] – What is the claimed benefit of alectinib in relation to the comparator(s)?

Alectinib
Alectinib is a small molecule, CNS-active, highly selective and potent orally administered second-generation inhibitor of ALK and rearranged during transfection (RET) tyrosine kinase receptors which acts as an antineoplastic agent [5].

Alectinib demonstrated in vitro and in vivo activity against mutant forms of the enzyme ALK, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar in vitro potency and activity. On the basis of preclinical data, alectinib is not a substrate of P-glycoprotein or breast cancer resistance protein, which are both efflux transporters in the blood–brain barrier, and is therefore able to distribute itself into and be retained within the CNS. Also, alectinib is not substrate of organic anion-transporting polypeptide 1B1/B3.

The approved indications for alectinib are:

- Alectinib as monotherapy is indicated for the first-line treatment of adult patients with *ALK*-positive advanced NSCLC.
- Alectinib as monotherapy is indicated for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib.

The claimed benefit of alectinib in relation to the comparators (crizotinib and ceritinib, approved first-line monotherapy for *ALK*-positive advanced NSCLC in the EU) is related to a significantly longer PFS, irrespective of whether patients had CNS metastases at the baseline; superior efficacy in the CNS (reducing the proportion of patients with new or progressive CNS metastases at 12 months); and lower incidence of AEs and greater tolerability reported by patients [17].

The main features of the intervention and comparators are listed in Table 3.1 and Table 3.2.

Comparators
Both crizotinib and ceritinib are approved for the first-line therapy of *ALK*-positive advanced NSCLC in the EU. Since ceritinib has been authorised only recently in this setting, European guideline published in 2016 currently recommend crizotinib as the standard of care [8]. Both compounds are considered as adequate comparators of alectinib for this indication, however.

Crizotinib
Crizotinib is an antineoplastic agent intended for treatment of adult patients with advanced NSCLC when the NSCLC is *ALK* positive or *ROS1* positive.

Ceritinib
Ceritinib is an orally highly selective and potent ALK inhibitor which belongs to the pharmacotherapeutic group of antineoplastic and immunomodulating agents. It inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signalling proteins and proliferation of ALK-dependent cancer cells both in vitro and in vivo.

As monotherapy it is indicated for the

- First-line treatment of adult patients with *ALK*-positive advanced NSCLC
- Treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib

Table 3.1. Features of the intervention and comparators

	Technology	Comparator	Comparator
Nonproprietary name	Alectinib	Crizotinib	Ceritinib
Proprietary name	Alecensa	Xalkori	Zykadia
Active substance	Alectinib hydrochloride	Crizotinib	Ceritinib
Pharmaceutical formulation(s)	150 mg hard capsules	200 mg hard capsules 250 mg hard capsules	150 mg hard capsules
ATC code	L01XE36	L01XE16	L01XE28

Abbreviation: ATC=Anatomical Therapeutic Chemical.
Sources: Alecensa SmPC (EMA), last updated:11th January 2018; Xalkori SmPC (EMA), last updated 22nd August 2017; Zykadia SmPC (EMA), last updated 31st August 2017.

Table 3.2. Administration and dosing of the intervention and comparators

	Technology: alectinib	Comparator: crizotinib	Comparator: ceritinib
Administration mode	Oral use. The hard capsules should be swallowed whole; must not be opened or dissolved; must be taken with food	Oral use. The capsules should be swallowed whole and should not be crushed, dissolved or opened; taken preferably with water, with or without food	Oral use. The capsules should be administered orally once daily at the same time every day; should be swallowed whole with water; should not be chewed or crushed; must be taken on an empty stomach and no food should be eaten for at least 2 hours before and 1 hour after the dose is taken

	Technology: alectinib	Comparator: crizotinib	Comparator: ceritinib
Total volume contained in packaging for sale	Pack size of 224 (four packs of 56) hard capsules 56 hard capsules 240 hard capsules	Crizotinib 200 mg: 60 hard capsules per bottle/carton Crizotinib 250 mg: 60 hard capsules per bottle/carton	Multipacks containing 150 (three packs of 50) hard capsules and unit packs containing 40 hard capsules
Dosing	The recommended dose of alectinib is 600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg). The dose of alectinib should be reduced in steps of 150 mg twice daily on the basis of tolerability. Details related to dose reduction, if needed, and dosing interruption can be found in the summary of product characteristics	250 mg twice daily (500 mg daily); taken continuously. Details related to dose reduction, if needed, and dosing interruption can be found in the summary of product characteristics	The recommended dose of ceritinib is 750 mg taken orally once daily at the same time each day. The maximum recommended dose is 750 mg daily. Details related to dose reduction, if needed, and dosing interruption can be found in the summary of product characteristics
Contraindications	Hypersensitivity to alectinib or to any of the excipients	Hypersensitivity to crizotinib or to any of the excipients. Severe hepatic impairment	Hypersensitivity to the active substance or to any of the excipients
Recommended duration of treatment	Until disease progression or unacceptable toxicity	As long as the patient is deriving clinical benefit from therapy[a]	As long as clinical benefit is observed

Sources: Alecensa SmPC (EMA), last updated 11th January 2018; Xalkori SmPC (EMA), last updated: 22nd August 2017; Zykadia SmPC (EMA), last updated 31st August 2017.

[a]Summary basis of decision for Xalkori (Canada).

[B0003] What is the phase of development and implementation of alectinib and the comparator(s)?

Alectinib

In February 2017, alectinib was approved by the EMA as monotherapy for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib. In March 2017, the MAH submitted to the EMA an application to extend the indication for alectinib to first-line treatment of adult patients with *ALK*-positive advanced NSCLC [17].

On 12th October 2017 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product alectinib. The CHMP adopted an extension to the existing indication as follows: 'Alecensa as monotherapy is indicated for the first-line treatment of adult patients with (ALK)-positive advanced NSCLC' [21]. The European Commission provided approval for Alecensa (alectinib) as first line- treatment for ALK positive lung cancer on the 21st Dec 2017.

Alectinib was first granted marketing approval in Japan in July 2014 for the treatment of 'ALK fusion gene positive unresectable, recurrent or advanced NSCLC.' The recommended dosage is 300 mg twice a day and it is marketed by Chugai Pharmaceutical Co. Ltd.

In the United States, alectinib was approved by the Food and Drug Administration (FDA) on December 2015 for the 'treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib'. The recommended dosage is 600 mg twice a day and it is marketed by Roche in 150-mg capsules to be taken orally. In May 2017 a rolling

supplemental new drug application for the treatment of patients with *ALK*-positive NSCLC who are treatment naïve was submitted to the FDA and was approved in November 2017.

As of October 2017, alectinib is approved in Japan for the treatment of *ALK*-positive NSCLC with no restriction with respect to treatment line, and in the United States, the EU, and 15 other countries (Switzerland, Israel, Canada, South Korea, Kuwait, Hong Kong, Taiwan [marketed by Chugai], Australia, Singapore, India, Thailand, Argentina, the United Arab Emirates, Turkey and Saudi Arabia) for the treatment of crizotinib-pretreated patients with *ALK*-positive NSCLC. Detailed information on the regulatory status can be found in Table A23 in Appendix 3: REGULATORY AND REIMBURSEMENT STATUS [17].

To further confirm the efficacy and safety of alectinib in the treatment of patients with *ALK*-positive NSCLC, the MAH should submit the clinical study report of the phase III study ALEX comparing alectinib versus crizotinib in treatment-naïve patients with *ALK*-positive NSCLC. The due date is 30th April 2018 [5, 22].

Crizotinib
Crizotinib is an antineoplastic agent intended for treatment of adult patients with advanced NSCLC when the NSCLC is *ALK* positive or *ROS1* positive [6].

Crizotinib can inhibit ALK receptor activation by blocking the ATP binding site [17]. By blocking the activity of ALK or ROS proto-oncogene 1 (ROS1), including their genetically altered versions, crizotinib inhibits cell proliferation, migration, invasion and motility in tumour or endothelial cells, which suggests that crizotinib has an effect on both tumour cell growth and survival, as well as on angiogenesis, thereby reducing the growth and spread of the cancer in *ALK*-positive or *ROS1*-positive NSCLC [4, 6].

Crizotinib is P-glycoprotein substrate, and after having passively crossed the blood–brain barrier, it is actively transported back across it [17].

Crizotinib monotherapy is indicated as

- First-line treatment of adults with *ALK*-positive advanced NSCLC
- Treatment of adults with previously treated *ALK*-positive advanced NSCLC
- Treatment of adults with *ROS1*-positive advanced NSCLC

The initial marketing authorisation for crizotinib (a conditional approval), valid throughout the EU, was granted on 3rd October, 2012 for the treatment of adults with previously treated *ALK*-positive advanced NSCLC. The indication was extended to first-line treatment of *ALK*-positive advanced NSCLC on 23th November 2015. On 21st July 2016 the CHMP gave a positive opinion and adopted a new indication for crizotinib, indicating this therapy for the treatment of adults with *ROS1*-positive advanced NSCLC.

Crizotinib is subjected to additional monitoring and restricted medical prescription, with necessary submission of periodic safety update reports [4, 6].

Ceritinib
On 26th February 2015 the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product ceritinib, 150 mg, hard capsule, intended for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib.

The initial marketing authorisation for ceritinib (a conditional approval), valid throughout the EU, was granted in May 2015 as monotherapy for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib. The indication was extended to first-line treatment of *ALK*-positive advanced NSCLC in June 2017.

Ceritinib is the subject of additional monitoring with requirements for submission of periodic safety update reports for this medicinal product [3, 7].

[B0004] Who administers alectinib and the comparator(s) and in what context and level of care are they provided?

Treatment with alectinib as well as with the comparators crizotinib and ceritinib should be initiated in a secondary care (hospital) setting and supervised by a physician experienced in the use of anticancer medicinal products. Alectinib, crizotinib and ceritinib are intended for oral use, so they are administered by the patients or their caregivers.

ALK-positive NSCLC status should be established before initiation of alectinib therapy. *ALK* positivity according to reverse transcription polymerase chain reaction, fluorescence in situ hybridisation (FISH) screening test or immunohistochemistry (IHC) needs to be confirmed before alectinib is prescribed to the patient by laboratories with demonstrated proficiency in the specific technology being used.

In the case of certain side effects, the therapy can be interrupted/stopped or the dose can be reduced. More information related to administration and dosing of the technology and comparators is presented in Table 3.2 under the assessment element question [B0001] – What are alectinib and the comparators – crizotinib and ceritinib [5-7].

[B0008] What kind of special premises are needed for alectinib and the comparator(s)?

Alectinib

The presence of genetic defects affecting ALK ('*ALK*-positive' status) has to be confirmed in advance by appropriate methods: reverse transcription polymerase chain reaction, FISH screening test or IHC. Assessment for *ALK*-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being used [5].

Crizotinib

Before initiation of crizotinib therapy, it is necessary to conduct ALK and ROS1 testing with an accurate and validated assay to determine *ALK*-positive or *ROS1*-positive NSCLC status. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being used. When the *ALK* or *ROS1* status of a patient is being assessed, it is important that a well-validated and robust method is chosen to avoid false-negative or false-positive determinations [6].

Ceritinib

An accurate and validated ALK assay is necessary for the selection of *ALK*-positive NSCLC patients. *ALK*-positive NSCLC status should be established before initiation of therapy, and the assessment should be performed by laboratories with demonstrated proficiency in the specific technology being used [7].

[A0021] What is the reimbursement status of alectinib?

First-line treatment

As the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for alectinib in October 2017, there are no reimbursement data for first-line indication to date. The reimbursement status of alectinib in different EU countries will be decided at the national level after marketing authorisation.

Second-line treatment

Marketing approval was granted in the EU as well as Iceland, Norway and Liechtenstein on 16th February 2017 for the crizotinib treatment failure indication. In European countries, for the second-line indication, alectinib is being reimbursed in Denmark, Germany, Luxembourg, the Netherlands and Switzerland. Full details on the reimbursement for this indication across European countries is provided Table A24 in Appendix 3: REGULATORY AND REIMBURSEMENT STATUS [17].

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is NSCLC in the scope of this assessment?
A0003	What are the known risk factors for ALK-positive NSCLC?
A0004	What is the natural course of (advanced) NSCLC?
A0005	What are the symptoms and the burden of advanced NSCLC for the patient?
A0024	How is (*ALK* positive advanced) NSCLC currently diagnosed according to published guidelines?
A0025	How is *ALK* positive advanced NSCLC in adults currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

4.2 Results

Overview of the disease or health condition

[A0002] – What is NSCLC in the scope of this assessment?
Lung cancer is histologically broadly classified in NSCLC and small cell lung cancer. NSCLC accounts for approximately 80 – 85% of all lung cancers [23-27].

Molecular analysis allows further subdivision of NSCLC and thus identification of patients eligible for specific targeted therapies, such as alectinib [23]. A number of oncogenic drivers have been identified in NSCLC, including rearrangement of the *anaplastic lymphoma kinase (ALK*) gene. *ALK* gene rearrangements are largely mutually exclusive with epidermal growth factor receptor (EGFR) or KRAS mutations, consistent with the notion that *ALK* gene rearrangements define a unique molecular subset of NSCLC [28].

ALK is a transmembrane receptor tyrosine kinase, a member of the insulin receptor superfamily [23]. The most common *ALK* rearrangements are fusions in the echinoderm microtubule-like protein 4 (EML4), which are found in approximately 2%–5% of patients with NSCLC and 3%–7% of adenocarcinomas [24, 29, 30].

ALK rearrangements lead to expression of constitutively active *ALK* fusion proteins that, in turn, activate intracellular signalling cascades, promoting tumour cell growth and survival [23, 24, 27, 31-33].

All lung cancers are staged according to the tumour, node, metastasis (TNM) system (in Europe the eighth version was adopted in January 2017 [34]), which takes the extent of the primary tumour, the involvement of regional lymph nodes and the presence or absence of distant metastases into account. These features are then summarised in four different stage groups (I–IV) which are linked to survival and also to treatment recommendations. Commonly, ‘advanced disease’ refers to stage IIIB and stage IIIC disease, which are associated with metastases in more distant lymph nodes and most advanced local disease, respectively, and to stage IV disease with distant metastases [9].

[A0003] What are the known risk factors for ALK-positive NSCLC?
Even though lung cancer is in general diagnosed at an age of about 70 years, with tobacco smoking being the main risk factor, *ALK* rearrangements occur more frequently in never smokers, adenocarcinomas and younger patients (mean age at diagnosis 52–58 years). Whether sex has an impact remains uncertain because of conflicting evidence [9, 35, 36].

[A0004] What is the natural course of (advanced) NSCLC?
Prognosis depends on several factors; early-stage disease at diagnosis, good performance status (ECOG performance status 0–2), weight loss of 5% or less and female sex are factors which positively impact prognosis [9]. However, since symptoms do not occur until the tumour is advanced or has metastasised, lung cancer is usually diagnosed at a late stage. In this setting, the goal of treatment is to prolong survival and to alleviate cancer symptoms. Accordingly, the 5-year survival in stage IIIB NSCLC is about 5%, and in stage IV NSCLC it remains as lower than 5%, with a median OS of about 8–10 months [25, 37]. Estimates specifically for *ALK*-positive NSCLC are not available; therefore it remains unclear if the presence of *ALK* mutations confers a better prognosis [35].

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of advanced NSCLC for the patient?
The most common symptoms of lung cancer are cough, dyspnoea, weight loss and chest pain [9, 38, 39]. These symptoms are mainly caused by the intrathoracic location of the tumour itself. Extrathoracic symptoms are caused by metastases, with the liver, bones, adrenal glands and brain being the most common sites of distant metastases.

In 7%–10% of patients, brain metastases are present at the time of diagnosis, but they occur more often in patients with adenocarcinoma, large primary tumours and involvement of regional lymph nodes [40]. They are also more frequently present in *ALK*-positive NSCLC than in *ALK*-negative tumours, with up to 20% of cases being reported at the initial diagnosis of NSCLC and 50% before initiation of targeted therapy; that is crizotinib therapy [37, 41]. Brain metastases were newly diagnosed in 20% of patients during the course of first-line therapy with crizotinib and in 10% of patients after crizotinib therapy [41, 42].

Most common symptoms of brain metastases include seizures, weakness, numbness in parts of the body and mental status change. In addition, development of brain metastases is also associated with an increase in symptoms; rates of fatigue, shortness of breath, nausea or vomiting and headaches showed increases in an analysis of three large administrative databases in the United States including 213 patients treated with crizotinib [23]. Also life expectancy is poor of these patients, with a median survival of 1–3 months when untreated [37, 40] and about 4–9 months when treated with chemotherapy and 7 months when treated with whole-brain radiation therapy (WBRT) [37, 43].

HRQoL of lung cancer patients is also linked to the prevalence and intensity of physical and psychological symptoms, and is being discussed as a potential predictor for OS [44-46]. Loss of appetite, cough, pain, shortness of breath and fatigue were correlated with HRQoL [47, 48].

Current clinical management of the disease or health condition

[A0024] How is *ALK*-positive advanced NSCLC currently diagnosed according to published guidelines and in practice?
According to guidelines, a complete medical history, including smoking history and comorbidities, weight loss, performance status and physical examination, must be recorded for all types of lung cancer.

Further, standard tests include laboratory testing (haematological, renal, hepatic and bone biochemistry) and a computed tomography (CT) scan of the complete abdomen. In the case of neurological symptoms, an assessment of the CNS with CT or – preferably – magnetic resonance imaging is performed, and when bone metastases are suspected, also a positron emission tomography scan (ideally coupled with CT) has to be performed [8].

A pathology evaluation is indicated to determine the histological type and the staging parameters (i.e., TNM staging) [9]. When the cancer is unresectable, minimally invasive techniques such as small biopsy and cytology are recommended for histological diagnosis and molecular testing. In Europe, molecular testing for *ALK* mutations is recommended in all patients with advanced *non-squamous* cell carcinoma and in patients with *squamous* cell carcinoma only for never/former light (<15 pack years) smokers [8]. In the United States, *ALK* testing is recommended for patients with adenocarcinomas and for mixed lung cancers with an adenocarcinoma component [49].

According to guidelines, FISH using dual-labelled break-apart probes is the standard for detection of *ALK* mutations and for selecting patients for *ALK* TKI therapy [8, 49].

[A0025] How is *ALK*-positive advanced NSCLC currently managed according to published guidelines and in practice?
The treatment strategy for lung cancer is determined by histology, molecular pathology, age, performance status, comorbidities and patient preferences [8].

For *ALK*-positive advanced NSCLC, most guidelines were published before the extension of the indication of ceritinib to the first-line setting and before the publication of trial results for alectinib in untreated patients (see Table A10, Appendix 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED).

Crizotinib is currently recommended for the first-line therapy for *ALK*-positive advanced NSCLC in Europe according to the 2016 European Society for Medical Oncology guideline [8]. Crizotinib has also demonstrated activity in treating brain metastases [50]. However, progression of pre-existing brain metastases or development of new intracranial lesions is common [43]. Acquired resistance to crizotinib and inadequate exposure because of inadequate CNS penetration have been discussed as potentially underlying causes [51]. Other local, nonpharmacological treatment options for brain metastases include WBRT, stereotactic radiosurgery and surgical resection, either alone or in combination or as sequential treatment. However, for limited brain metastases, WBRT is not used very often because of the neurocognitive side effects [9]. The most common symptoms in patients with post brain WBRT toxicity syndrome include headache, fatigue, somnolence, neurocognitive deficits such as decline in memory and change in mental status [52].

In the United States, the recently updated National Comprehensive Cancer Network (NCCN) guideline on NSCLC (September 2017) already includes ceritinib and alectinib (see Figure 4.1) [9]. Ceritinib, crizotinib and alectinib are all category 1 recommendations based on high-level evidence (i.e., there is uniform NCCN consensus that the intervention is appropriate) for the first-line therapy for *ALK*-positive lung cancer. From voting of NCCN members, alectinib is the 'preferred' option.

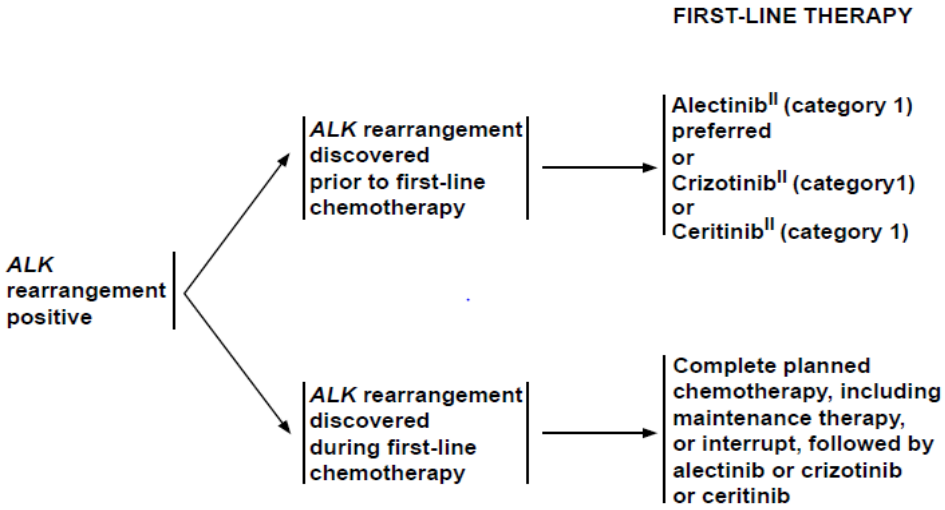


Figure 4.1: Treatment algorithm for *ALK*-positive non-small cell lung cancer.
Source: [9]

Target population

[A0007, A0023] What is the target population of this assessment and how many people belong to the target population?

The target population comprises treatment-naïve adult patients with *ALK*-positive advanced NSCLC.

Lung cancer has been the most common cancer overall for several decades worldwide and is the most frequently diagnosed cancer in men. In 2012, about 1.8 million new cases were estimated. Lung cancer is also the most common cause of cancer-related death worldwide [53]. The 2012 worldwide estimates of mortality by GLOBOCAN, indicate a total of 1.6 million lung cancer-related deaths, accounting for 19.4% (nearly 1 in 5 cancer deaths) of all cancer deaths (except nonmelanoma skin cancers) [28, 54]. While mortality is declining in men (by 6% from 2009 to 2013), death rates increased in women by 7%, thereby approaching those of male counterparts [8].

In the 28 EU countries, 331,725 new lung cancer cases were reported in 2012 [55]. The target population of treatment-naïve adult patients with *ALK*-positive advanced NSCLC was estimated from published epidemiology data on the incidence of *ALK*-positive advanced NSCLC in France, Italy, Germany, Spain and the United Kingdom provided by the MAH.

Based on epidemiology data, the MAH stated in the submission file that 7,637 patients in the EU-5 and 11,816 in the 28 European countries would be eligible for the first-line therapy with alecensa [17]. Since the underlying assumptions could not be reproduced, the absolute numbers from the epidemiology data provided for five countries in the submission file were used to calculate the respective percentages for each country based on the total lung cancer incident population. These probabilities were then applied to calculate a range for the overall numbers in Europe based on the total lung cancer incident population by GLOBOCAN.

This led to slightly lower estimates: NSCLC accounted for 82%–86% of all lung cancers diagnosed, of which 81%–85% are de novo advanced or metastatic or are recurrent from early stages (see also Table A11 in Appendix 1. EXTRAPOLATION OF PFS AND OS/SURVIVAL ANALYSIS). About 3%–5% of these are estimated to be *ALK*-positive. Taking factors such as non-squamous histological type, tissue availability or testing for *ALK* rearrangements into account, 1.0%–1.4% of the total lung cancer incident cases are actually treated. Applying these probabilities to the total lung cancer incident population, about 11,000 patients would be eligible for ALK TKI therapy, whereas a maximum of 5000 patients are expected to be treated in Europe (see Table 4.1).

Table 4.1 Estimated incidence of (*ALK*-positive) NSCLC in Europe in 2012

	Proportion, %	**EU5[c]**	**EU28[d]**
Total lung cancer incident population[a]	100	214,410	331,725
Total NSCLC incident population	82–86	175,816–184,393	272,015–285,284
Total NSCLC patients eligible for first-line therapy[b]	67–72	143,655–154,375	222,256–238,842
Total *ALK*-positive NSCLC patients eligible for first-line therapy	3.4–3.5	7290–7504	11,279–11,610
Total *ALK*-positive NSCLC patients treated with first-line therapy	1.0–1.4	2144–3002	3317–4644

Source: [17]
[a]Total lung cancer incident population was obtained from GLOBOCAN 2012, IARC -27.9.2017.
[b]De novo advanced/metastatic patients and recurrent patients from early stages.
[c]France, Germany, Italy, Spain, United Kingdom.
[d]All 28 current European Union counties.

5 CLINICAL EFFECTIVENESS

5.1 Research questions

Table 5.1. Research questions and element IDs

Element ID	Research question
D0001	What is the effect on overall survival for alectinib compared to other approved treatments in the 1st line therapy?
D0005	How does alectinib affect symptoms and findings (e.g. time to CNS progression, objective response rate (ORR), overall survival (OS), health-related quality of life (HRQoL)) of adults with *ALK-positive* advanced NSCLC?
D0006	How does alectinib affect progression-free survival of adults with *ALK-positive* advanced NSCLC, compared to other approved treatments in the 1st line therapy?
D0012	What is the effect of alectinib on generic health-related quality of life?
D0013	What is the effect of alectinib on disease-specific quality of life?
D0016	How does alectinib affect activities of daily living?

5.2 Results

Included studies
The assessment of clinical effectiveness is based primarily on three phase III randomised active-controlled trials: ALEX [2] (alectinib vs. crizotinib), ASCEND-4 [56] (ceritinib vs. chemotherapy) and PROFILE 1014 [57] (crizotinib vs. chemotherapy). For a tabular summary of the studies, see Section 0.

Direct and indirect evidence
The ALEX study provides a direct comparison between alectinib and the relevant comparator crizotinib, whereas ASCEND-4 and PROFILE 1014 are used in an NMA that also included ALEX to provide a comparison against the other most relevant comparator, ceritinib (Figure 5.5).

The estimations derived from the NMA should be interpreted with caution because of the limitations inherent in any across-study comparison (e.g., with regard to potential differences in patient populations). In addition, there are some differences between the comparator regimens, the impact of which is unknown (see further discussion later). In ASCEND-4, four cycles of pemetrexed plus cisplatin or carboplatin therapy, followed by maintenance pemetrexed therapy, was used, whereas in PROFILE 1014, up to six cycles of the same regimen were allowed, but there was no maintenance pemetrexed therapy. The results of the NMA are therefore viewed primarily as supportive of the direct evidence and are discussed in a separate section. A further discussion on the comparability of the studies based on the results is provided in the NMA section (Table 5.7).

For comparison with ceritinib, evidence for all the research questions listed above is not available; however, results for OS, PFS, ORR and safety are presented in the NMA.

Description of individual studies

The ALEX trial

This was a phase III multicentre, open-label, randomised study of orally administered alectinib (600 mg twice daily) versus crizotinib (250 mg twice daily) in previously untreated adult patients with *ALK*-rearranged (*ALK*-positive), stage IIIB not amenable for multimodality treatment or IV, non-squamous NSCLC with WHO performance status 0–2. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) IHC was required before randomisation in the study. The primary endpoint was investigator-assessed PFS. Secondary endpoints were IRC-assessed PFS, time to CNS progression, ORR and OS. Per protocol, crossover between the trial groups was not allowed. A total of 303 patients were included in the trial: 151 patients were randomised to the crizotinib arm and 152 patients were randomised to the alectinib arm. Tumour response was assessed every 8 weeks with the use of the Response Evaluation Criteria in Solid Tumors (RECIST) 1. [2] [5] [22].

The PROFILE 1014 trial

This was a phase III, randomised, open-label study of the efficacy and safety of crizotinib (250 mg BID) until RECIST-defined progression versus pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or carboplatin (area under the curve [AUC] 5 or 6) for up to 6 three-week cycles in previously untreated patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the *ALK* gene locus and ECOG/WHO performance score of 0–2. *ALK*-positive status was determined by the Abbott Molecular IUO (investigational use only) test performed by a central laboratory under US FDA investigational device exemption. Patients whose disease progressed while they were receiving chemotherapy were allowed to cross over to receive crizotinib treatment. The primary endpoint was IRC-assessed PFS per RECIST 1.1. The study included 343 patients (171 of 172 patients randomised to receive crizotinib received crizotinib, and 169 of 171 randomised to receive chemotherapy received chemotherapy). Crossover to crizotinib therapy was done in 120 patients after progression of their disease while they were receiving chemotherapy [4].

The ASCEND-4 trial

This was a phase III multicentre, open-label, randomised study of orally administered ceritinib (750 mg once daily, fasted) versus standard chemotherapy in previously untreated adult patients with *ALK*-rearranged (*ALK*-positive), stage IIIB or IV, non-squamous NSCLC with WHO performance status 0-2. Chemotherapy consisted of pemetrexed at 500 mg/m^2 and cisplatin at 75 mg/m^2 or carboplatin (AUC 5 or 6) for up to 4 three-week cycles, followed by pemetrexed maintenance therapy in patients without progressive disease after 4 cycles . *ALK*-positivity was confirmed by the Ventana ALK (D5F3) CDx assay IHC test by a central laboratory. Patients enrolled were previously not treated with any systemic anticancer therapy (including an ALK inhibitor) with exception of patients who received neoadjuvant or adjuvant therapy if progression/relapse had not occurred within 12 months after the end of neoadjuvant or adjuvant therapy. Crossover of patients allocated in the chemotherapy arm to the ceritinib treatment arm was allowed in the extension treatment phase only after blinded IRC-confirmed RECIST-defined progressive disease had been documented. The primary endpoint was IRC-assessed PFS per RECIST 1.1. The study included 376 patients (all 189 randomised to receive ceritinib received ceritinib, and 175 of 187 randomised to receive chemotherapy received chemotherapy) [3].

PROFILE 1029

This was a phase III, randomised, active-controlled, open-label study comparing crizotinib at a dosage of 250 mg twice daily versus pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6) for up to 6 three-week cycles in patients with locally advanced, recurrent or metastatic non-squamous NSCLC with *ALK* positivity determined by FISH with ECOG performance status of 2 or less and no prior systemic treatment for NSCLC. Patients with brain metastases were included only if they had been treated and were neurologically stable with no ongoing requirement for corticosteroids. The primary endpoint was PFS (by IRC assessment).

This study was excluded from the base case NMA because the study population included Asian patients only. It was included in sensitivity analyses, however.

Excluded studies
In addition to ALEX, PROFILE 1014, PROFILE 1029 and ASCEND-4, there was one reported study in the *ALK*-positive first-line setting: J-ALEX (alectinib 300 mg vs. crizotinib). For other, ongoing, studies no data were available.

J-ALEX
This was a phase III RCT in Japanese patients with advanced stage IIIB/IV *ALK*-positive NSCLC comparing orally administered alectinib at a dosage of 300 mg twice daily against orally administered crizotinib at a dosage of 250 mg twice daily. Patients were treatment naïve (64% of patients) or had received one line of chemotherapy at the study baseline (36% of patients).

This study was excluded because of the mixed population (i.e., chemotherapy-naïve and chemotherapy-experienced patients), the lower dose of alectinib, and the Japanese-only population.

Baseline characteristics
Baseline characteristics of the patients in the included studies are shown in Table 5.2.[2]

Table 5.2. Baseline characteristics of patients across relevant studies

	ALEX		PROFILE 1014		PROFILE 1029[a]		ASCEND-4	
	Alectinib	Crizotinib	Crizotinib	PEMpositive CIS/CARB	Crizotinib	PEMpositive CIS/CARB	Ceritinib	PEMpositiveCIS/CARB positive maintenance PEM
N, randomised	152	151	172	171	104	103	189	187
Age, years, median (range)	58 (25–88)	54 (18–91)	52 (22–76)	54 (19–78)	Mean 48.2	Mean 48.9	55 (22–81)	54 (22–80)
Male, *n* (%)	68 (45)	64 (42)	68 (40)	63 (37)	50 (48.1)	43 (41.7)	87 (46.0)	73 (39.0)
Race, *n* (%)								
Asian	69 (45)	69 (46)	77 (45)	80 (47)	104 (100)	103 (100)	76 (40)	82 (44)
Other	83 (55)	82 (54)	95 (55)	91 (53)	—	—	113 (60)	105 (56)
ECOG/WHO PS, *n* (%)								
0–1	142 (93)	141 (93)	161 (94)	163 (95)	99 (95)	98 (95)	176 (93)	175 (93)
2	10 (7)	10 (7)	10 (6)	8 (5)	5 (5)	5 (5)	13 (7)	11 (6)[b]
Stage at baseline, *n* %								
IIIB/locally advanced	4 (3)	6 (4)	4 (2)	3 (2)	NR	NR	9 (5)	5 (3)
IV/metastatic	148 (97)	145 (96)	168 (98)	168 (98)	NR	NR	180 (95)	182 (97)
Histology/cytology, *n* (%)								
Adenocarcinoma	136 (90)	142 (94)	161 (94)	161 (94)	NR	NR	180 (95)	183 (98)
Other	16 (10)	9 (6)	11 (6)	10 (6)	NR	NR	9 (5)	4 (2)
Smoking history, *n* (%)								
Active smoker	12 (8)	5 (3)	10 (6)	5 (3)	NR	NR	15 (8)	15 (8)
Nonsmoker	92 (61)	98 (65)	106 (62)	112 (65)	NR	NR	108 (57)	122 (65)
Past smoker	48 (32)	48 (32)	56 (33)	54 (32)	NR	NR	66 (35)	50 (27)
Brain/CNS metastasis, *n* (%)	64 (42)	58 (38)	45 (26)	47 (27)	21 (20)	32 (31)	59 (31)	62 (33)
Prior brain radiation, *n* (%)	26 (17)	21 (14)	NR	NR	NR	NR	24 (13)	26 (14)

Abbreviations: CARB=carboplatin; CIS=cisplatin; CNS=central nervous system; ECOG PS=Eastern Cooperative Oncology Group; NR=not reported; PEM=pemetrexed; PS=performance status; WHO=World Health Organization

[a]Not included in base case network meta-analysis.

[b]Does not sum to 100% because of missing observations.

Sources: Peters et al. 2017; Solomon et al, 2014; Lu et al 2016a; Soria et al 2017. **[17]**, Table 16

Most baseline characteristics described in Table 5.2 for the studies included in the NMA were largely balanced across study arms and were similar across studies. ECOG performance status was 0–1 in approximately 95% of patients across studies, more than 95% had stage IV disease, approximately 60%–65% of patients were nonsmokers, and more than 90% had adenocarcinoma histological type.

Differences were observed for age, with slightly higher median age in ALEX (58 vs. 54 years, alectinib vs. crizotinib – a small imbalance is noted) compared with PROFILE 1014 (52 vs. 54 years, crizotinib therapy vs. chemotherapy) and ASCEND-4 (55 vs. 54 years, ceritinib therapy vs. chemotherapy).

The proportion of male patients was largely similar across studies, approximately 37%–48%. In ASCEND-4 there was a slightly larger difference between arms in the percentage of males (46% vs. 39%, ceritinib therapy vs. chemotherapy). The impact of sex for ALK-inhibitor efficacy has not been determined. No consistent trend with regard to efficacy and sex can be observed in first-line studies for ceritinib and crizotinib, nor in the second-line setting for alectinib. (In the alectinib phase I/II study NP28673, ORR was 51% in male patients and 45% in female patients; in the ceritinib study ASCEND-4, PFS HR was 0.41 in male patients and 0.63 in female patients; while in the crizotinib study PROFILE 1014, PFS HR was 0.54 in male patients and 0.45 in female patients. That is, there is a possible tendency of better efficacy in male patients in the former two studies and a possible tendency of better efficacy in female patients in the latter study [3-5].

The presence of baseline CNS metastasis was largely balanced across study arms, but the proportions differed across the three studies included in the NMA. There were higher frequencies in the ALEX study (approximately 40%) compared with less than 30% in PROFILE 1014 and approximately 30% in ASCEND-4. The higher frequency of CNS metastases at baseline observed in the ALEX study may be explained by the requirement for all patients to have CNS imaging at baseline. The presence of CNS metastasis confers a poorer prognosis, and these differences may therefore affect across-study comparisons.

Limited baseline data were provided for the excluded study PROFILE 1029. Apart from 100% of patients being of Asian race, a somewhat lower median age (48 years) was observed compared with the other studies. Furthermore, an imbalance in the proportion of patients with baseline brain metastasis is noted, 20% versus 31% *(n*=21 and *n*=32) in the crizotinib therapy arm versus the chemotherapy arm, respectively. This is expected to affect prognosis, and may have favoured the crizotinib therapy arm.

Mortality

[D0001] What is the effect on overall survival for alectinib compared to other approved treatments in the 1st line therapy?

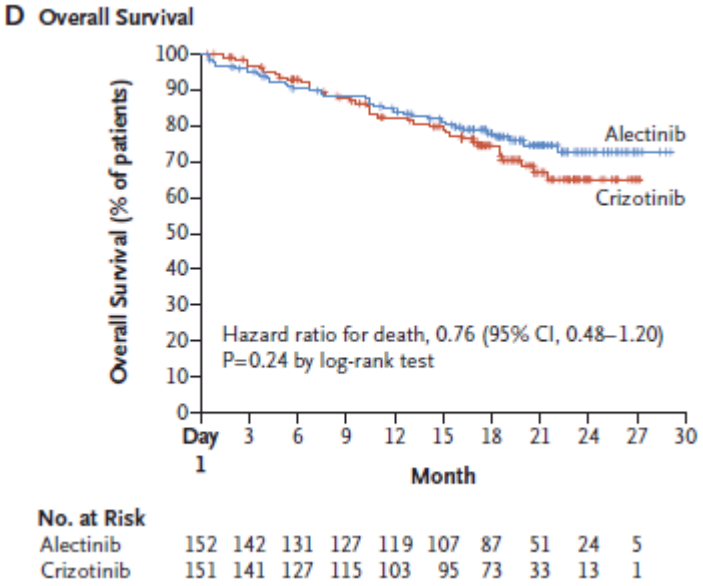
Alectinib versus crizotinib (ALEX trial, direct comparison)
At the data cutoff point, 23% of patients in the alectinib arm and 27% patients in the crizotinib arm had died, with a 1-year survival rate of 84.3% and 82.5%, respectively (HR 0.76; 95% CI: 0.48, 1.20). Median OS was not reached in either treatment arm. Survival analysis has been planned after 50% of events have occurred [17].

Table 5.3. Overall survival

Study reference/ID	Measurement	Intervention, median, months (95% CI)	Outcome comparator, median, months (95% CI)	Relative difference, HR (95% CI)	Comment
ALEX (BO28984)	Interim overall survival, unadjusted for crossover	**Alectinib** (*N*=152) NE (19.9 to NE)	**Crizotinib** (*N*=151) NE (17.1 to NE)	0.76 (0.48–1.20); *p*=0.24	Immature after 35 (23%) deaths had occurred in 152 patients

Abbreviations: CI=confidence interval; HR=hazard ratio; NE=not estimable.
Source: [17]

Figure 5.1. Overall survival, alectinib versus crizotinib, ALEX trial[2]



Abbreviation: CI=confidence interval.

Progression-free survival

[D0006] How does alectinib affect progression-free survival of adults with *ALK-positive* advanced NSCLC, compared to other approved treatments in the 1st line therapy?

Alectinib versus crizotinib (ALEX trial, direct comparison)
The trial met its primary endpoint at the primary analysis, demonstrating a statistically significant increase in PFS by investigator assessment. In the entire population the median PFS measured by the investigator for alectinib was not reached (95% CI, 17.7 months to not estimable) versus 11.1 months for crizotinib (95% CI, 9.1, 13.1); HR 0.47 (95% CI, 0.34, 0.65, p<0.0001).

IRC-assessed PFS was also significantly longer with alectinib than with crizotinib (median PFS 25.7 months (95% CI 19.9 months to not estimable) vs. 10.4 months (95% CI, 7.7, 14.6 months); HR for disease progression or death 0.50, (95% CI, 0.36, 0.70; p<0.001)).

The PFS benefit was consistent for patients with CNS metastases at the baseline (HR 0.40, 95% CI 0.25–0.64) and without CNS metastases at the baseline (HR 0.51, 95% CI, 0.33, 0.80). In both subgroups, the median PFS was not reached in the alectinib arm (95% CI 9.2, not estimable; and 95% CI not estimable, not estimable, respectively), but was estimated for the crizotinib arm at 7.4 months (95% CI, 6.6, 9.6 months) in the CNS metastasised group and 14.8 months 95% CI, 10.8, 20.3 months) in the non-CNS metastasised group, respectively [5].

The treatment effect did not show major differences between the subgroups. The benefit was lower in the subgroups of active smokers and patients with an ECOG performance status of 2, although the numbers of patients in these subgroups were small [2].

Table 5.4. Progression-free survival by investigator and independent review committee assessments for alectinib versus crizotinib in the ALEX trial (intent-to-treat population)

Endpoint	Alectinib *N* = 152	Crizotinib *N* = 151
Median duration of follow-up, months (range)	18.6 (0.5–29.0)	17.6 (0.3–27.0)
Primary endpoint		
PFS (investigator)		
Patients with event, *n* (%)	62 (40.8)	102 (67.5)
Median, months (95% CI)	NE (17.7 to NE)	11.1 (9.1, 13.1)
HR (95% CI)[a]	0.47 (0.34, 0.65)	
Stratified log-rank *p*	<0.0001	
1-year event-free rate, % (95% CI)	68.4 (61.0, 75.9)	48.7 (40.4, 56.9)
Key secondary endpoints		
PFS (IRC)		
Patients with event, *n* (%)	63 (41.4)	92 (60.9)
Median, months (95% CI)	25.7 (19.9 to NE)	10.4 (7.7, 14.6)
Stratified HR (95% CI)[a]	0.50 (0.36, 0.70)	
Stratified log-rank *p*	<0.0001	

Abbreviations: CI=confidence interval; HR=hazard ratio; IRC=independent review committee; NE=not estimable; PFS=progressionfree- survival.

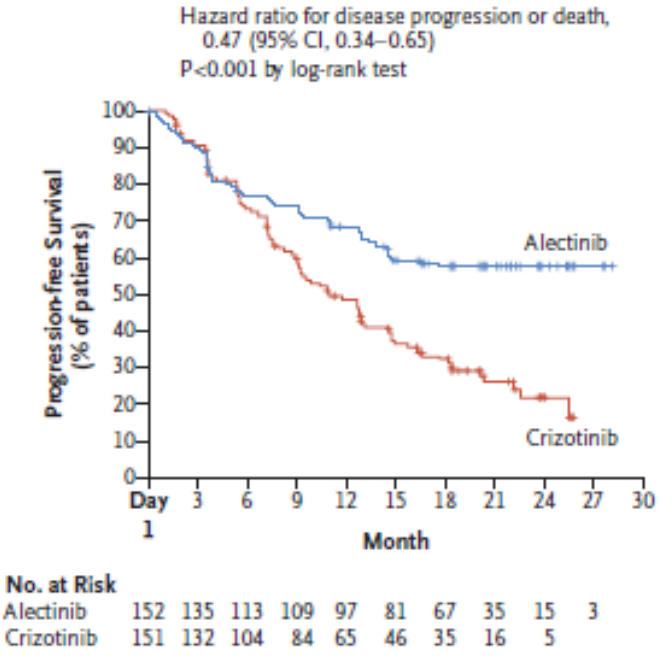
[a]HR was estimated by Cox regression.

Stratified HRs and *p* values were stratified for the covariates race (Asian vs. non-Asian) and central nervous system metastases at the baseline by the IRC.

Notes: Data cutoff: 9th February 2017 (primary analysis).

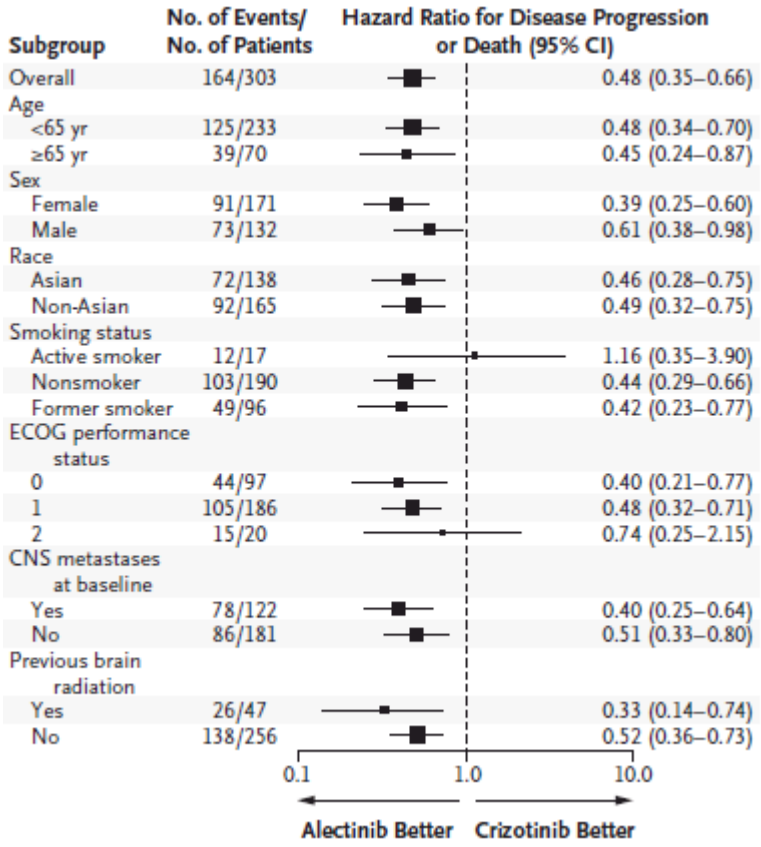
Source: [17]

Figure 5.2. Kaplan–Meier plot of investigator-assessed progression-free survival [2]



Abbreviation: CI=confidence interval.

Figure 5.3. Subgroup analysis of progression-free survival for alectinib versus crizotinib, ALEX trial [2]



Abbreviations: CI=confidence interval; CNS=central nervous system; ECOG Eastern Cooperative Oncology Group; yr=years.

Morbidity

[D0005] How does alectinib affect symptoms and findings (e.g. time to CNS progression, objective response rate (ORR), health-related quality of life (HRQoL)) of adults with *ALK-positive* advanced NSCLC?

Key secondary outcomes are separated into results in the intent-to-treat (ITT) population referring to whole-body outcomes (ORR and duration of response), and CNS results, either as subgroup analyses or endpoints specifically addressing CNS efficacy. The results are summarised in Tables 0.1.

ORR and duration of response

Alectinib versus crizotinib (ALEX trial, direct comparison)

More patients in the alectinib arm than in the crizotinib arm in ALEX were considered responders (83% vs. 76%). This difference of approximately 7 percentage points (95% CI -1.7% to 16.5%) was not statistically significant *(p*=0.09). In the alectinib arm, 4% of patients were considered complete responders compared with 1% in the crizotinib arm (Table 5.5).

Fewer responders in the alectinib arm than in the crizotinib arm has disease progression or died (32% vs. 64%) in ALEX. Because most of responses were ongoing in the alectinib arm, the median duration of response (DOR) assessed by the investigator was not yet reached (95% CI not estimable) whereas the median was 11.1 months (95% CI 7.9–13.0 months) in the crizotinib arm. The difference was statistically significant (*p*<0.0001) (Table 5.5) [2].

Table 5.5. Objective response rate and duration of response, ALEX trial

Endpoint	**Alectinib *N*=152**	**Crizotinib *N*=151**
Median duration of follow-up, months (range)	18.6 (0.5–29.0)	17.6 (0.3–27.0)
Key secondary endpoints		
ORR (investigator)		
Response rate, *n* (%)	126 (82.9)	114 (75.5)
Response rate, 95% CI, %	75.95–88.51	67.84–82.12
Difference percentage points (95% CI)	7.40 (–1.71 to 16.50)	
p (Mantel–Haenszel)	0.09	
Complete response, *n* (%)	6 (4)	2 (1)
Partial response, *n* (%)	120 (79)	112 (74)
Stable disease	9 (6)	24 (16)
Exploratory endpoints		
DOR (investigator)	***n*=126**	***n*=114**
Patients with event, *n* (%)	40 (32)	73 (64)
Median, months (95% CI)	NE (NE)	11.1 (7.9–13.0)
HR (95% CI)[a]	0.36 (0.24–0.53)	
p (stratified log-rank)	<0.0001	

Abbreviations: CI=confidence interval; DOR=duration of response; HR=hazard ratio; NE=not estimable; ORR=objective response rate.

[a]HR was estimated by Cox regression.

Notes: Data cutoff 9th February 2017 (primary analysis).

Source: [17] and [2]

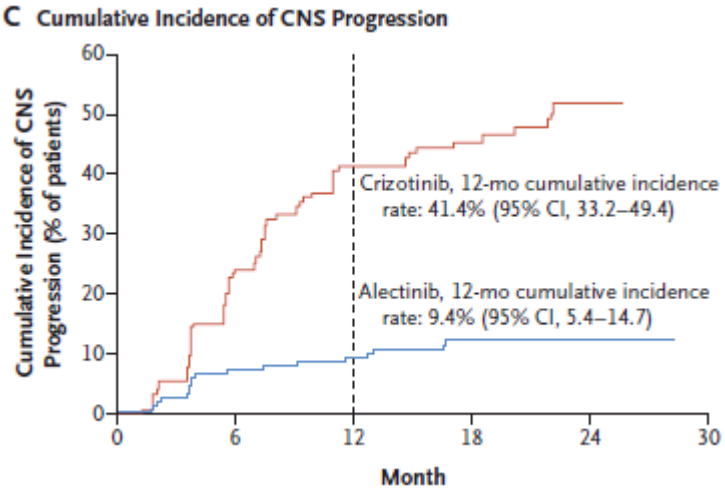
CNS results

Alectinib versus crizotinib
The time to CNS progression was significantly longer with alectinib than with crizotinib in the ITT population (cause-specific HR 0.16, (95% CI, 0.10, 0.28)) (Table 5.6) The cumulative incidence rate of CNS progression was consistently lower over time with alectinib than with crizotinib, and the 12-month cumulative incidence rate of CNS progression was 9.4% (95% CI, 5.4%,14.7%) versus 41.4% (95% CI, 33.2%–49.4%) with crizotinib (Figure 5.4).

In patients without CNS metastases at the baseline, at 12 months, 4.6% of alectinib-treated patients versus 31.3% of crizotinib-treated patients had CNS metastases at the time of first progression, suggesting alectinib is protective against the development of CNS progression (HR 0.14, 95% CI, 0.06, 0.33, $p<0.0001$) [17].

In ALEX, intracranial ORR (exploratory endpoint) was numerically improved with alectinib compared with crizotinib, irrespective of prior radiotherapy. A total of 122 patients had baseline CNS metastasis, 47 of whom had received prior radiotherapy. In patients with baseline measurable CNS disease (n= 43), CNS ORR was 85.7% vs 71.4%, respectively, in patients with prior radiotherapy, and 78.6% vs 40.0% in patients without prior radiotherapy. In patients with measurable and non-measurable CNS disease (n=79) CNS ORR was 36.0% vs 28.6%, respectively, in patients with prior radiotherapy, and 74.4% vs 24.3% in patients without prior radiotherapy. The substantial difference observed in the previously unirradiated group may suggest that the need for radiotherapy with its associated toxicity is reduced or postponed by alectinib [58].

Figure 5.4. Cumulative incidence of central nervous system progression by independent review committee for alectinib versus crizotinib in the ALEX trial [2].



Abbreviation: CI=confidence interval; CNS=central nervous system; mo=month.

*Cumulative incidence of CNS progression, as assessed by the independent review committee according to Response Evaluation Criteria in Solid Tumours, version 1.1. Values were adjusted for the competing risks of non-CNS progression and death.

Table 5.6. Central nervous system efficacy outcomes in the ALEX trial

Endpoint	Alectinib *N*=152	Crizotinib *N*=151
Median duration of follow-up, months (range)	18.6 (0.5–29.0)	17.6 (0.3–27.0)
Key secondary endpoints		
Time to CNS progression (IRC)		
Patients with event, *n* (%)	18 (11.8)	68 (45.0)
Cause-specific HR (95% CI)[a]	0.16 (0.10, 0.28)	
Stratified log-rank *p*	<0.0001	
1-year cumulative incidence rate of CNS progression (IRC), % (95% CI)	9.4 (5.4, 14.7)	41.4% (33.2%, 49.4%)
Exploratory endpoints		
CNS ORR for patients with measurable CNS lesions at the baseline (IRC)	***n*=21**	***n*=22**
Patients with event, *n* (%)	17 (81.0)	11 (50.0)
95% CI (%)	58.1–94.6	28.2–71.8
CNS complete response[b] *n* (%)	8 (38)	5 (1)
CNS ORR for patients with measurable and/or nonmeasurable CNS lesions at the baseline (IRC)	***n*=64**	***n*=58**
Patients with event, *n* (%)	38 (59.4)	15 (25.9)
95% CI	46.4–71.5	15.3–39.0
CNS complete response* *n* (%)	29 (45)	5 (9)
CNS DOR for patients with measurable CNS lesions at the baseline (IRC)*	***n*=21**	***n*=22**
Median, months[b]	17.3	5.5
95% CI, months[b]	14.8 to NE	2.1–17.3

Abbreviations: CI=confidence interval; CNS=central nervous system; DOR=duration of response; HR=hazard ratio; IRC=independent review committee; NE=not estimable; ORR=objective response rate; PFS=progression-free- survival.

[a]HR was estimated by Cox regression.

[b]Data from Peters et al. [1]

Stratified HRs and *p* values were stratified for the covariates race (Asian vs. non-Asian) and CNS metastases at the baseline by the IRC.

Notes: Data cutoff 9th February 2017 (primary analysis).

Source: [17]

Indirect comparison

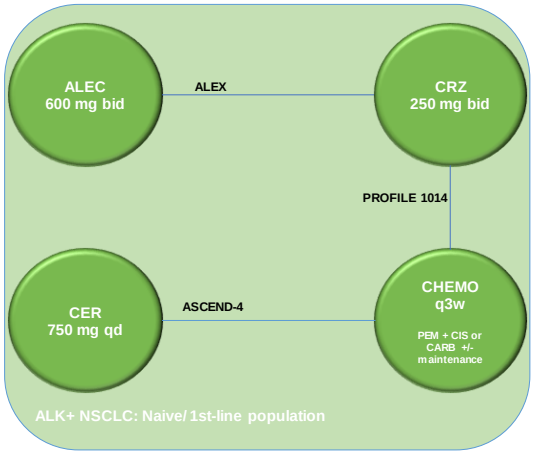
An NMA was performed by the MAH company using Bayesian Markov chain Monte Carlo methods in WinBUGS, with a fixed-effects and a random effects model. The NMA MAH base case as conducted using a fixed effects model and included the ALEX, ASCEND-4 and PROFILE 1014 studies. For the sensitivity analysis more than one study (PROFILE 1014 and PROFILE 1029) were available to evaluate the comparison between crizotinib and chemotherapy which allowed for both a fixed effects and random effects NMA to be conducted. Both sensitivity analyses were performed with the results included from the PROFILE 1029 study.

The results should be interpreted with caution due to limitations in the analyses and data that may have affected the results. These are further addressed in Appendix 6. Indirect comparisons – statistical aspects.

Additionally to the Bayesian fixed effects NMA, also indirect comparisons known as the Bucher method were presented by the MAH. The results are nearly identical because the network is elementary enough, such that the more complex fixed effects NMA does not use its additional capabilities in processing the data, compared with the simple Bucher method (see Appendix 6. Indirect comparisons – statistical aspects). Thus only the NMA is presented, with focus on the MAH base case fixed effects.

Alectinib versus ceritinib (NMA, indirect comparison)
See section 5.2 on Included studies for a discussion on the included studies and their baseline data.

Figure 5.5. Studies included in the base case network meta-analysis



Abbreviations: ALEC=alectinib; ALK+=*ALK* positive; bid=twice daily; CARB=carboplatin; CER=ceritinib; CHEMO=chemotherapy; CIS=cisplatin; CRZ=crizotinib; NSCLC=non-small cell lung cancer; PEM=pemetrexed; q3w=every 3 weeks; qd=once daily.

Source: [17]

Table 5.7. Summary of objective response rate, duration of response and progression-free survival outcomes across studies

Study (assessment)	Objective response rate, %		Duration of response, months (95% CI)		PFS (median), months (95% CI)	
ALEX	Alectinib	Crizotinib	Alectinib	Crizotinib	Alectinib	Crizotinib
(Inv[a])	83	76	NE (NE)	11.1 (7.9, 13.0)	NE (17.7 to NE)	11.1 (9.1, 13.1)
(IRC)	78.9	72.2	—	—	25.7 (19.9 to NE)	10.4 (7.7, 14.6)
PROFILE 1014 (IRC)	Crizotinib	Chemotherapy	Crizotinib	Chemotherapy	Crizotinib	Chemotherapy
	74	45	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
PROFILE 1029[b] (IRC)	Crizotinib	Chemotherapy	Crizotinib	Chemotherapy	Crizotinib	Chemotherapy
	87.5	45.6	—	—	11.1 (8.3, 12.6)	6.8 (5.7, 7.0)
ASCEND-4 (IRC)	Ceritinib	Chemotherapy	Ceritinib	Chemotherapy	Ceritinib	Chemotherapy
	73	27	23.9 (16.6 to NE)	11.1 (7.8, 16.4)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)

Abbreviations: CI=confidence interval; IRC=independent review committee; Inv=investigator; NE=not estimable; PFS=progression-free survival.
[a] Inv: investigator
[b]Not included in base case network meta-analysis.
Source: [17]

ORR measures tumour shrinkage and can thereby provide direct information on a therapeutic agent's antitumour effect, particularly for cytotoxic agents. The ORR of the comparator chemotherapy arms is essentially the same in the two PROFILE studies (45%), but is markedly lower in the ASCEND-4 study (27%) (Table 5.7). In ASCEND-4, only up to 4 cycles of pemetrexed plus platinum therapy were administered, followed by maintenance pemetrexed therapy in patients without progression, whereas in the PROFILE studies, up to 6 cycles were administered, without maintenance therapy. The marked difference in ORR for the chemotherapy arms could potentially suggest the presence of important differences in the study populations with regard to prognosis, and/or that the maintenance pemetrexed therapy did not result in additional responses to outweigh the lower number of standard chemotherapy cycles. (See the discussion on baseline characteristics above). On the other hand, the duration of response was considerably longer in the chemotherapy arm of ASCEND-4 compared with PROFILE 1014, as might be expected with continued, compared with interrupted, treatment.

The ORR for crizotinib was consistent across the two trials used in the NMA, ALEX (75%) and PROFILE 1014 (74%), but was higher in the (excluded) PROFILE 1029 study (87%). The median PFS for crizotinib was also consistent across studies (10–11 months), including PROFILE 1029 (Table 5.7).

Table 5.8. Summary of treatment effect estimates in the network meta-analysis (base case)

	Endpoint (analysis)				
	HR (95% credible interval)		Odds ratio (95% credible interval)		HR (95% credible interval)
Comparison	PFS by IRC	OS	ORR by IRC	DCR by IRC	PFS by IRC in a subgroup of patients with CNS metastases at the baseline
Alectinib versus chemotherapy	**0.23 (0.15–0.34)**	0.63 (0.34–1.15)	**5.06 (2.51–10.22)**	1.41 (0.60–3.35)	**0.21 (0.10, 0.44)**
Alectinib versus crizotinib	**0.50 (0.36–0.70)**	0.76 (0.49–1.20)	1.45 (0.86–2.46)	0.83 (0.41–1.69)	**0.37 (0.22–0.63)**
Alectinib versus ceritinib	**0.41 (0.25–0.67)[a]**	0.85 (0.41–1.73)	0.69 (0.30–1.61)	0.72 (0.26–1.95)	**0.30 (0.13–0.71)[a]**
Crizotinib versus chemotherapy	**0.45 (0.35–0.58)[a]**	0.82 (0.54–1.24)	**3.49 (2.21–5.57)**	**1.70 (1.05–2.77)**	**0.57 (0.35–0.93)[a]**
Ceritinib versus chemotherapy	**0.55 (0.42–0.72)**	0.73 (0.50–1.06)	**7.30 (4.68–11.61)**	**1.97 (1.19–3.32)**	0.70 (0.43–1.11)
Ceritinib versus crizotinib	1.22 (0.84–1.79)	0.90 (0.52–1.57)	**2.09 (1.10–3.99)**	1.16 (0.57–2.35)	1.22 (0.62–2.43)

Abbreviations: CNS=central nervous system; DCR=disease control rate; HR=hazard ratio; IRC=independent review committee; OS=overall survival; ORR=objective response rate; PFS=progression free survival.

Bold indicates significance based on 95% credible intervals.

Note: HR of 1 indicates no effect, HR<1 indicates lower risk of PFS/OS or better response compared with control.

Odds ratio of 1 indicates no effect, Odds ratio greater than 1 indicates a better response compared with the control.

[a]The relative effect of crizotinib versus chemotherapy may be overestimated and thus the effect of alectinib versus ceritinib may be overstated because of the inclusion of pemetrexed maintenance therapy in the ASCEND-4 chemotherapy arm.

Source: [17]

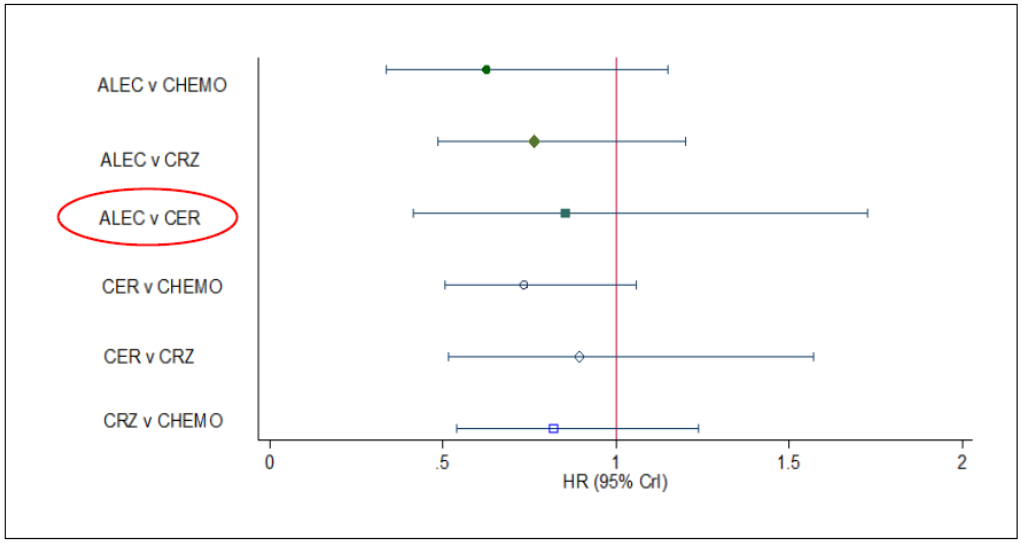
Mortality – NMA

Alectinib versus ceritinib (NMA, indirect comparison)

There were no statistically significant differences in OS between alectinib and ceritinib according to the NMA (Figure 5.6). The results may be affected by treatment arm crossover and data

immaturity (median OS was not observed for some treatment arms in the trials). See also summary efficacy estimates, including OS, for the NMA in Table 5.8.

Figure 5.6. Caterpillar plot of network meta-analysis hazard ratio for overall survival unadjusted (base case, fixed effect)



- Potentially confounded by treatment arm cross-over and it should be noted that the median OS was not observed (i.e. immaturity of data) for some arms given the early data cut-off.

Red line: Hazard ratio = 1 is line of no effect and <1 indicates lower risk of PFS or OS compared to control

95% CrI ● ALEC v CHEMO ◆ ALEC v CRZ ■ ALEC v CER
○ CER v CHEMO ◇ CER v CRZ □ CRZ v CHEMO

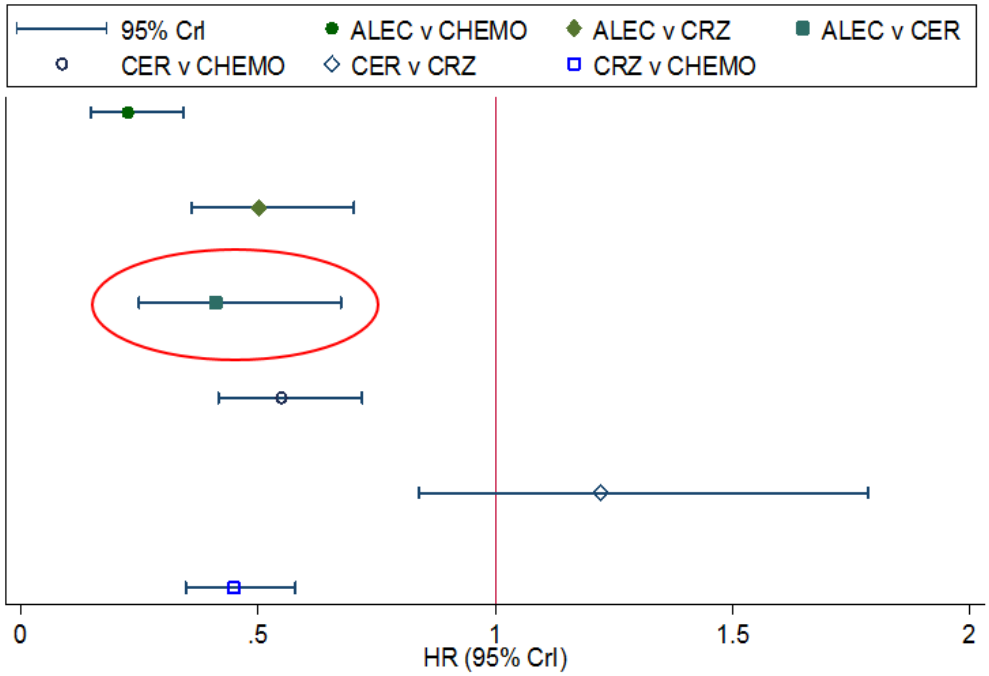
Abbreviations: ALEC=alectinib; CER=ceritinib; CHEMO=chemotherapy; CrI=credible interval; CRZ=crizotinib; HR=hazard ratio; OS=overall survival; PFS=progression-free survival.
Source: [17]

Progression-free survival – NMA

Alectinib versus ceritinib (NMA, indirect comparison)
The key efficacy findings for the fixed effects base case (including ALEX, ASCEND 4 and PROFILE 1014) were as follows (Figure 5.7;Table 5.8)

- Significantly longer IRC PFS for alectinib versus ceritinib
- Significantly longer IRC PFS in the subgroup of patients with CNS metastases at the baseline with alectinib versus ceritinib

Figure 5.7. Caterpillar plot of network meta-analysis hazard ratio for progression-free survival by independent review committee (base case, fixed effect)



Abbreviations: ALEC=alectinib; CER=ceritinib; CHEMO=chemotherapy; CrI=credible interval; CRZ=crizotinib; HR=hazard ratio.
Source: MAH submission (network meta-analysis report).

Quality of life

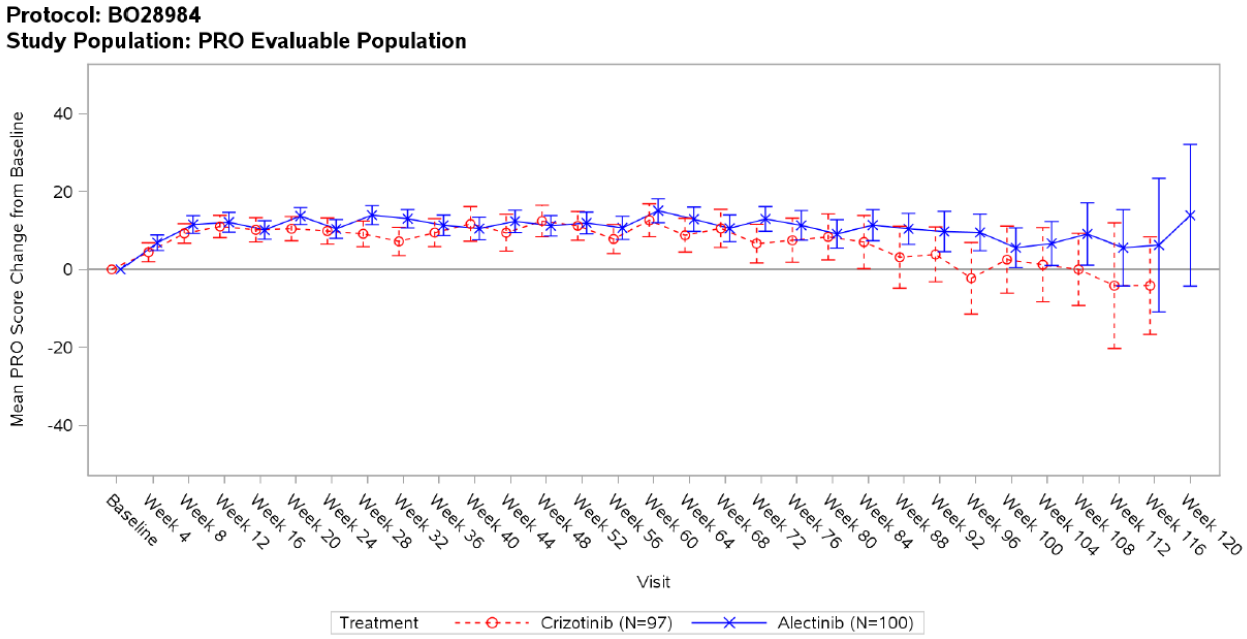
[D0016] How does alectinib affect activities of daily living?
No evidence was available on activities of daily living.

[D0012] What is the effect of alectinib on generic health-related quality of life?
With use of both the self-administered European Organisation for Research and Treatment of Cancer quality-of-life questionnaire QLQ-C30 and its lung cancer module QLQ-LC13, the impact of disease symptoms and treatment on patients' functioning and HRQoL were assessed.

The proportions of compliance at the baseline were similar in both treatment arms, with 64% of patients in the alectinib arm and 66% of patients in the crizotinib arm completing the baseline patient-reported outcomes assessment. Among patients who had PRO baseline data compliance rates were 60% or greater throughout the study with the exception of Week 112 and 116 were observed in the alectinib-treated arm. A point change in scale score, reported by a patient, that is greater than 10 is considered clinically meaningful.

The findings of the patient-reported outcomes analyses indicated that patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. On average, patients treated with alectinib reported durable clinically meaningful improvement in HRQoL (from the baseline) until week 88. For patients treated with crizotinib, clinically meaningful improvements in HRQoL (from the baseline) were reported at multiple time points until week 68.

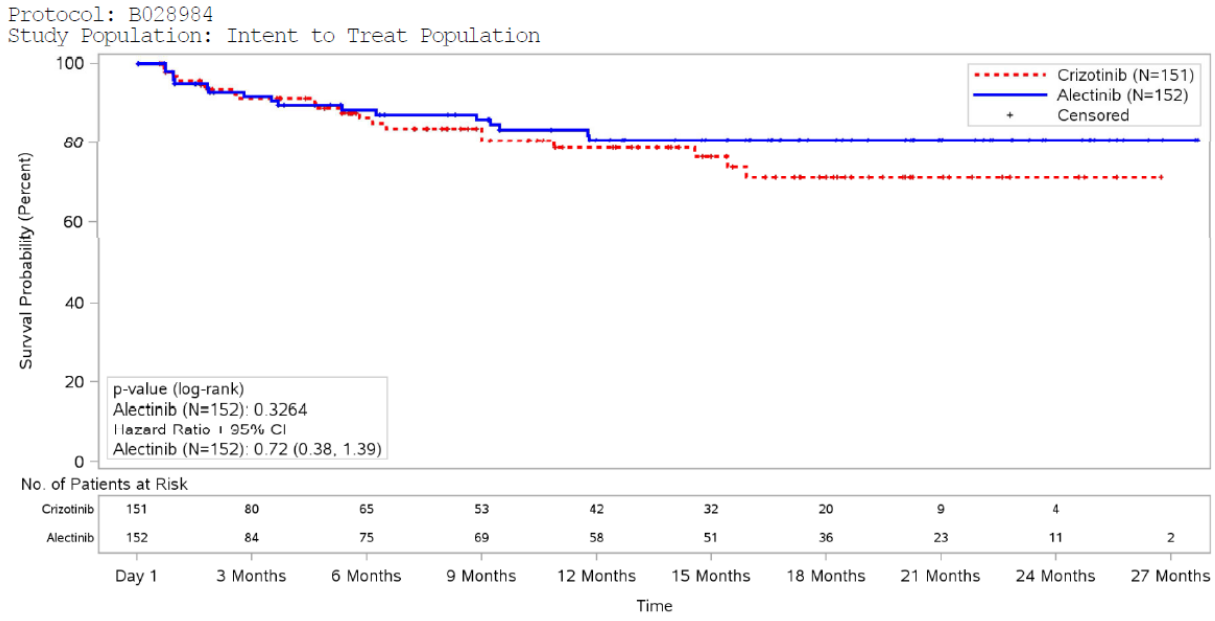
Figure 5.8. Mean change from the baseline in European Organisation for Research and Treatment of Cancer QLQ-30 global health score (ALEX)



Abbreviation: PRO=patient-reported outcome.
Source: [17]

No statistical significance of a difference in the time to confirmed deterioration for patient-reported global health status/HRQoL was found between treatments (HR 0.72, 95% CI, 0.38, 1.39). The proportion of patients with confirmed deterioration events was less than 13.2% in both arms.

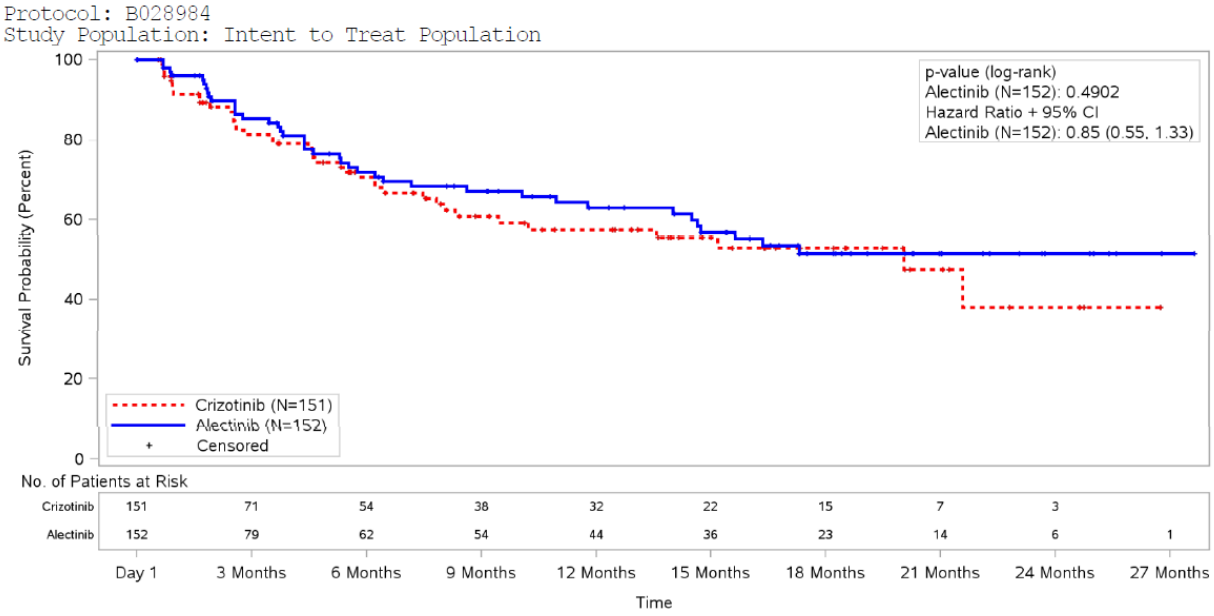
Figure 5.9. Time to deterioration in European Organisation for Research and Treatment of Cancer QLQ-30 global health score (intent-to-treat population) (ALEX)



Abbreviation: CI=confidence interval.
Source: [17]

No statistical significance of a difference in the time to deterioration in cognitive functioning was found between alectinib and crizotinib. In the alectinib arm, the median time to deterioration in cognitive functioning was not reached; in the crizotinib arm it was 20 months (HR 0.85, 95% CI, 0.55, 1.33).

Figure 5.10. Kaplan–Meier plot of European Organisation for Research and Treatment of Cancer QLQ-C30 cognitive functioning time to deterioration (intent-to-treat population) (ALEX)



Abbreviation: CI=confidence interval.
Source: [17]

HRQoL of patients with CNS metastases at the baseline

The finding that patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration in comparison with patients receiving crizotinib was particularly evident in the predefined subgroup of patients with CNS metastases at the baseline. For this subgroup (starting at week 12 and persisting for most assessments to week 84) a lower proportion of patients receiving alectinib reported clinically meaningful worsening in HRQoL in comparison to patients receiving crizotinib. In addition, fewer patients treated with alectinib reported clinically meaningful worsening in cognitive functioning through many assessments between week 4 and week 84. For patients with CNS metastases at the baseline, similar patterns were observed for fatigue, physical function and social function scores.

[D0013] What is the effect of alectinib on disease-specific quality of life?

The analysis indicates that there is no statistically significant difference between alectinib and crizotinib regarding clinically meaningful reduction in lung cancer symptoms (including patient-reported cough, chest pain, pain in other parts, fatigue and dyspnoea). However, on average patients receiving alectinib reported clinically meaningful reduction (from the baseline) of multiple lung cancer symptoms for a longer duration compared with patients receiving crizotinib
(see Appendix 5. Health-related quality of life).

6 SAFETY

6.1 Research questions

Element ID	Research question
C0008	What is the frequency of any adverse events of alectinib compared to other approved treatments in the 1st line therapy? What are the most frequent AEs of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of discontinuation of treatment due to adverse events of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of AE leading to dose reduction of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency and what are serious adverse events (SAE) of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of serious adverse events (SAE) leading to death for alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of adverse events of special interest for alectinib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of alectinib?

6.2 Results

Included studies
The safety results are based on the ALEX trial and the SmPC containing pooled data from ALEX and two single-arm phase II clinical trials of alectinib (NP28761, NP28673; *N*=405).

In the phase II clinical trials (NP28761, NP28673; *N*=253), the median duration of exposure to alectinib was 11 months. In ALEX trial; *N*=152, the median duration of exposure to alectinib was 17.9 months, whereas the median duration of exposure to crizotinib was 10.7 months.

In addition, ADR frequencies are presented from the SmPCs of Xalkori and Zykadia. The SmPC frequencies reflect the EMA established safety profile and are based on all relevant studies at the approved dose.

Patient safety

Alectinib versus crizotinib (ALEX trial, direct comparison)
In the ALEX trial the median duration of treatment was shorter in patients in the crizotinib arm (10.7 months; range 0–27 months) compared with patients in the alectinib arm (17.9 months; range 0–29 months); this was mainly driven by fewer treatment discontinuations due to disease progression in the alectinib arm. A lower proportion of patients in the crizotinib arm than in the alectinib arm completed more than 12 months (45% vs. 66%) and more than 18 months (27% and 49%) of study treatment.

The mean dose intensity was comparable between treatment arms (92% for crizotinib and 96% for alectinib); however, the proportion of patients in the crizotinib arm (42%) who missed at least one dose of treatment was higher than the proportion of patients in the alectinib arm (32%) (Table 6.1).

Table 6.1.Overview of treatment exposure and incidence of adverse events, ALEX trial (safety population)

	Crizotinib ***N*=151**	**Alectinib** ***N*=152**
Median treatment duration, months (range)	10.7 (0–27)	17.9 (0–29)
Patient-years of observation	158.0	194.7
Proportion of patients treated for >12 months	45%	66%
Proportion of patients treated for >18 months	27%	49%
Mean dose intensity, % (SD)	92.4 (14.1)	95.6 (10.3)
Total number of patients with ≥1 AE, *n* (%)	146 (97)	147 (97)
Total number of AEs, *n*	1365	1196
Total number of patients with ≥1, *n* (%)	151 (100)	152 (100)
AE with fatal outcome (grade 5)	7 (5)	5 (3)
Grade ≥3 AE	76 (50)	63 (41)
Serious AE	44 (29)	43 (28)
Treatment-related AE	134 (89)	117 (77)
AE leading to treatment discontinuation	19 (13)	17 (11)
AE leading to dose reduction	31 (21)	24 (16)
AE leading to drug interruption	38 (25)	29 (19)

Abbreviations: AE=adverse event; SD=standard deviation.
Source: [17]

[C008] What are the most frequent AEs of alectinib compared to other approved treatments in the 1st line therapy?

Alectinib versus crizotinib (ALEX trial, direct comparison)
The majority of the most common AEs (≥10% of patients in either arm) in the ALEX trial occurred in a higher proportion of patients (≥5% absolute difference) in the crizotinib arm compared with the alectinib arm. Crizotinib was associated with higher proportion of gastrointestinal AEs and liver enzyme abnormalities than alectinib. The AEs with a higher incidence with alectinib versus crizotinib were anaemia, myalgia, increased blood bilirubin level, increased weight, musculoskeletal pain and photosensitivity reaction. Constipation, fatigue, arthralgia, and rash were reported with a similar frequency (<5% absolute difference) between treatment arms (Table 6.2).

Table 6.2. Adverse events with ≥5% difference in incidence between arms, ALEX trial

	Patients with adverse event (%)			
	Crizotinib		**Alectinib**	
	***N*=151**		***N*=152**	
Event	Any grade	Grade 3–5	Any grade	Grade 3–5
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhoea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
ALT level increased	45 (30)	22 (15)	23 (15)	7 (5)
AST level increased	37 (25)	16 (11)	21 (14)	8 (5)
Blood bilirubin level increased	2 (1)	0	23 (15)	3 (2)
Weight increased	0	0	15 (10)	1 (1)
Myalgia	3 (2)	0	24 (16)	0
Dysgeusia	29 (19)	0	4 (3)	0
Anaemia	7 (5)	1 (1)	30 (20)	7 (5)
Visual impairment	18 (12)	0	2 (1)	0
Dizziness	21 (14)	0	12 (8)	0
Vision blurred	11 (7)	0	3 (2)	0
Photopsia	9 (6)	0	0	0
Musculoskeletal pain	3 (2)	0	11 (7)	0
Alopecia	11 (7)	0	1 (1)	0
Photosensitivity reaction	0	0	8 (5)	1 (1)
GGT level increased	10 (7)	2 (1)	1 (1)	1 (1)
Peripheral oedema	42 (28)	1 (1)	26 (17)	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase, GGT=γ-glutamyltransferase.

Source: [17]

Comparison of ADR frequencies according to the SmPCs of Alecensa, Xalkori and Zykadia

In a naïve comparison of the ADR frequencies in the SmPCs, and without consideration of the longer median treatment length for alectinib, the frequencies were lower for alectinib than for crizotinib and ceritinib for diarrhoea (16%, 54% and 82%, respectively), vomiting (11%, 51% and 63%, respectively), nausea (19%, 57% and 75%, respectively), and fatigue (not identified as ADR, 30% and 48%, respectively). These are ADRs that impact tolerability and everyday quality of life.

Other reactions that may impact quality of life include oedema, which was not identified as an ADR for ceritinib, but was common with alectinib (30%) and crizotinib (47%), and myalgia, which was reported only for alectinib (28%).

Pneumonitis/interstitial lung disease was also less frequent with alectinib than with crizotinib and ceritinib (0.7%, 3% and 2%, respectively).

For all three agents the frequency of anaemia was 15%–17%, while neutropenia also occurred with crizotinib (22%). No infections were identified as ADRs for crizotinib, however.

The frequencies of vision disorders were similar for alectinib and ceritinib at 7%–9%, but the frequency was markedly higher for crizotinib (63%).

Abnormal liver laboratory results appeared least common with alectinib, while acknowledging that a comparison based on the varying items in the SmPCs is difficult.

The frequencies of severe liver reactions appeared largely similar across the drugs (drug-induced liver injury 0.7% (alectinib), hepatic failure <1% (crizotinib) and hepatotoxicity 1.1% (ceritinib).

Bradycardia was less common with ceritinib (2%) compared with alectinib (9%) and crizotinib (13%). Unlike alectinib, both crizotinib and ceritinib are associated with QT interval prolongation (4% and 10%, respectively). This can have potentially serious consequences, including sudden death, but such outcomes are very rare. The risk of QT interval prolongation affects the handling of the patients however, and may require more monitoring of some patients.

Rash occurred in 18% of patients treated with alectinib, 13% of patients treated with crizotinib and 20% of patients treated with ceritinib.

Photosensitivity is identified as an ADR for alectinib (9%), but not for the other two ALK inhibitors.

See the full list of ADRs in Table 6.3.

Table 6.3. Summary of adverse drug reaction frequencies across summaries of product characteristics of Alecensa, Xalkori and Zykadia

	ADR frequencies, %		
System organ class ADRs (MedDRA)	**Alecensa (alectinib)** ***N*=405**	**Xalkori (crizotinib)** ***N*=1722**	**Zykadia (ceritinib)** ***N*=925**
Blood and lymphatic system disorders			
Neutropenia	—	22	—
Anaemia	17	15	15
Leukopenia	—	15	—
Metabolism and nutrition disorders			
Decreased appetite	—	30	39
Hyperglycaemia	—	—	9
Hypophosphataemia	—	6	5
Nervous system disorders			
Neuropathy	—	25	—
Dysgeusia	5	21	—
Eye disorders			
Vision disorders	9	63	7
Cardiac disorders			
Dizziness	—	26	—
Bradycardia	9	13	2.3
Pericarditis	—	—	6
Electrocardiogram QT interval prolonged	—	4	10
Syncope	—	3	—
Cardiac failure	—	1	—
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/pneumonitis	0.7	3	2.1
Gastrointestinal disorders			
Constipation	35	43	24
Nausea	19	57	75
Diarrhoea	16	54	82
Vomiting	11	51	63
Abdominal pain	—	21	46
Dyspepsia	—	8	—
Stomatitis	3.0	—	—
Oesophagitis/oesophageal disorder	—	Oesophagitis 2	Oesophageal disorder 14
Gastrointestinal perforation	—	<1	—
Pancreatitis	—	—	0.5
Hepatobiliary disorders (including investigations)			
Liver laboratory test abnormalities	—	—	60
Elevated levels of transaminases	—	32	—
Abnormal liver function test results	—	—	2.2
Increased bilirubin level	18	—	—
Increased AST level	15	—	—
Increased ALT level	14	—	—
Increased alkaline phosphatase level	6.2	7	—
DILI/hepatotoxicity (including DILI)	DILI 0.7	—	Hepatotoxicity 1.1
Hepatic failure	—	<1	—
Skin and subcutaneous tissue disorders			
Rash	18	13	20
Photosensitivity	9.1	—	—

	ADR frequencies, %		
System organ class ADRs (MedDRA)	**Alecensa (alectinib)** ***N*=405**	**Xalkori (crizotinib)** ***N*=1722**	**Zykadia (ceritinib)** ***N*=925**
Musculoskeletal and connective tissues disorders			
Myalgia	28	—	—
Increased blood creatine phosphokinase level	10	—	—
Renal and urinary disorders (including Investiga—tions)			
Blood creatinine level increased	7.2	8	22
Renal cyst	—	3	—
Acute kidney injury	1.0	—	—
Acute renal failure/renal failure	—	<1/<1	1.8
Renal impairment	—	—	1.0
General disorders and administration site conditions			
Oedema	30	47	—
Fatigue	—	30	48
Investigations			
Weight increased	12	—	—
Weight decreased	—	—	28
Lipase level increased	—	—	4.8
Amylase level increased	—	—	7
Blood testosterone decreased	—	2	—

Abbreviations: ADR=adverse drug reaction; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DILI=drug-induced liver injury; MedDRA=Medical Dictionary for Regulatory Activities.
Note: Frequencies ≥5% have been abbreviated to have no decimal.
Source: Alecensa SmPC, Xalkori SmPC, Zykadia SmPC.

Table 6.4. Overview of adverse events across relevant studies

	ALEX		ASCEND-4
	Alectinib (*N*=152)	**Crizotinib (*N*=151)**	**Ceritinib (*N*=189)**
Total number of AEs **Total number of deaths**	1196 35 (23)	1365 40 (27)	NA 48 (25.4)
Any AE, n (%)	147 (97)	146 (97)	189 (100)
Serious AE, n (%)	43 (28)	44 (29)	70 (37)
Related AE, n (%)	117 (77)	134 (89)	184 (97)
AE leading to treatment discontinuation, n (%)	17 (11)	19 (13)	21 (11)
AE leading to dose reduction, n (%)	24 (16)	31 (21)	152 (80)[a]
AE leading to dose interruption, n (%)	29 (19)	38 (25)	131 (69)
AE leading to withdrawal from study, n (%)	0	2 (1)	NA
Grade ≥3 AE, n (%)[b]	63 (41)	76 (50)	148 (78)
AE with fatal outcome (grade 5), n(%)	5 (3)	7 (5)	11 (6)

Abbreviations: AE=adverse event; NA=not available.
[a]Dose adjustment or interruption in ASCEND-4.
[b]Grade 3 or 4 in ASCEND-4.

Sources: [17], Zykadia EPAR variation II/12.

In the ALEX trial serious AEs (SAEs) occurred at a similar frequency in patients in both treatment arms (28% with alectinib, 29% with crizotinib).

Common individual SAEs included pneumonia (3% of patients in the alectinib arm vs. 3% of patients in the crizotinib arm), pneumonitis (1% vs. 3%), pulmonary embolism (1% vs. 2%) and increased alanine aminotransferase level (1% vs. 3%).

The only SAEs which occurred at a higher (≥2% difference) incidence in the alectinib arm were acute kidney injury (3% with alectinib vs. 0% with crizotinib) and lung infection (2% vs. 0%). Nausea was more frequent among patients receiving crizotinib ((0% vs. 2%) [17].

Table 6.5. Serious adverse events in the safety population occurring in greater than 2% patients in either arm, ALEX trial

	Alectinib (*N*=152)	**Crizotinib (*N*=151)**
Patients with an SAE, *n* (%)	43 (28)	44 (29)
Pneumonia, *n* (%)	5 (3)	4 (3)
Lung infection, *n* (%)	3 (2)	0 (0)
Pneumonitis, *n* (%)	2 (1)	4 (3)
Pulmonary embolism, *n* (%)	2 (1)	3 (2)
Pyrexia, *n* (%)	1 (1)	3 (2)
ALT level increased, *n* (%)	1 (1)	4 (3)
Acute kidney injury, *n* (%)	4 (3)	0 (0)
Nausea, *n* (%)	0 (0)	3 (2)

Abbreviations: ALT=alanine aminotransferase; SAE=serious adverse event.
Source: Supplementary appendix from ALEX trial

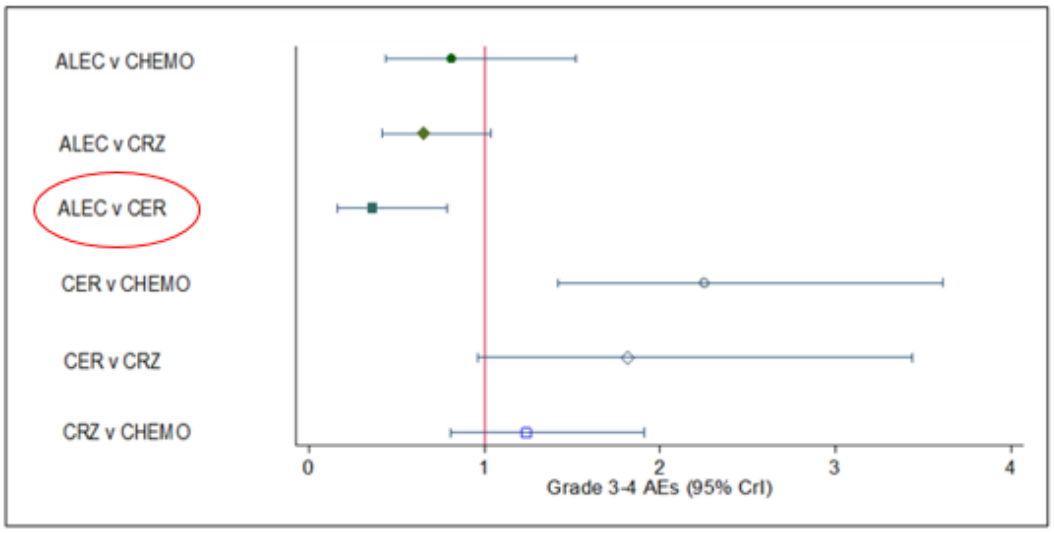
Network meta-analysis

Alectinib versus ceritinib (NMA, indirect comparison)
The MAH performed a Bayesian fixed effects NMA and an indirect comparison according to the Bucher method. The results are nearly identical because the network is elementary enough, such that the more complex fixed effects NMA does not use its additional capabilities in processing the data, compared to the simple Bucher method; see the efficacy section (5.2). Thus only the NMA is presented, with focus on the MAH base case fixed effects.

The NMA performed by the MAH indicates:

- Significantly fewer grade 3 or 4 AEs with alectinib than with ceritinib.
- Significantly more grade 3 or 4 AEs with ceritinib than with chemotherapy.
- Significantly more dose reductions or treatment interruptions with alectinib, ceritinib and crizotinib than with chemotherapy. This result is driven by the PROFILE 1014 crizotinib versus chemotherapy comparison. In PROFILE 1014, data are Grade 3 or 4 elevations of ALT managed with dose interruptions or dose reductions. For ASCEND-4 and ALEX, data are any treatment interruptions or dose reductions due to an AE. Additionally, the differences in dose reductions or treatment interruptions may be due to differences in time on treatment/drug exposure.
- No significant differences for discontinuations due to AEs.

Figure 6.1. Network meta-analysis odd ratios for grade 3 or 4 adverse events (base case)



Red line: Odds ratio of 1 is the line of no effect and odds ration less than 1 indicates lower odds of event (fewer adverse events) compared with the control.
Abbreviations: AE=adverse event; ALEC=alectinib; CER=ceritinib;CHEMO=chemotherapy; CrI=credible interval; CRZ=crizotinib.
Source: [17].

Table 6.6. Network meta-analysis summary of safety (base case)

	Endpoint (analysis), odds ratio (credible interval)		
Comparison	**Grade 3 or 4 AEs**	**Discontinuation due to AEs**	**Treatment interruption or dose reduction**
Alectinib versus chemotherapy	0.81 (0.44–1.52)	0.50 (0.20–1.27)	**5.25 (1.73–22.92)**
Alectinib versus crizotinib	0.65 (0.41–1.04)	0.87 (0.43–1.77)	0.71 (0.44–1.15)
Alectinib versus ceritinib	**0.36 (0.16–0.79)**	0.62 (0.19–2.05)	1.02 (0.30–4.68)
Crizotinib versus chemotherapy	1.24 (0.81–1.91)	0.58 (0.31–1.05)	**7.36 (2.72–29.50)**
Ceritinib versus chemotherapy	**2.25 (1.42–3.61)**	0.81 (0.38–1.67)	**5.15 (3.26–8.39)**
Ceritinib versus crizotinib	1.82 (0.96–3.44)	1.41 (0.54–3.61)	0.70 (0.16–2.15)

Abbreviation: AE=adverse event.
Note: Odds ratio of 1 indicates no effect, and odds ratio of less than 1 indicates lower odds of an event compared with the control. Bold indicates significance based on 95% credible intervals.

Source: [17]

[C0008] What is the frequency of adverse events of special interest for alectinib?
Hy's law is a set of clinical and laboratory signs indicating drug-induced liver injury. Cases were defined as increases of aspartate aminotransferase or alanine aminotransferase level of more than three times the upper limit of normal or baseline value (if baseline values were already increased), together with concomitant increases of total bilirubin level of more than two times the upper limit of normal in the absence of cholestasis. The scatter plot analysis of total bilirubin level versus alanine aminotransferase and aspartate aminotransferase level revealed five patients (two in the crizotinib arm and three in the alectinib arm) falling into the potential Hy's law quadrant.

Two patients (both in the alectinib arm) did not qualify as true Hy's law cases after detailed review because there was not a close temporal relationship between the increase of the levels of the

aminotransferases and bilirubin, or being indicative of cholestasis and underlying hepatic pathology. One of these patients experienced grade 4 drug-induced liver injury, which was considered treatment related, and treatment was permanently discontinued because of the event.

On review, the other three patients (two patients in the crizotinib arm and one patient in the alectinib arm) met Hy's law criteria.

The two patients in the crizotinib arm experienced grade 4 drug-induced liver injury; both events were considered treatment related. One of these patients permanently discontinued treatment because of the event. One had discontinued treatment because of grade 4 elevated alanine aminotransferase level before the diagnosis of drug-induced liver injury. The patient in the alectinib arm experienced grade 4 hepatoxicity; this was considered treatment related and led to treatment discontinuation [17] .

[C0005] What are the susceptible patient groups that are more likely to be harmed through the use of alectinib?

Generally, patients with an preexisting condition that overlaps the toxicity profile of alectinib might be considered at greater risk by the treatment. Patients with bradycardia may thus have an increased risk of symptomatic toxicity, since the preexisting bradycardia might be aggravated with alectinib.

Patients with moderate to severe hepatic impairment may be more likely to be harmed since the elimination of alectinib is predominantly through metabolism in the liver, and hepatic impairment may increase the plasma concentration of alectinib and/or its major metabolite M4. On the basis of a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients with mild hepatic impairment and normal hepatic function, however.

Age, body weight, race and sex had no clinically meaningful effect on the systemic exposure of alectinib and M4 [5].

7 PATIENT INVOLVEMENT

HTA doers recognise that patients and those who support them have unique knowledge about what it is like to live with a specific disease or medical condition. Patients can help to understand unique perspectives by presenting patients' and carers/care-givers' views and experiences. Patients can describe advantages and disadvantages of health interventions based on patients' experiences and values concerning a new intervention [19]. Thus, one patient could be identified who volunteered to participate in this assessment.

With this patient, an one hour telephone interview was performed on the 5th of January 2018. The patient provided orally informed consent.

The patient was diagnosed with *ALK*-positive advanced NSCLC and with bone but not CNS metastases in fall 2017. The patient had received crizotinib for four weeks, prescribed by an oncologist. The patient had never smoked and has no further chronic diseases.

The summary of the most important answers related to the different questions on the impact of condition; experience with currently available medicines; expectations of the medicines being assessed; and additional information which the patient believed would be helpful to the HTA researchers are provided in Table 7.1.

Table 7.1 Main results from the interview

Questions related to	**Patient's (*ALK*-positive advanced NSCLC) view**
Impact of *ALK*-positive advanced NSCLC	The patient highlighted that dealing with advanced NSCLC has a significant impact on physical, psychological and emotional well-being (such as uncertainty and mood oscillation) as well as quality of life. Difficulties in daily activities like housework, office work or sports activities (swimming, walking and cycling) were prominent at the beginning of the disease, before starting a specific therapy and pain medications primarily for pain related to bone metastases. The patient has almost no lung cancer symptoms (two times chest pain in the morning) and acknowledges the importance of sport activities and healthy nutrition for a better physical and emotional life during the illness. The impact on informal caregivers (i.e., partner, mother and father) was also recognised, especially the emotional part. No financial implications were currently expected. The patient emphasised that lack of specific lung symptoms could have impacted on experiences and answers related to specific questions.
Experience with currently available medicines (crizotinib)	The patient highlighted the importance of reducing pain related to bone metastases, decreasing pain medication and increasing physical well-being and quality of life for emotional well-being. Even light sporting activities become possible. The twice daily oral administration did not cause problems. After four weeks of crizotinib treatment, an increase in liver enzymes necessitated treatment interruption for one week. At the beginning of the treatment the patient described vision problems of short duration four times. A number of times patient had a sort of strange feeling in left arm, described as very annoying (like arm did not belong to the body; not when touch it [arm], but more mentally). The patient emphasised that this short treatment duration with crizotinib could impact on experiences and answers related to specific questions.
Expectations of the medicine being assessed (alectinib)	The patient identified three highly important expectations concerning new treatment options: life extension, fewer side effects and a better quality of life. The patient does not have brain metastases but read about them on a Facebook group where new treatment options and clinical trials are discussed; patients with brain metastases are highly interested in alectinib. The patient mentioned that access should not be constrained due to financial restriction, especially for people with brain metastases. The patient highlighted that that lack of specific lung symptoms and the short treatment duration with crizotinib could impact on experiences and answers related to specific questions.

Additional information which patient believe would be helpful to the HTA researchers	No further issues were raised by the patient.

The patient could not envisage any special group of patients with particular issues in managing their condition, with using currently available medicines or who could benefit the most from alectinib. The patient stressed the importance of a good communication with physicians concerning information on the condition, treatment choices, adverse effects, treatment plans and the overall process; patients want to be good informed and need to have a trust in physicians who have the knowledge and the main responsibility.

At the end of the interview the patients was asked for the key messages. The patient stressed the importance of extending the life, fewer side effects and no financial implications for patients.

8 DISCUSSION

Efficacy

Direct comparison with crizotinib

Alectinib first-line therapy for patients with *ALK*-positive NSCLC was compared with crizotinib therapy in one open-label randomised phase III trial. Alectinib therapy resulted in a substantial and statistically significant increase in PFS (the primary outcome) compared with crizotinib therapy in the ALEX study. While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs 10.4 months, respectively).The PFS curves for alectinib and crizotinib from the ALEX study did not separate until 6 months. Possible causes or explanations for this pattern could be:

- A difference in the propensity for secondary resistance to the two agents. This is supported by the longer duration of response observed for alectinib versus crizotinib, and might potentially be the primary mechanism for the overall difference in efficacy.

- The presence of subpopulations within the study population with more aggressive tumours progressing early. The pattern could thus indicate less (and similar) efficacy of both agents in more aggressive tumours. Theoretically it could be caused by primary resistance to both agents.

The PFS benefit was consistent for patients with CNS metastases at the baseline. The results for the key secondary endpoint of time to CNS progression clearly demonstrated superiority of alectinib over crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients. This finding may partly be explained by the fact that crizotinib unlike alectinib is a substrate for the P-glycoprotein efflux pump, which is responsible for transporting substances over the blood–brain barrier.

Median OS was not reached in either treatment arm; the event rate was 23% and 27%, for alectinib and crizotinib respectively. The OS analysis was outside the test hierarchy since the previous secondary endpoint (ORR) was not statistically significant. The study was not powered to demonstrate any statistically significant difference in OS between alectinib and crizotinib. Also, even though further OS analyses will be conducted, the results of this endpoint will be impacted by subsequent therapies. With the caveat that applying GRADE to an interim outcome might scientifically be not sound, the results presented for OS have currently a high degree of uncertainty ('low quality of evidence").

In the direct comparison of alectinib and the comparator crizotinib, the quality of evidence is high for the majority of outcomes (PFS, ORR, Time to CNS progression), moderate for major safety outcomes and very low for the outcome related to QoL - Time to deterioration in EORTC QLQ-30 global health score. The latter is associated with a high risk of bias due to the open-label design and low baseline values of completed questionnaires at the baseline. The primary investigator-assessed PFS results were consistent with those of the blinded independent reviewers, suggesting a lack of bias in investigator assessments. More patients in the alectinib arm than in the crizotinib arm in ALEX were considered responders, but the difference was not statistically significant.

Indirect comparison with ceritinib

Alectinib also resulted in a statistically significant increase in PFS compared with ceritinib in an indirect comparison. No significant differences were observed between alectinib and ceritinib with regard to OS. The OS results may be affected by treatment arm crossover and data immaturity (median OS was not observed for some treatment arms in the trials). Because of the limited number of studies, no adjustment of patient characteristics was made at the study level. The NMA model in the base case presented by the MAH assumes no between-study heterogeneity. This assumption cannot be validated through a data-derived heterogeneity estimation because of the inclusion of only a single study in each direct treatment comparison. Analyses to check the sensitivity of the results for varying heterogeneity are not included in the submission, except for the computation of a random effects NMA with a vague a priori between-study-heterogeneity assumption. This analysis showed wide credible intervals leading to non-significant results and

therefore reveals the dependency of the the fixed effects NMA results on the assumed between-study-heterogeneity. In conclusion, the results derived from the fixed effects NMA model are partly based on an unvalidated assumption.

In the absence of a direct comparison, despite the uncertainties involved, the results of the NMA are presented in the assessment of relative efficacy compared with the relevant comparator ceritinib. Because of the uncertainties described above, regarding the adequacy of the comparison, the observed results have to be regarded as unsure.

Additional limitations to interpretation of the NMA results included

- The potential confounding of OS data due to cross-over that was allowed in three of the trials (PROFILE 1014, PROFILE 1029 and ASCEND-4) and immaturity of OS data reported
- The differences in the chemotherapy arms of the ASCEND-4 and PROFILE trials
- The results from the PROFILE 1029 clinical study were excluded in the base case result of the NMA. In an alternative analysis where the results from PROFILE 1029 were included in the NMA, the HRs were slightly lower. Therefore, the exclusion of PROFILE 1029 does not affect the results in a major way. In addition, a Bucher analysis was done, showing similar results as the NMA.

Safety

Direct comparison with crizotinib
The same numbers of AEs of any grade were reported for both alectinib and crizotinib (97%) in the randomized phase III ALEX trial. Serious AEs occurred at a similar frequency in patients in both treatment arms (29% with crizotinib, 28% with alectinib).

In the ALEX trial the incidence of AEs leading to treatment discontinuation was similar with alectinib compared with crizotinib (11% vs. 13%). The patients in the alectinib arm had longer exposure to treatment (17.9 months vs. 10.7 months for crizotinib) but numerically lower incidence of treatment interruptions and dose reductions and a lower cumulative frequency of grade 3 or higher adverse events (41% vs. 50% in the crizotinib arm).

The only serious AEs which occurred at a higher (≥2% difference) incidence in the alectinib arm were acute kidney injury (3% with alectinib vs. 0% with crizotinib) and lung infection (2% vs. 0%). For any grade AE, myalgia was reported more frequently for alectinib than crizotinib (16% vs. 2%) and anemia (20% vs. 5%).

Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious AEs that tend to affect quality of life, such as nausea, diarrhoea and vomiting, as well as severe (Grade ≥3) events. This impression is also supported by lower observed frequencies of treatment interruptions and dose reductions.

Since there was a very small proportion of patients who were older than 65 years, the information about AEs in this group is limited. However, as the *ALK*-positive patient population is generally younger, this is of minor importance.

Because of limited patient numbers included in the studies and because of limited follow-up times, the final safety profiles of the products remain to be established. Given that all approvals are based on phase III RCTs, it appears very unlikely that major differences in the frequencies of common AEs will be seen, however.

Also a naïve comparison of established AE frequencies in the SmPCs was made in the report in order to investigate the safety of the products in a broader population, since several other studies were included. The lower frequencies for alectinib of diarrhoea, vomiting and nausea noted in the ALEX study, were supported in this analysis.

Indirect comparison with ceritinib

Indirect comparisons between alectinib and ceritinib were performed using NMA and a naive comparison of the established AE frequencies as per the SmPCs, respectively. Both analyses indicated an overall superior safety profile for alectinib over ceritinib, with the exception of a few non-serious AEs. Due to the high degree of uncertainty naturally inherent in any indirect comparison, no firm or formal conclusion is possible. Based on the available data, it might be considered reasonable to assume that the overall burden of toxicity from alectinib is at least not worse than that of ceritinib.

Quality of life

A statistically non-significant trend favouring alectinib over crizotinib was observed for patient-reported global health status/health-related quality of life (HRQoL) (HR 0.72, 95% CI, 0.38–1.39). In both arms a clinically meaningful improvement in HRQoL and multiple lung cancer symptoms was observed. The duration of such improvement was markedly longer in the alectinib arm. This is not unexpected, given the longer progression-free interval and the reduced risk of, and time to, CNS-metastases observed for the alectinib patients. As the design of the study was open label, there is a risk that the results of the patient-reported AEs and the quality of life could be skewed, affecting the validity of the results. Only 65% of the patients answered the quality-of-life questions at the baseline, potentially affecting the reliability of the results.

Extrapolation

In addition to the assessment of relative efficacy and safety, an extrapolation of survival data was performed. Such data can be used for modelling within health economics. The aim of this section is to discuss extrapolation models, estimating survival data over time.

There is uncertainty about the treatment sequence after progression that affects the extrapolation results. In the publication of the ALEX trial the following was written: ‘Per protocol, crossover between trial groups was not allowed; patients assigned to crizotinib may have received alectinib after disease progression (in countries where alectinib was already approved or available).’ Data were not collected and reported in the study. The efficacy of crizotinib after failure of alectinib therapy is presently unknown. From a pharmacological point of view, activity of crizotinib in a post-alectinib setting might not necessarily be assumed, while activity in subsets of patients, depending on resistance mechanisms, may at this point not be ruled out. Moreover, no statistically significant increase of OS has yet been shown for any of the currently approved ALK inhibitors.

Patient involvement

Even though patient groups with *ALK*-positive NSCLC could not be involved in this assessment, thankfully one individual patient living with ALK-positive NSCLC agreed to participate in a one hour telephone interview. The most important issues concerning new therapeutic options life extension, fewer side effects and no financial implications for patients.

Limitations of including only one patient in this rapid REA are related to the lack of the broader patient view. Specifically, due to the of lack of specific lung symptoms and a short treatment duration with crizotinib the patient's experiences with the condition, treatment and expectations might not be applicable to heavily pre-treated patients with severe symptoms.

9 CONCLUSION

From direct comparison, based on high quality evidence, alectinib demonstrated a substantial and statistically significant increase in PFS. It is also associated with a statistically significant longer time to CNS progression compared to crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients. The OS data are immature and therefore preclude firm conclusions.

From an indirect comparison, an advantage of alectinib versus ceritinib is indicated for PFS, but because of uncertainties regarding the adequacy of the comparison, this observed result has to be regarded as unsure.

From direct comparison, the serious AEs and AEs leading to treatment discontinuation occurred at similar frequencies for both alectinib and crizotinib. Alectinib appears to have a more favourable safety profile compared with crizotinib with regard to non-serious AEs that tend to affect quality of life as well as severe (grade ≥3) events. This notion is supported by the lower frequencies of treatment interruptions and dose reductions observed for alectinib in the direct comparison to crizotinib. Thus markedly lower frequencies for alectinib were reported for diarrhoea, vomiting and nausea. For any grade AEs, myalgia and anaemia was reported more frequently for alectinib than crizotinib.

While conclusions on relative safety compared with ceritinib should be made with caution, both the NMA and the comparison of the established adverse events profiles in the SmPCs indicate an overall superior safety profile of alectinib.

Patients receiving alectinib had clinically meaningful improvement in HRQoL for a longer duration compared with patients receiving crizotinib. Overall a trend favouring alectinib was observed in HRQoL, but the difference was not statistically significant.

As only one patient was interviewed, no general conclusions can be drawn.

APPENDIX 1. EXTRAPOLATION OF PFS AND OS/SURVIVAL ANALYSIS

Introduction

The aim of this section is to discuss extrapolation models, estimating survival data over time. Assessing interventions that have an impact on survival requires accurate estimation of the survival benefit associated with the new intervention. This is often difficult since clinical trials commonly have a limited observation period and censored survival data; therefore extrapolation techniques need to be used to obtain the estimates of the full survival benefit. Where such analyses are not completed, estimates of the survival benefit will be restricted to what is directly observed in relevant clinical trial(s). This will most likely represent an underestimation of the true survival gain [59].

There are a number of methods available to extrapolate survival data, such as the exponential, Weibull, Gompertz, log-logistic, log-normal and gamma parametric models, as well as the more complex or flexible models. The different methods have varying functional distributions and often result in diverse survival estimates, especially when an extensive amount of the observed survival data needs to extrapolated. Consequently it is important to justify the particular extrapolation method that is selected[59].

Statistical tests are often used to compare different extrapolation models and their relative fit to the observed trial data. This is important when the observed data are mature and have a small amount of censoring present and the extrapolation required is negligible. When a large portion of the survival curves need to be extrapolated, it is of even greater importance to justify the plausibility of the extrapolated portion of the survival model chosen, as this is likely to have a very large impact on the estimated mean survival. Techniques used for validation may include external data sources, the biological plausibility of the extrapolated survival curves or clinical expert opinions [59].

The clinical and statistical assessment performed by the MAH concludes that the two most plausible options for Progression Free Survival (PFS) and three most plausible options for Overall Survival (OS) were identified and shown in the summary table (Table A1). In all of these scenarios a survival benefit for alectinib compared to crizotinib was estimated. The estimated mean increase in PFS ranged from 18.9 months to 32.3 months while the estimated mean increase in OS ranged from 13.4 to 47.5 months. It can be seen that when considering the observed survival time, only a small amount of the total expected gain can be observed.

Table A1. Summary of estimated mean survival in months

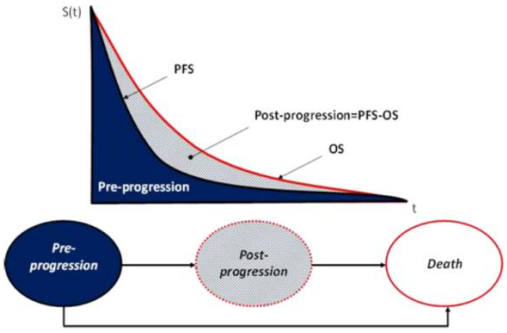
		Mean upto 24 months*		Mean beyond 24 months		Total Mean	
Options	**Parametric distribution**	**Alectinib**	**Crizotinib**	**Alectinib**	**Crizotinib**	**Alectinib**	**Crizotinib**
PFS							
KM	N/A	17.1	13.0	N/A	N/A	N/A	N/A
1	Exponential	17.7	12.8	17.7	3.7	35.4	16.5
2	Weibull	17.4	13.1	29.7	1.7	47.1	14.8
OS							
KM	N/A	20.7	20.2	N/A	N/A	N/A	N/A
1	Exponential	20.9	20.3	51.1	38.3	72.0	58.6
2	Generalised Gamma	20.7	20.3	88.2	69.2	108.9	89.5
3	Log-normal	20.7	20.2	102.9	55.9	123.6	76.1

* 24 months was chosen to represent the observed trial period

Model Description

Model framework
The model that the MAH has used is a partitioned survival model often referred to as an area under the curve (AUC) model, where health states are based on the partitioning of overall survival (OS) into progression free survival (PFS) and post progression survival (PPS). At each discrete point in time, the proportion of patients in the progressed health state is assumed to be the difference between OS and PFS (progression=OS – PFS). At randomisation, all patients are assumed to be alive and progression free and can either remain within the same health state or move to the progressed or death states at the end of each subsequent cycle.

Figure A1. Model structure.



Abbreviations: OS=overall survival; PFS=progression-free survival.

Cycle Length
The cycle length used in the model is one week. As stated by the MAH, shorter cycle lengths allow a more accurate estimation of the time patients remain in each health state.

Time Horizon
The model allows for a time horizon of up to 30 years, so the expected lifetime horizon of a non small lung cancer patient can be captured. 30 years was chosen because 95% or more of the patients are dead at this time, independent of the OS extrapolation.

Discounting
In the analysis, there is no discounting of future health benefits. However, the model allows for different discount rates to be applied, which are applied after the first year and on a yearly basis thereafter.

Statistical Analysis of Survival Data
The parametric functions assessed in this model include log-logistic, Weibull, log-normal, generalised gamma, Gompertz and exponential functions. The AUC can be calculated on the basis of:

1. A parametric function from randomisation extrapolated to lifetime

2. Kaplan–Meier data with a parametric extrapolation of the tail

The model allows for the option where the extrapolated treatment effect of alectinib is not maintained; thus after a user-defined time point the hazards of alectinib and crizotinib are set equal.

Survival data in ALEX
The PFS benefit of alectinib versus crizotinib was statistically significant in the log-rank test stratified for the covariates race (Asian vs. non-Asian) and CNS metastases at the baseline. PFS

results were consistent in both investigator (INV) and Independent Review Comittee (IRC) assessments. At the date of data cutoff, death had occurred in 75 patients in the ITT population (35 patients, 23%, in the alectinib group and 40 patients, 26%, in the crizotinib group). The HR of death was 0.76 (95% CI 0.48–1.20), and the median OS was not estimable in either group. Table A2 summarises the PFS and OS results. Figure A2 and

Figure A3 show the Kaplan–Meier curves for PFS and OS, respectively.

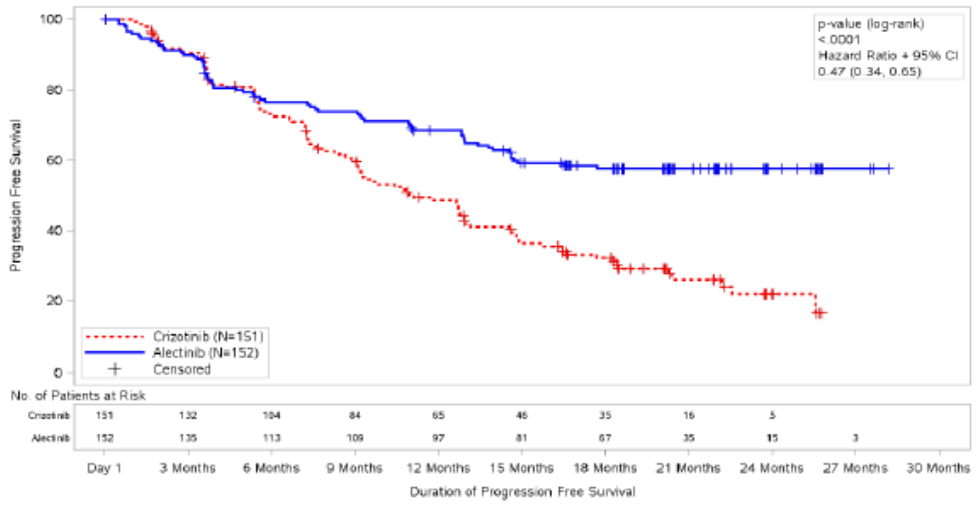
Table A2. Progression-free survival and overall survival summaries

	PFS INV (1°EP)		OS	
	Alectinib	**Crizotinib**	**Alectinib**	**Crizotinib**
50 percentile (median)[a]	NR	11.1	NR	NR
(95% CI)	(17.7 – NR)	(9.1 – 13.1)	(NR)	(NR)
25 and 75 percentile[a]	7.6, NR	5.6, 22.2	19.9, NR	17.1, NR
Hazard ratio[b]	0.47 (0.34, 0.65)		0.76 (0.48, 1.20)	
(95% CI)				
Log-rank p-value[c]	<0.0001		0.2405	

1°EP – Primary endpoint; NR – Not reached; CI – Confidence interval.
[a]Kaplan-Meier estimates for time to event (months).
[b]Hazard ratios were estimated by Cox regression and are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
[c]Log-rank p-values are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

Abbreviations: CI confidence interval; CNS=central nervous system; EP=endpoint; INV=investigator assessed; IRC=independent review committee; OS=overall survival; NR=not reached: PFS=progression-free survival,
Source: MAH extrapolation file.

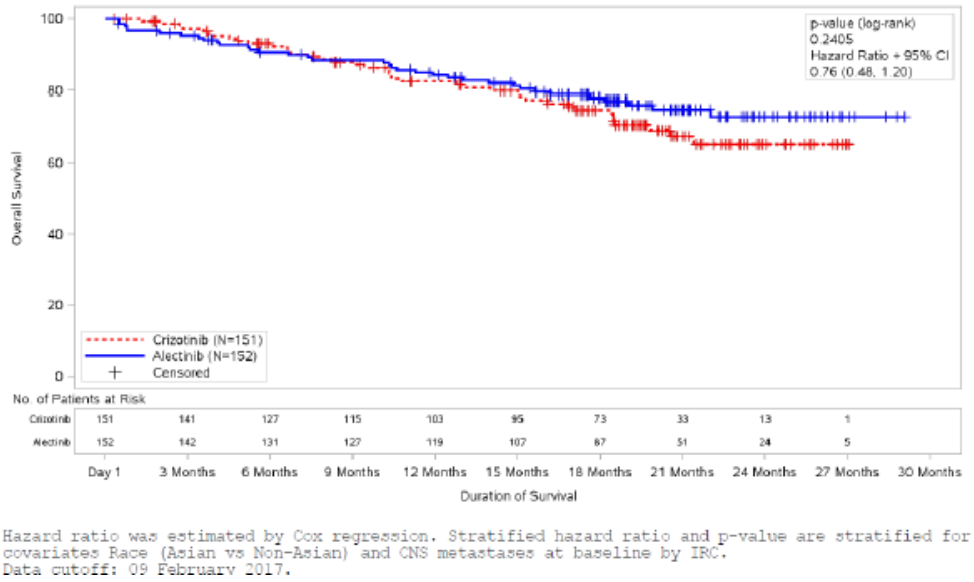
Figure A2. Kaplan–Meier plot of investigator-assessed progression-free survival (intent-to-treat population)



Hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

Abbreviations: CI=confidence interval; CNS=central nervous system; IRC=independent review committee.
Source: MAH extrapolation file.

Figure A3. Kaplan–Meier plot of overall survival (intent-to-treat population)



Hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.

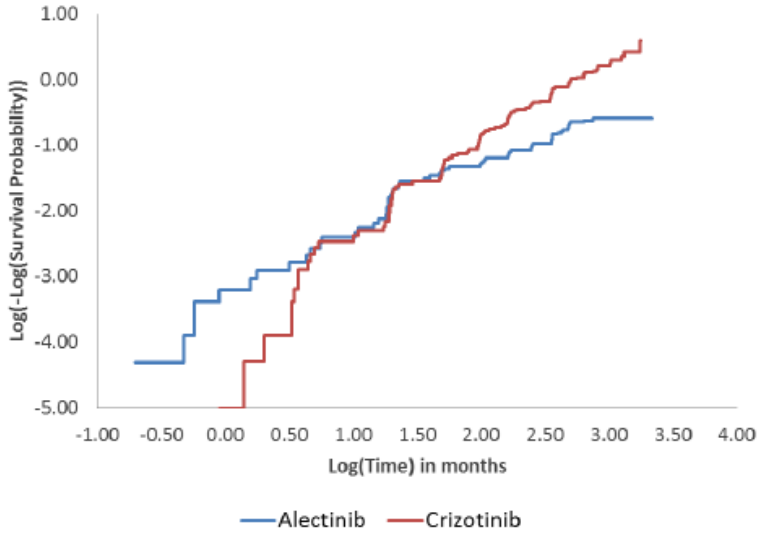
Abbreviations: CI=confidence interval; CNS=central nervous system; IRC=independent review committee.
Source: MAH extrapolation file.

Selection of Parametric Function

Cumulative Hazard Plots and Interpretation

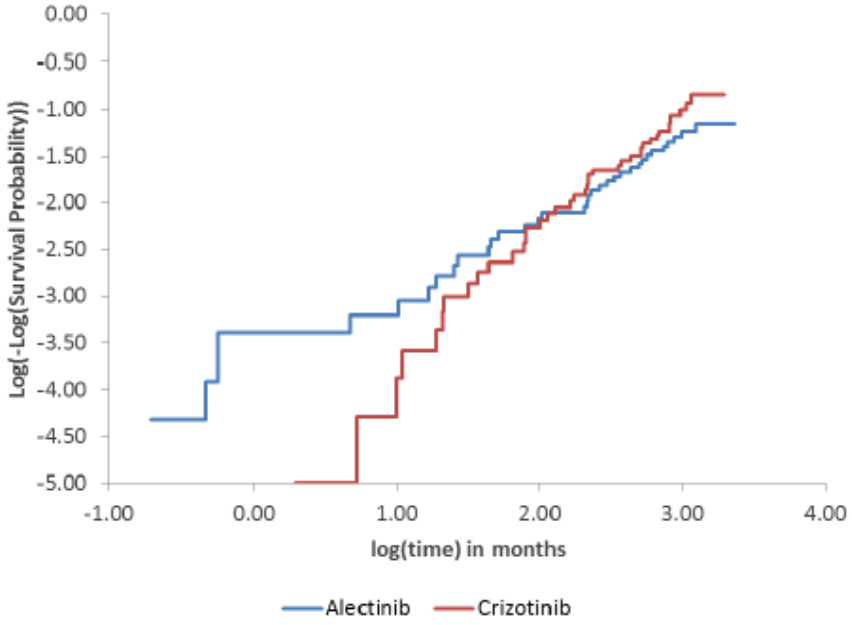
Cumulative hazard plots are analysed to assess whether each treatment arm should be analysed separately or both treatment arms should be analysed jointly. The proportional hazards assumption is thought to hold if the lines are parallel. Figure A4 and Figure A5 show the log-cumulative hazard plots for PFS and OS, respectively, which are transformations of the Kaplan–Meier plots. The plots intersect at multiple points, indicating that the proportional hazards assumption may not hold and that each treatment arm should be analysed separately for the purpose of extrapolation.

Figure A4. Log-cumulative hazard plots of PFS (INV) (cutoff date February 9th 2017)



Source: MAH extrapolation file.

Figure A5. Log-cumulative hazard plots of overall survival (cutoff date February 9th 2017)



Source: MAH extrapolation file.

Parametric Extrapolations and Statistical Fit

Statistical measures such as Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) as well as hazard and residual plots are methods of assessing the fit of alternative models to underlying data from the clinical trial. In addition, visual inspection is used to assess the clinical plausibility of the outcomes when different extrapolation methods are applied. However, the use of such measures is useful only for determining the fit of the models to the observed data – these measures do not tell us anything about the plausibility of the extrapolations [59].

Because of the non-parallel log-cumulative hazards indicating that the proportional hazards assumption does not hold, separate parametric models were fitted to the observed trial data by the MAH. Parametric functions were assessed on the basis of model goodness of fit with the use of (AIC) and (BIC), as well as a visual assessment of each parametric function. On the basis solely of AIC and BIC statistics (the lowest being the best fit), the log-normal function had the best fit for both the alectinib arm and the crizotinib arm for PFS.

Similarly to PFS, OS displayed intersecting log-cumulative hazards. Separate parametric models were therefore fitted to each treatment arm. On the basis of statistical goodness of fit, the exponential model provides the best fit for alectinib and the log-normal model provides the best fit for crizotinib.

Table A3. Parametric functions goodness of fit for ALEX PFS (INV)

Parametric Model PFS	Alectinib arm		Crizotinib arm	
	AIC	BIC	AIC	BIC
Exponential	372.50 (5)	375.52 (4)	381.97 (6)	384.99 (5)
Weibull	370.83 (4)	376.88 (5)	375.26 (4)	381.30 (4)
Log-normal	363.61 (2)	369.66 (1)	368.66 (1)	374.70 (1)
Generalised gamma	362.42 (1)	371.50 (2)	370.66 (3)	379.72 (3)
Log-logistic	367.43 (3)	373.48 (3)	370.66 (2)	376.69 (2)
Gompertz	374.50 (6)	380.55 (6)	381.20 (5)	387.23 (6)

Abbreviations: AIC=Akaike's information criterion; BIC=Bayesian information criterion; PFS=progression-free survival.
Source: MAH extrapolation file.

Table A4. Parametric functions foodness of fit for ALEX OS

Parametric Model OS	Alectinib arm		Crizotinib arm	
	AIC	BIC	AIC	BIC
Exponential	246.59 (1)	249.61 (1)	234.24 (5)	237.26 (2)
Weibull	247.98 (4)	254.03 (4)	232.71 (3)	238.74 (4)
Log-normal	247.97 (2)	254.03 (3)	230.88 (1)	236.91 (1)
Generalised gamma	249.79 (6)	258.86 (6)	232.79 (4)	241.84 (6)
Log-logistic	247.91 (3)	253.96 (2)	232.10 (2)	238.13 (3)
Gompertz	248.60 (5)	254.63 (5)	234.72 (6)	240.76 (5)

Abbreviations: AIC=Akaike's information criterion; BIC=Bayesian information criterion; OS=overall survival.
Source: MAH extrapolation file.

Hazard trends

Table A3 and

Table A4 provide the hazard trends for each extrapolation and treatment arm.

Table A5. Hazard trends of investigator-assessed progression-free survival

Parametric distribution	Alectinib (N=152)	Crizotinib (N=151)
Exponential	constant	constant
Weibull	decreasing	increasing
Log-logistic	decreasing	increasing until month 9, then decreasing
Log-normal	increasing until month 2, then decreasing	increasing until month 6, then decreasing
Generalised Gamma[1]	increasing until month 3, then decreasing	-
Gompertz	constant	increasing

[1]The model converged; however, the hazard function was not estimable for the crizotinib arm

Source: MAH extrapolation file.

Table A6. Hazard trends of overall survival

Parametric distribution	Alectinib (N=152)	Crizotinib (N=151)
Exponential	constant	constant
Weibull	decreasing	increasing
Log-logistic	decreasing	increasing until month 20, then reaching a plateau
Log-normal	increasing until month 2, then decreasing	increasing until month 10, then decreasing
Generalised Gamma	increasing until month 1, then decreasing	increasing until month 9, then decreasing
Gompertz	constant	increasing

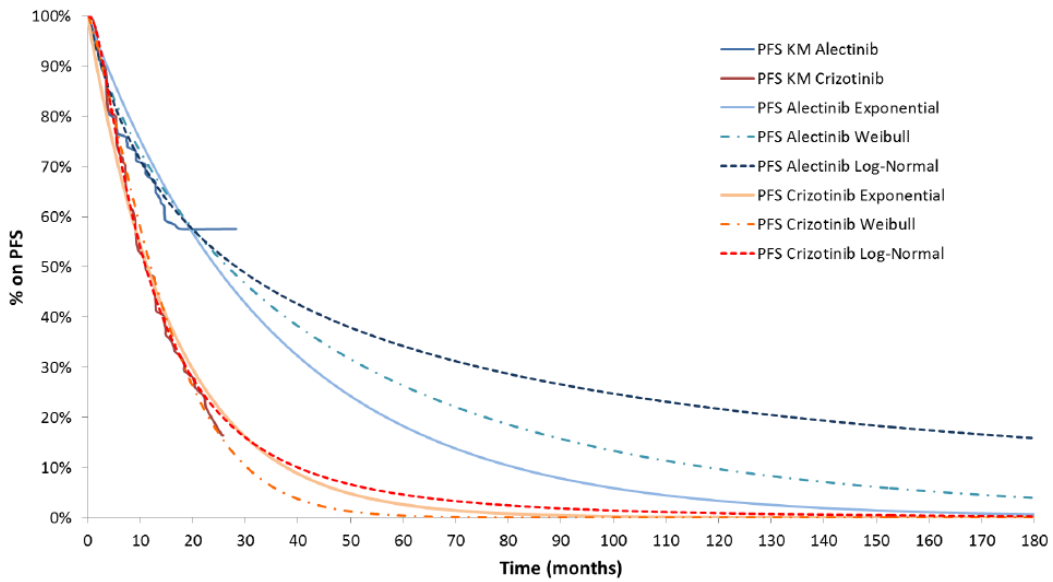
Source: MAH extrapolation file.

Results for Preferred Extrapolation Models

Preferred PFS extrapolation models

According to the MAH PFS, based on statistical fit, visual inspection and external validation, three models were considered to have an optimal fit – exponential, Weibull and log-normal models (illustrated in Figure A6 and Table A7**).**

Figure A6. Progression-free survival extrapolations



Abbreviations: KM=Kaplan–Meier; PFS=progression-free survival.
Source: MAH extrapolation file.

Table A7. Results of selected progression-free survival extrapolations

Option	Parametric distribution	Mean PFS (months)		Strength	Weakness
		alectinib	crizotinib		
1	exponential	35.4	16.5	Clinically plausible	Less good statistical fit*
2	Weibull	47.1	14.8	Clinically plausible	Less good statistical fit*
3	Log-normal	80.4	18.3	Best statistical fit*	Less clinically plausible

*Based upon AIC, BIC.

Abbreviations: AIC=Akaike's information criterion; BIC=Bayesian information criterion; PFS=progression-free survival.
Source: MAH extrapolation file.

As stated by the MAH, the log-normal function has a statistically and visually good fit with regards to the observed data. However, the longer tail after the observed period is considered clinically implausible on the basis of clinical feedback; the results are also inconsistent with PFS for crizotinib in the randomised controlled trial PROFILE 1014. In this context the MAH argues that the most plausible extrapolations are either exponential or Weibull functions for both arms with either investigator or individual review committee datasets.

According to the MAH the exponential parametric model for both treatment arms had a good fit on the basis of clinical feedback. The feedback was that the proportion of patients with PFS within a five year time frame, as predicted in the model, was considered realistic and potentially clinically plausible. From a technical point of view, the MAH recognises that the use of the exponential distribution results in a constant hazard, which inevitably leads to proportional hazards that apparently does not hold on the basis of the log-cumulative hazards crossing. The MAH argues that it is not sufficient to exclude the parametric distribution solely on the basis of the log-cumulative hazard plots. The choice should also be based on:

- Clinical plausibility of the model predictions

- Whether the log-cumulative hazard plots are relatively straight lines (implies that a Weibull model would be appropriate)
- Whether they indicate radical fluctuations or shifts that require piecewise or more flexible models
- Whether each model sufficiently fits the observed data both statistically and visually

Taking these elements into account, the MAH considers the exponential function as an appropriate option for PFS extrapolation, despite its limitations.

Discussion regarding the PFS extrapolations

The authoring team discussed the methods used for extrapolating PFS for comparing alectinib with crizotinib, in the context of the identified pros and cons of using the parametric functions presented by the MAH.

When reviewing the exponential function, the authoring team agrees that it has a suboptimal fit to the observed data with regard to the AIC and BIC statistics. Another limitation when extrapolating both treatment arms with the exponential function is that it results in a constant hazard ratio throughout the model's time horizon. A constant hazard contradicts the cumulative hazards plot that indicated a nonparallel log-cumulative hazard with multiple intersecting points.

The authoring team does, however, agree with the MAH that the exponential function results in a clinically plausible relative effectiveness between alectinib and crizotinib. Even though the log-cumulative hazards plot indicates that the proportional hazards assumption does not hold, it is important to understand that the exponential function might still be the best extrapolation method when considering the results it generates.

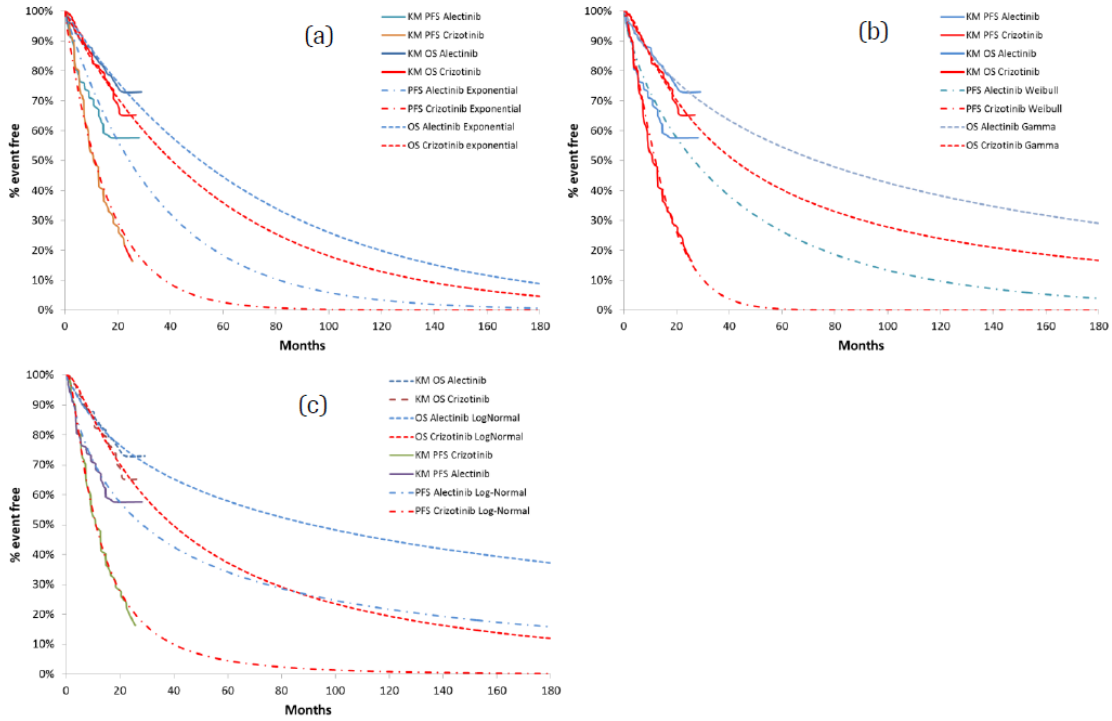
The Weibull function has a better fit when compared with the exponential function with regard to the goodness of fit statistics from AIC and the BIC. The Weibull function results in a decreasing momentary (cycle to cycle) hazard ratio in the model, which could indicate a plausible method of extrapolation when considering the results from the log-cumulative hazards plot. However, when the PFS curves are extrapolated with the Weibull function, the momentary (cycle to cycle) hazard ratio ranges from 0.98 (cycle 6) to 0.063 at the end of the model's time horizon. While the authoring team agrees with the MAH that the Weibull function results in a clinically plausible scenario, there is a degree of uncertainty that the hazard ratio would continue to decrease throughout the model's time horizon and result in such so low hazard ratios.

Although the log-normal function has the best statistical fit, the function results in a long tail. The authoring team recognises the lack of evidence that would support such a tail and the extrapolation method results in a clinically implausible PFS as stated by the clinical expert that the MAH consulted.

Preferred OS extrapolation models

The different options for extrapolating OS are shown in Figure A7 and Table A8.

Figure A7. Extrapolation options for progression-free survival and overall survival



a = Option 1, **b** = Option 2, **c** = Option 3

Abbreviations: KM=Kaplan–Meier: OS=overall survival; PFS=progression-free survival.
Source: MAH extrapolation file.

Table A8. Results of selected extrapolation models

Option	Mean OS (months)		Pros (+)	Cons (-)
	Alectinib	Crizotinib		
1	Exponential (72.0)	Exponential (58.6)	Best statistical fit for alectinib and appropriate visual fit for crizotinib. Conservative tail in the long run extrapolation	Potential underestimation of OS in the long run as compared with PROFILE 1014
2	Generalised Gamma (108.9)	Generalised Gamma (89.5)	Visual fit in line with PROFILE 1014. HR reaches 1 in the long run, capturing the PFS benefit as per clinicians' recommendation	Less good statistical fit
3	Log-normal (123.6)	Log-normal (76.1)	Good statistical fit in both arms	Implausible separation of the curves

Abbreviations: HR=hazard ratio; OS=overall survival; PFS=progression-free survival.
Source: MAH extrapolation file.

Given the immaturity of the OS data (as of February 9th 2017, 27% of patients in the crizotinib arm had died and 23% of patients in the alectinib arm had died), applications of Kaplan–Meier curves with parametric tails would add no additional value in the extrapolation according to the MAH.

Option 1
As stated by the MAH, option 1 has a good statistical and visual fit for both arms. The concern with using the exponential function for OS in both arms is that there are few long-term survivors and the long-term predictions for the crizotinib arm are lower than what was observed in the PROFILE 1014 clinical trial; see Table A9

Option 2
The generalised gamma extrapolation for both alectinib and crizotinib generates a plausible scenario, firstly because it satisfies the clinical feedback that the curves need to start converging in the long run, rather than being separated further apart. Secondly, the estimated OS benefit of crizotinib (based on ALEX) is closer to the 4-year landmark analysis of crizotinib in the PROFILE 1014 study.

Option 3
According to the MAH, it was deemed implausible to use the log-normal function for OS because of a greater separation of the curves at around 150 months compared with 50 months. In addition to option 3, a scenario was assessed assuming no additional OS benefit beyond the mean extrapolated PFS (approximately 35 months). According to the MAH, this scenario was considered conservative.

External Data
Given the short-term OS data for ALEX, more long-term OS data for crizotinib were sought to validate the most appropriate distribution. In September 2017, updated results from the PROFILE 1014 study were received. PROFILE 1014 and ALEX are different studies and differ, for example, in the proportion of patients with brain metastases at the baseline (27% in PROFILE 1014 vs 40% in ALEX). The Kaplan–Meier curve from PROFILE 1014 was digitised and assessed against the OS predictions of the parametric models used for crizotinib, in order to validate the results

Table A9. **Crizotinib overall survival model comparisons with PROFILE 1014**

		12 months	24 months	36 months	48 months
PROFILE 1014 KM data	Numbers at risk*	138	101	77	40
	Digitized data*	83%	65%	58%	55%
Difference compared to the digitized data**	Exponential	-1%	2%	-4%	-11%
	Weibull	1%	-1%	-12%	-22%
	Log-normal	-1%	0%	-5%	-11%
	Generalised Gamma	-1%	1%	-4%	-9%
	Log-logistic	0%	-1%	-8%	-15%

*Subject to some uncertainty due to digitization of the KM curve. **The difference is calculated as proportion alive estimated by the parametric distribution minus the value from the digitized curve.

Abbreviation: KM=Kaplan–Meier.
Source: MAH extrapolation file.

Discussion regarding the OS extrapolations (authoring team)
According to the MAH, the exponential and generalised gamma functions are reasonable extrapolation methods for OS. The exponential function has the best statistical and visual fit for the alectinib arm, and the log-normal function has the best statistical and visual fit for the crizotinib arm. The results indicate that the different treatment arms could be fitted with separate parametric functions (e.g., exponential and generalised gamma functions). The authoring team does, however, agree with the MAH that the treatment arms should be modelled with the same parametric function but with different fits, as it would require substantial justification to use differently shaped distributions.

The MAH does, however, highlight a concern that the exponential function underestimates the crizotinib arm when compared with long-term results from the PROFILE 1014 study. Although this is true, the difference between the exponential and generalised gamma functions is small, roughly 2%. From these results it is not fully clear which parametric function generates the most plausible outcome.

The authoring team does, however, agree that the generalised gamma function results in a more plausible long-term extrapolation with regard to the converging effect of the survival curves. There is a degree of uncertainty regarding the relative effectiveness between alectinib and crizotinib: the relative effectiveness continues to increase and is at its largest after what was observed in the ALEX study. The exponential function might result in a more plausible relative effectiveness, but as discussed in the PFS section, this results in a constant hazard ratio, which the log-cumulative hazard plot does not support.

The authoring team agrees with the MAH that the log-normal function results in an implausible separation of the survival curves.

Another aspect that needs to be considered when the OS benefit is discussed, is the importance of the follow-up therapy options available for patients. Clinicians will have three first-line options to choose from (alectinib, crizotinib and ceritinib), and it is hard to predict what the optimal treatment sequence will be. Therefore it is hard to predict long-term survival outcomes.

Impact of follow-up-therapy and treatment switching

Impact of follow-up-therapy
At the time of the data cut-off, a greater proportion of patients in the crizotinib arm (68%) had progressed or died compared to the alectinib arm (41%). Of the 90 and 54 patients with a disease progression event, 61% of the patients in the crizotinib arm and 67% of the patients in the alectinib arm had at least one anti-cancer treatment administered after progression, including trial treatment exposure for at least 30 days beyond progressive disease.

Overall, 40 patients in the crizotinib arm and five patients in the alectinib arm had isolated asymptomatic CNS progression, where local therapy could be given (e.g., stereotactic radiotherapy or surgery) followed by continuation of either crizotinib therapy (in the crizotinib arm) or alectinib therapy (in the alectinib arm) until systemic disease progression or symptomatic CNS progression.

Treatment switching
Ten patients in the crizotinib arm switched to alectinib therapy after they had discontinued the assigned trial treatment. As a substitute for a naïve per-protocol analysis, the MAH used a discount method approach to assess the potential impact of treatment switching on the intention to treat (ITT) comparison for OS [60]. The argument is that the patients who were treated with crizotinib and then switched to alectinib might benefit from the new treatment, and this could in turn lead to an underestimation of the OS advantage of alectinib.

To assess the potential impact of treatment switching, the MAH multiplied (discounted) the observed survival time after the first dose of alectinib until censoring or death by 0.1–1.2 for the 10 patients in the crizotinib arm who switched to alectinib. Thereafter the MAH calculated the hazard ratio (HR) between treatment arms with the total duration (for the crizotinib arm, time to first dose of alectinib positive multiplied observed time until censoring or death, and for the alectinib arm, time to event without any adjustments).

As of the data cutoff of 9th February 2017, the median time patients had received alectinib therapy was 5.2 months (interquartile range 2.3–7.9 months) for patients switching from crizotinib. If the MAH assumed that the treatment effect of alectinib after switching from crizotinib was as large as a HR of 0.2, the estimated (stratified) OS HR for the ITT comparison was 0.75 (95% CI 0.47–1.18) as compared with an estimated (stratified) OS HR of 0.76 (95% CI 0.48–1.20) when treatment switching is ignored.

The MAH argues that it may not be necessary to perform an adjustment for treatment switching at this stage, since the beneficial effect of treatment switching is minimal. However, the MAH argues that it might be worthwhile to apply a rank-preserving structural failure time model (RPSFTM) when more long-term OS data become available.

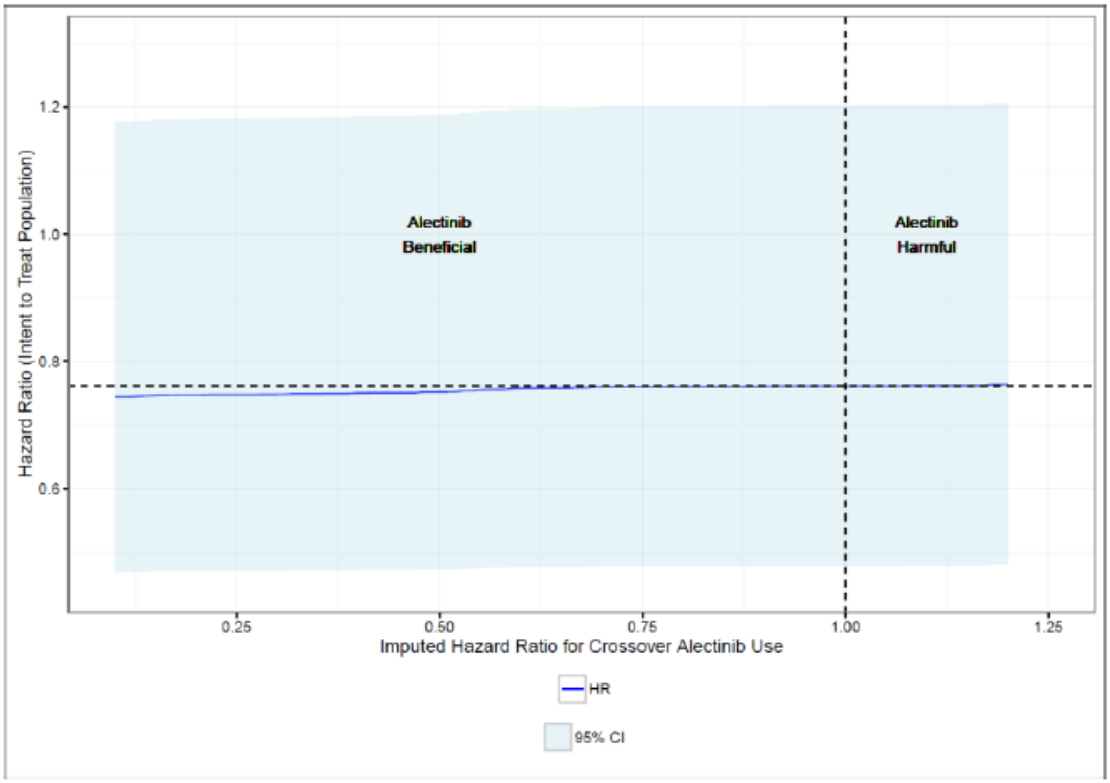


Figure A8. Impact of treatment switching on the OS hazard ratio

Abbreviations: CI=confidence interval; HR=hazard ratio.
Source: MAH extrapolation file.

APPENDIX 2: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Literature search inclusion and exclusion criteria

Inclusion criteria	Population: Adult patients (≥18 years) with *ALK*-positive[a] metastatic NSCLC (if mixed lung cancer type, at least 80% had to be NSCLC); oligometastatic populations; patients with brain or CNS metastases; any combination of chemotherapy naïve or chemotherapy experienced or ALK TKI treatment naïve or ALK TKI treatment experienced in any treatment line (advanced or metastatic); subgroups of interest: patients with brain metastases, Asian versus non-Asian patients Intervention(s) and comparator(s): Licensed or investigational doses or formulations of pharmacological interventions in at least one treatment arm (chemotherapy or targeted therapy) for *ALK*-positive metastatic NSCLC; comparison with another pharmacological treatment, standard of care or placebo; combination with other agents eligible; chemotherapy studies not reporting subgroup results by *ALK* status were excluded Outcomes: At least one primary or secondary outcome of efficacy (PFS, TTP, OS, response, DOR, duration of benefit after stopping treatment, CNS response); patient-reported outcomes; HRQoL; serious AEs; grade III/IV/V AEs (grouped); prespecified AEs of interest ; duration of treatment and duration of treatment beyond progression; tolerability (dose reductions and interruptions, discontinuation). Not all time points might have been included in the NMA Study design: Prospective parallel design phase II–IV RCTs with active or placebo controls; parallel randomised studies allowing for crossover; in the SLR, also other clinical studies (interventional, prospective, nonrandomised) and case series were included Language restrictions: Any foreign language article with an English abstract if sufficient information present to ensure the eligibility criteria are met[b] Other search limits or restrictions: Systematic reviews and NMAs limited by searches from 2012 onwards; individual studies not limited
Exclusion criteria	Population: Not *ALK*-positive NSCLC (unselected NSCLC population with no *ALK*-positive subgroup data reported; primary *EGFR* mutation [not A*LK*]; wild-type *ALK* or wild-type *EGFR*; single other types of mutation, e.g., *ROS1*, *KRAS* or *RET*); paediatric populations or mixed paediatric/adult populations (adult population sought only); mixed *ALK*-positive/non-*ALK*-positive population (<80% of the enrolled patients are *ALK* positive and the results are not reported separately for the *ALK*-positive patient subset); mixed stage population (<80% of the enrolled patients are advanced/metastatic disease patients and the results are not reported separately for the advanced/metastatic disease patient subset); mixed line of treatment (<80% of enrolled patients have a specific line of therapy and the results not reported separately per line) Intervention(s) and comparator(s): No comparator of interest; whole-brain radiotherapy or cranial radiotherapy as comparator or in combination with an ALK TKI treatment of interest (treatments of interest were any pharmacological agents) Outcomes: Articles that do not report at least one outcome of interest or do not report an outcome of interest sufficiently specified such as week of follow-up or intent-to-treat/modified intent-to-treat population (to avoid biased outcome data entering the dataset) Study design: Not an RCT (phase II, III, IV), or a nonrandomised controlled trial or a single-arm study; phase I studies only, or phase I/II studies reporting only the phase I data; observational, real-world, expanded access programme, or database studies, retrospective analyses, retrospective medical record reviews (prospective interventional studies of interest only); case series may be relevant but not individual case reports; PK/PD studies only (no outcome of interest); cluster randomised trials (individual participants not randomised); non-systematic reviews (any particularly interesting clinical-type reviews may be noted for discussion in the report but, in general, non-systematic reviews were excluded); naïve indirect comparisons of single-arm studies, particularly where no adjustment is made

	(comparative trials of interest only); systematic reviews (relevant systematic reviews and meta-analyses were kept in at the first pass for cross-referencing purposes but were excluded after the second pass.); post hoc pooled analyses (to avoid the same data being included twice. The original trials going into the pooled analysis, if relevant, were included.); pilot studies (not powered to detect significant differences); economic analyses or budget impact analyses (clinical outcomes only); in vitro studies or animal studies (human in vivo only); extension studies and post-marketing safety surveillance studies (intended to be captured by the search strings for listing purposes so were tagged during screening but were excluded) Language restrictions: Full text in language outside of language capabilities (English, French, German, Spanish, Portuguese, Italian, Hungarian, Polish, Czech) Other search limits or restrictions applied: Publication type not of interest, e.g., editorials, commentaries, letters, notes, protocol-only articles (excluded but tagged and listed in the report alongside the ClinicalTrials.gov search); exact duplicates or copy abstracts; date limit of 2012 for systematic reviews/meta-analyses, 2007 for RCTs/trials; child abstract or sub-study with no unique data

Abbreviations: AE=adverse event, ALK=anaplastic lymphoma kinase; CNS=central nervous system; DOR=duration of response; HRQoL=health-related quality of life; NMA=network meta-analysis; NSCLC=non-small cell lung cancer; OS=overall survival; PD=pharmacodynamic; PFS=progression-free survival; PK=pharmacokinetic; RCT=randomised controlled trial; SLR=systematic literature review; TKI=tyrosine kinase inhibitor; TTP=time to progression.

[a]Either single or multiple mutation. If non-mutation specific, *ALK*-positive subgroup data had to be reported separately or at least 80% (cutoff could be revised during screening and the rationale documented) of patients had to have *ALK*-positive NSCLC; if mixed, at least 80% must be advanced (stage IIIB) and/or metastatic (stage IV).

[b]English, Czech, French, German, Hungarian, Italian, Polish, Portuguese and Spanish.

Source: [17]

The search was done on 2nd February 2017 in the following databases:

Database	Platform	Span of search	Date searched
Embase	Embase.com	Database inception (1974) to date of search	2nd February 2017
MEDLINE	Embase.com	From 1966 to date of search	2nd February 2017
MEDLINE in-process and electronic publications ahead of print	PubMed interface http://www.ncbi.nlm.nih.gov/pubmed/	From inception to the day before the searches	2nd February 2017 and alerts followed to cutoff date of 20th March 2017
Cochrane Library DARE	http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to Issue 2 of 4, April 2015 (database was closed as of 31st March 2015)	2nd February 2017
Cochrane Library CDSR	http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to Issue 2 of 12, February 2017 (database updated monthly)	2nd February 2017
Cochrane Library CENTRAL	http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to Issue 1 of 12, January 2017 (CENTRAL is updated monthly)	2nd February 2017
US NIH registry and results database	https://clinicaltrials.gov	#	15th January 2017
WHO ICTRP registry	http://apps.who.int/trialsearch/	§	15th January 2017
EU CTR	https://www.clinicaltrialsregister.eu/	¶	15th January 2017

Abbreviations: CDSR=Cochrane Database of Systematic Reviews; CENTRAL=Central Register of Controlled Trials CTR=Clinical Trials Register; DARE=Database of Abstracts of Reviews of Effects; EU=European Union; ICTRP=International Clinical Trials Registry Platform; NIH=National Institues of Health; WHO=World Health Organization.

ALK AND EXACT "Interventional" [STUDY-TYPES] AND (advanced NSCLC OR metastatic NSCLC) [DISEASE] AND EXACT (Adult OR Senior) [AGE-GROUP] AND EXACT (Phase 2 OR Phase 3 OR Phase 4) [PHASE]
§ ALK AND NSCLC in Condition / Recruitment Status is ALL / Phase 2 or 3 or 4
¶ ALK AND NSCLC / Adult or elderly / Phase 2 or 3 or 4

Databases: Embase and MEDLINE
Platform: Embase.com
*URL: www.embase.com
Date searched: 2nd February 2017
Hits: 998

No.	Query	Results
#1	'non small cell lung cancer'/exp OR 'lung metastasis'/exp OR 'brain metastasis'/exp OR 'central nervous system metastasis'/exp OR ((lung OR poumon) NEAR/3 (neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR angiosarcoma* OR chrondosarcoma* OR sarcoma* OR teratoma* OR blastoma* OR microcytic* OR carcinogenesis OR tumour* OR tumor* OR metasta* OR métastasé OR métastatique OR avancé OR 'progression localisée')):ab,ti OR nsclc*:ab,ti OR mnsclc*:ab,ti OR 'm nsclc':ab,ti OR ansclc*:ab,ti OR 'a nsclc':ab,ti OR msqnsclc*:ab,ti OR 'msq nsclc':ab,ti OR nonsqnsclc:ab,ti OR 'non sqnsclc':ab,ti OR 'non sq nsclc':ab,ti OR sqclc*:ab,ti OR 'ns nsclc':ab,ti OR nsnsclc*:ab,ti OR 'n s nsclc':ab,ti OR 'la nsclc':ab,ti OR lansclc*:ab,ti OR cpnpc*:ab,ti OR (lac NEAR/3 (lung OR adenocarcinoma)):ab,ti OR ((scc NEAR/3 'squamous cell carcinoma'):ab,ti AND lung:ab,ti) OR (non NEAR/3 small NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (('non small' OR nonsmall) NEAR/3 lung NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (('non small' OR nonsmall) NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (bronchial NEAR/3 ('non small' OR nonsmall) NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ('non small cell' NEAR/3 (lung OR bronchial OR pulmonary OR bronchopulmonary OR bronchus) NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ('non small' NEAR/3 cell NEAR/3 (cancer* OR carcinoma*) NEAR/3 lung*):ab,ti OR (pulmonary NEAR/3 'non small cell' NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (large NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ((squamous OR non-squamous OR 'non squamous') NEAR/5 (cell OR 'non small cell') NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (bronchus NEAR/3 squamous NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung NEAR/3 epidermoid NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung NEAR/3 squamous NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung:ab,ti OR poumon:ab,ti AND (nsclc*:ab,ti OR cpnpc*:ab,ti OR 'non small':ab,ti OR nonsmall:ab,ti OR large:ab,ti OR squamous:ab,ti OR 'non squamous':ab,ti OR non-squamous:ab,ti OR 'non à petites cellules':ab,ti)) OR ((adenocancer OR adenocarcinoma) NEAR/3 (lung OR pulmonary)):ab,ti OR (((cancer OR tumeur) NEAR/3 (poumon OR bronchique)):ab,ti AND ('non à petites cellules':ab,ti OR 'non-lié à de petites cellules':ab,ti)) OR ((brain OR cns OR 'central nervous system' OR cerebral) NEAR/3 (metastasis OR metastases OR metastatic)):ab,ti	333,209
#2	'anaplastic lymphoma kinase'/exp OR alk:ab,ti OR alkfusion:ab,ti OR eml4alk*:ab,ti OR (anaplastic NEAR/3 lymphoma NEAR/3 kinase*):ab,ti OR (alk*:ab,ti AND (anaplastic:ab,ti OR lymphoma:ab,ti OR kinase:ab,ti))	22,200
#3	l1196m:ab,ti OR c1156y:ab,ti OR l1152*:ab,ti OR 1151tins:ab,ti OR g1202r:ab,ti OR v118l:ab,ti OR i1171t:ab,ti OR s1206y:ab,ti OR f1174c:ab,ti OR d1203n:ab,ti OR g1269a:ab,ti OR g1123s*:ab,ti OR ((crizotinib* OR ceritinib* OR alectinib* OR 'alk tki' OR alktki OR alki) NEAR/3 (experienced OR treated OR pretreated OR 'pre treated' OR 'previously treated' OR 'treated previously' OR resistan* OR refractory OR naïve)):ab,ti	783
#4	#2 OR #3	22,257
#5	anaplastic lymphoma kinase inhibitor'/exp OR 'alk tki':ab,ti OR alktki:ab,ti OR (alk NEAR/3 (inhibitor OR inhibitors)):ab,ti OR ((anaplastic NEAR/3 lymphoma NEAR/3 kinase):ab,ti AND (inhibitor:ab,ti OR inhibitors:ab,ti)) OR alectinib*:ab,ti OR 'af 802':ab,ti OR af802:ab,ti OR 'ch 5424802':ab,ti OR ch5424802:ab,ti OR ro5424802:ab,ti OR rg7853:ab,ti OR alecensa:ab,ti OR crizotinib*:ab,ti OR 'pf 02341066':ab,ti OR pf02341066:ab,ti OR 'pf 1066':ab,ti OR pf1066:ab,ti OR 'pf 2341066':ab,ti OR pf2341066:ab,ti OR xalkori:ab,ti OR ceritinib*:ab,ti OR 'ldk 378':ab,ti OR ldk378:ab,ti OR 'nvp ldk	5751

	378':ab,ti OR 'nvp ldk378':ab,ti OR 'nvp ldk378nx':ab,ti OR zykadia:ab,ti OR entrectinib*:ab,ti OR 'nms e 628':ab,ti OR 'nms e628':ab,ti OR 'rxdx 101':ab,ti OR rxdx101:ab,ti OR brigatinib*:ab,ti OR 'ap 26113':ab,ti OR ap26113:ab,ti OR lorlatinib*:ab,ti OR 'pf 06463922':ab,ti OR pf06463922:ab,ti OR 'tsr 011':ab,ti OR tsr011:ab,ti OR 'cep 37440':ab,ti OR cep37440:ab,ti OR 'x 396':ab,ti OR x396:ab,ti OR 'x 276':ab,ti OR x276:ab,ti OR 'asp 3026':ab,ti OR asp3026:ab,ti OR 'nvp tae 684':ab,ti OR 'nvp tae684':ab,ti OR 'tae 684':ab,ti OR tae684:ab,ti OR 'cep 28122':ab,ti OR cep28122:ab,ti OR 'cep 14083':ab,ti OR cep14083:ab,ti OR 'cep 14513':ab,ti OR cep14513:ab,ti OR 'gsk 1838705a':ab,ti OR gsk1838705a:ab,ti	
#6	'heat shock protein 90 inhibitor'/exp OR 'heat shock protein 90'/exp OR 'hsp 90 inhibitor':ab,ti OR 'hsp90 inhibitor':ab,ti OR luminespib*:ab,ti OR 'auy 922':ab,ti OR auy922:ab,ti OR 'nvp auy 922':ab,ti OR 'nvp auy922':ab,ti OR 'ver 52296':ab,ti OR ver52296:ab,ti OR ganetespib*:ab,ti OR 'sta 9090':ab,ti OR sta9090:ab,ti OR onalespib*:ab,ti OR 'at 13387':ab,ti OR at13387:ab,ti OR ribociclib*:ab,ti OR 'lee 011':ab,ti OR lee011:ab,ti OR 'ipi 504':ab,ti OR ipi504:ab,ti OR retaspimycin:ab,ti OR tanespimycin*:ab,ti OR 'kos 953':ab,ti OR kos953:ab,ti OR 'nsc 330507':ab,ti OR nsc330507:ab,ti OR geldanamycin*:ab,ti OR 'nsc 122750':ab,ti OR nsc122750:ab,ti OR gamendazole*:ab,ti OR gambogic*:ab,ti OR 'beta guttiferin':ab,ti OR 'guttic acid':ab,ti OR celastrol*:ab,ti OR tripterin:ab,ti OR 'biib 028':ab,ti OR biib028:ab,ti OR alvespimycin:ab,ti OR 'bms 826476':ab,ti OR bms826476:ab,ti OR 'kos 1022':ab,ti OR kos1022:ab,ti OR 'nsc 707545':ab,ti OR nsc707545:ab,ti OR debio0932:ab,ti OR 'debio 0932':ab,ti	15,999
#7	'protein kinase b'/exp OR ((akt OR 'c akt') NEAR/3 (kinase OR protein OR proteins)):ab,ti	67,167
#8	'gold standard'/exp OR ((gold OR golden) NEAR/3 standard):ab,ti OR 'best supportive care':ab,ti OR 'standard of care':ab,ti OR (bsc NEAR/3 (best OR supportive OR care)):ab,ti OR (soc NEAR/3 (standard OR care)):ab,ti	118,767
#9	'placebo'/exp OR placebo*:ab,ti	386,174
#10	'docetaxel'/exp OR 'paclitaxel'/exp OR daxotel:ab,ti OR dexotel:ab,ti OR docefrez:ab,ti OR docetaxel*:ab,ti OR 'lit 976':ab,ti OR lit976:ab,ti OR deacetyltaxol:ab,ti OR 'nsc 628503':ab,ti OR nsc628503:ab,ti OR oncodocel:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti OR taxoter:ab,ti OR taxotere*:ab,ti OR texot:ab,ti OR taxespira:ab,ti OR 'abi 007':ab,ti OR abi007:ab,ti OR abraxane:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR biotax:ab,ti OR 'bms 181339':ab,ti OR bms181339:ab,ti OR bristaxol:ab,ti OR britaxol:ab,ti OR coroxane:ab,ti OR formoxol:ab,ti OR genexol:ab,ti OR 'genexol pm':ab,ti OR hunxol:ab,ti OR ifaxol:ab,ti OR infinnium:ab,ti OR intaxel:ab,ti OR 'mbt 0206':ab,ti OR mbt0206:ab,ti OR medixel:ab,ti OR mitotax:ab,ti OR 'nab paclitaxel':ab,ti OR 'nsc 125973':ab,ti OR nsc125973:ab,ti OR oncogel:ab,ti OR onxol:ab,ti OR pacitaxel:ab,ti OR paclitaxel*:ab,ti OR 'paclitaxel nab':ab,ti OR pacxel:ab,ti OR padexol:ab,ti OR parexel:ab,ti OR paxceed:ab,ti OR paxene:ab,ti OR paxus:ab,ti OR praxel:ab,ti OR taxocris:ab,ti OR taxol:ab,ti OR taxus:ab,ti OR taycovit:ab,ti OR yewtaxan:ab,ti	114,807
#11	'pemetrexed'/exp OR 'carboplatin'/exp OR 'cisplatin'/exp OR 'gemcitabine'/exp OR 'navelbine'/exp OR pemetrexed*:ab,ti OR alimta*:ab,ti OR ciambra:ab,ti OR elimta:ab,ti OR 'ly 231514':ab,ti OR ly231514:ab,ti OR blastocarb:ab,ti OR boplatex:ab,ti OR carboplat:ab,ti OR carboplatin*:ab,ti OR carbosin:ab,ti OR 'carbosin lundbeck':ab,ti OR carbotec:ab,ti OR carplan:ab,ti OR cbdca:ab,ti OR cycloplatin:ab,ti OR 'delta west carboplatin':ab,ti OR erbakar:ab,ti OR ercar:ab,ti OR ifacap:ab,ti OR 'jm 8':ab,ti OR kemocarb:ab,ti OR 'nsc 241240':ab,ti OR oncocarbin:ab,ti OR paraplatin*:ab,ti OR platinum*:ab,ti OR abiplatin:ab,ti OR biocisplatinum:ab,ti OR biocysplatinum:ab,ti OR blastolem:ab,ti OR briplatin:ab,ti OR 'cddp ti':ab,ti OR 'cis ddp':ab,ti OR 'cis diamine dichloroplatinum':ab,ti OR 'cis diaminechloroplatinum':ab,ti OR 'cis diaminedichloroplatinum':ab,ti OR 'cis diammine dichloroplatinum':ab,ti OR 'cis diamminedichloroplatinum':ab,ti OR 'cis dichloridiammineplatinum':ab,ti OR 'cis dichloroadiamine platinum':ab,ti OR 'cis dichlorodiamine platinum':ab,ti OR 'cis dichlorodiammineplatinum':ab,ti OR 'cis platinous diamino dichloride':ab,ti OR 'cis platinum':ab,ti OR (cis* NEAR/3 platinum*):ab,ti OR cisplatin*:ab,ti OR cisplatyl:ab,ti OR citoplatino:ab,ti OR cytoplatin:ab,ti OR cytosplat:ab,ti OR 'diamine dichloroplatinum':ab,ti OR diaminodichloroplatinum:ab,ti OR diamminedichloroplatinum:ab,ti OR 'dichlorodiamine platinum':ab,ti OR dichlorodiammineplatinum:ab,ti OR docistin:ab,ti OR elvecis:ab,ti OR kemoplat:ab,ti OR lederplatin:ab,ti OR lipoplatin:ab,ti OR 'liposomal cisplatin':ab,ti OR 'mpi 5010':ab,ti OR mpi5010:ab,ti OR neoplatin:ab,ti OR niyaplat:ab,ti OR 'nk 801':ab,ti OR noveldexis:ab,ti OR 'nsc 119875':ab,ti	231,814

	OR platamine:ab,ti OR 'platamine rtu':ab,ti OR platiblastin:ab,ti OR platidiam:ab,ti OR platimine:ab,ti OR platinex:ab,ti OR platinil:ab,ti OR platinol*:ab,ti OR platinoxan:ab,ti OR platiran:ab,ti OR platistil:ab,ti OR platistin:ab,ti OR platosin:ab,ti OR randa:ab,ti OR romcis:ab,ti OR sicatem:ab,ti OR 'spi 077':ab,ti OR tecnoplatin:ab,ti OR gemcitabine*:ab,ti OR gemzar*:ab,ti OR difluorodeoxycytidine:ab,ti OR gemcite:ab,ti OR 'ly 188011':ab,ti OR ly188011:ab,ti OR vinorelbine*:ab,ti OR noranhydrovinblastine:ab,ti OR anhydrovinblastine:ab,ti OR 'anx 530':ab,ti OR anx530:ab,ti OR eunades:ab,ti OR exelbine:ab,ti OR 'kw 2307':ab,ti OR kw2307:ab,ti OR navelbin:ab,ti OR navirel:ab,ti OR vinbine:ab,ti OR vinelbine:ab,ti	
#12	'programmed death 1 ligand 1'/exp OR 'nivolumab'/exp OR 'pembrolizumab'/exp OR 'avelumab'/exp OR 'atezolizumab'/exp OR 'durvalumab'/exp OR 'ticilimumab'/exp OR 'pd l1':ab,ti OR pdl1:ab,ti OR 'pd 1':ab,ti OR pd1:ab,ti OR nivolumab*:ab,ti OR 'bms 936558':ab,ti OR bms936558:ab,ti OR 'mdx 1106':ab,ti OR mdx1106:ab,ti OR 'ono 4538':ab,ti OR ono4538:ab,ti OR opdivo:ab,ti OR pembrolizumab*:ab,ti OR keytruda:ab,ti OR lambrolizumab:ab,ti OR 'mk 3475':ab,ti OR mk3475:ab,ti OR avelumab*:ab,ti OR 'msb 0010718c':ab,ti OR msb0010718c:ab,ti OR atezolizumab*:ab,ti OR 'mpdl 3280a':ab,ti OR mpdl3280a:ab,ti OR 'rg 7446':ab,ti OR rg7446:ab,ti OR durvalumab*:ab,ti OR medi4736:ab,ti OR 'medi 4736':ab,ti OR ticilimumab*:ab,ti OR tremelimumab*:ab,ti OR 'cp 675 206':ab,ti OR 'cp 675, 206':ab,ti OR 'cp 675206':ab,ti OR 'cp675 206':ab,ti OR 'cp675, 206':ab,ti OR cp675206:ab,ti	17,470
#13	'rabusertib'/exp OR 'prexasertib'/exp OR rabusertib*:ab,ti OR ly2603618:ab,ti OR 'ly 2603618':ab,ti OR prexasertib*:ab,ti OR 'ly 2606368':ab,ti OR ly2606368:ab,ti OR (('chk 1' OR chk1) NEAR/3 inhibitor*):ab,ti	680
#14	'somatomedin c receptor'/exp OR 'figitumumab'/exp OR figitumumab*:ab,ti OR 'cp 751871':ab,ti OR cp751871:ab,ti OR 'insulin like growth factor':ab,ti OR 'igf type 1':ab,ti OR 'igf 1r':ab,ti OR igf1r:ab,ti OR 'igf 1 receptor':ab,ti	48,419
#15	'epidermal growth factor receptor kinase inhibitor'/exp OR afatinib:ab,ti OR canertinib:ab,ti OR dacomitinib:ab,ti OR erlotinib:ab,ti OR gefitinib:ab,ti OR genistein:ab,ti OR icotinib:ab,ti OR lapatinib:ab,ti OR naquotinib:ab,ti OR nazartinib:ab,ti OR neratinib:ab,ti OR olmutinib:ab,ti OR osimertinib:ab,ti OR pelitinib:ab,ti OR poziotinib:ab,ti OR rociletinib:ab,ti OR sapitinib:ab,ti OR tarloxotinib:ab,ti OR varlitinib:ab,ti OR (('egf receptor' OR 'epidermal growth factor receptor') NEAR/3 inhibit*):ab,ti	61,728
#16	'bevacizumab'/exp OR bevacizumab*:ab,ti OR altuzan:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti	43,708
#17	'antineoplastic agent'/exp OR 'immunotherapy'/exp OR 'drug therapy'/exp OR 'protein tyrosine kinase inhibitor'/exp	3,448,065
#18	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	3,866,381
#19	'systematic review'/exp OR 'meta analysis'/exp OR metaanalysis:ab,ti OR 'meta analysis':ab,ti OR 'systematic review':ab,ti OR 'adjusted indirect comparison':ab,ti OR (systematic* NEAR/3 review*):ab,ti OR ((mixed OR indirect) NEAR/3 treatment* NEAR/3 comparison*):ab,ti OR (simulated NEAR/3 (treatment* OR tx) NEAR/3 comparison*):ab,ti OR (match* NEAR/4 adjust* NEAR/3 (indirect OR comparison*)):ab,ti OR (nma NEAR/3 (network OR metaanalysis OR 'meta analysis')):ab,ti OR (itc NEAR/3 (indirect OR treatment* OR comparison*)):ab,ti OR (mtc NEAR/3 (mixed OR treatment* OR comparison*)):ab,ti OR (maic NEAR/4 (match* OR adjust* OR indirect OR comparison*)):ab,ti OR (stc NEAR/3 (simulated OR treatment* OR comparison*)):ab,ti OR (nma NEAR/3 (fp OR 'fractional polynomial')):ab,ti AND [2012-2017]/py	143,380
#20	#19 AND 'conference abstract'/it	29,641
#21	#19 NOT #20	113,739
#22	'controlled clinical trial'/exp OR randomized:ab,ti OR randomised:ab,ti OR randomly:ab,ti OR placebo:ab,ti OR trial:ab,ti OR 'randomized controlled trial':de OR 'controlled clinical trial':de	1,548,897
#23	'case study'/exp OR (('single arm' OR 'single agent') NEAR/3 (trial OR study)):ab,ti OR (historical* NEAR/3 control*):ab,ti OR ('case series':ab,ti AND prospective*:ab,ti)	66,025

#24	'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'open study'/exp OR 'postmarketing surveillance'/exp OR bayesian:ab,ti OR 'expanded access':ab,ti OR ((postmarketing OR 'post marketing') NEAR/2 surveillance):ab,ti OR (('2 arm' OR '3 arm' OR '4 arm' OR 'non inferiority' OR superiority OR 'proof of concept' OR 'proof of principle' OR 'proof of correlation' OR 'phase 1 2' OR 'phase1 2' OR 'phase i ii' OR 'phasei ii' OR 'phase ii' OR 'phaseii' OR 'phase 2' OR 'phase2' OR 'ph ii' OR phii* OR 'ph 2' OR ph2* OR 'phase 2 3' OR 'phase2 3' OR 'phase ii iii' OR 'phaseii iii' OR 'phase iii' OR phaseiii* OR 'phase 3' OR phase3* OR 'ph 3' OR ph3* OR 'ph iii' OR phiii* OR 'phase iv' OR phaseiv* OR 'phase 4' OR phase4* OR 'ph 4' OR ph4* OR 'ph iv' OR phiv* OR pivotal OR efficacy OR adaptive) NEAR/5 (trial OR study OR design)):ab,ti OR (extension NEAR/3 (trial OR study OR phase)):ab,ti OR (control* NEAR/3 ('clinical trial' OR 'clinical study')):ab,ti	329,469
#25	#22 OR #23 OR #24	1,749,894
#26	'phase 1':ti OR 'phase i':ti OR 'phase 1a':ti OR 'phase 1b':ti OR 'phase ia':ti OR 'phase ib':ti OR phase1:ti OR phasei:ti NOT ('phase 1 2':ti OR 'phase 1b 2':ti OR 'phase 1b 2a':ti OR 'phase i ii':ti OR 'phase ib ii':ti OR 'phase ib iia':ti OR 'phase i iia':ti OR 'phase1 2':ti OR 'phase1b 2':ti OR 'phase1b 2a':ti OR 'phase 1 2a':ti OR 'phasei ii':ti OR 'phaseib ii':ti OR 'phaseib iia':ti OR 'phasei iia':ti OR 'phase 1 and 2':ti OR 'phase i and ii':ti)	19,334
#27	#25 NOT #26	1,737,354
#28	#21 OR #27	1,809,557
#29	#1 AND #4 AND #18 AND #28	1024
#30	#29 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	26
#31	#29 NOT #30	998

* Individuals may be redirected based on individual licensing

Databases: MEDLINE in-process and electronic publications ahead of print

Platform: PubMed

URL: http://www.ncbi.nlm.nih.gov/pubmed/

Date searched: 2nd February 2017

Hits: 104 (from search on 2nd February 2017)

Two further publications [61] [55] identified from e-alerts tracked from 3rd February 2017 to 20th March 2017 (cutoff date)

One further publication noted after cutoff date, for the J-ALEX study [62]

No.	Query	Results
#1	Search ("Carcinoma, Non-Small-Cell Lung"[mh] OR ((lung[tiab] OR poumon[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR angiosarcoma*[tiab] OR chrondosarcoma*[tiab] OR sarcoma*[tiab] OR teratoma*[tiab] OR blastoma*[tiab] OR microcytic*[tiab] OR carcinogenesis[tiab] OR tumour*[tiab] OR tumor[tiab] OR tumors[tiab] OR metasta*[tiab] OR métastasé[tiab] OR métastatique[tiab] OR avancé[tiab] OR "progression localisée"[tiab])) OR NSCLC*[tiab] OR mNSCLC*[tiab] OR "m NSCLC"[tiab] OR aNSCLC*[tiab] OR "a NSCLC"[tiab] OR msqNSCLC*[tiab] OR "msq NSCLC"[tiab] OR nonsqNSCLC[tiab] OR "non sqNSCLC"[tiab] OR "non sq NSCLC"[tiab] OR SqCLC*[tiab] OR "ns NSCLC"[tiab] OR nsNSCLC*[tiab] OR "n s NSCLC"[tiab] OR "la NSCLC"[tiab] OR laNSCLC*[tiab] OR CPNPC*[tiab] OR (LAC[tiab] AND (lung[tiab] OR adenocarcinoma[tiab])) OR ((SCC[tiab] AND "squamous cell carcinoma"[tiab]) AND lung[tiab]) OR (non[tiab] AND	253,817

	small[tiab] AND cell[tiab] AND lung[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR ((“non small”[tiab] OR nonsmall[tiab]) AND lung[tiab] AND cell[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR ((“non small”[tiab] OR nonsmall[tiab]) AND cell[tiab] AND lung[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (bronchial[tiab] AND (“non small”[tiab] OR nonsmall[tiab]) AND cell[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (“non small cell”[tiab] AND (lung[tiab] OR bronchial[tiab] OR pulmonary[tiab] OR bronchopulmonary[tiab] OR bronchus[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab])) OR (“non small”[tiab] AND cell[tiab] AND (cancer*[tiab] OR carcinoma*[tiab]) AND lung*[tiab]) OR (pulmonary[tiab] AND “non small cell”[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (large[tiab] AND cell[tiab] AND lung[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR ((squamous[tiab] OR non-squamous[tiab] OR “non squamous”[tiab]) AND (cell[tiab] OR “non small cell”[tiab]) AND lung[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (bronchus[tiab] AND squamous[tiab] AND cell[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (lung[tiab] AND epidermoid[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR (lung[tiab] AND squamous[tiab] AND cell[tiab] AND (cancer*[tiab] OR carcinoma*[tiab])) OR ((lung[tiab] OR poumon[tiab]) AND (NSCLC*[tiab] OR CPNPC*[tiab] OR “non small”[tiab] OR nonsmall[tiab] OR large[tiab] OR squamous[tiab] OR “non squamous”[tiab] OR non-squamous[tiab] OR “non à petites cellules”[tiab])) OR ((adenocancer[tiab] OR adenocarcinoma[tiab]) AND (lung[tiab] OR pulmonary[tiab])) OR (((cancer[tiab] OR tumeur[tiab]) AND (poumon[tiab] OR bronchique[tiab])) AND (“non à petites cellules”[tiab] OR “non-lié à de petites cellules”[tiab])) OR ((brain[tiab] OR CNS[tiab] OR “central nervous system”[tiab] OR cerebral[tiab]) AND (metastasis[tiab] OR metastases[tiab] OR metastatic[tiab]))))	
#2	Search ("anaplastic lymphoma kinase" [Supplementary Concept] OR ALK[tiab] OR ALKfusion[tiab] OR EML4ALK*[tiab] OR (anaplastic[tiab] AND lymphoma[tiab] AND kinase*[tiab]))	6615
#3	Search (L1196M[tiab] OR G1269A[tiab] OR C1156Y[tiab] OR L1152*[tiab] OR 1151Tins[tiab] OR G1202R[tiab] OR V118L[tiab] OR I1171T[tiab] OR S1206Y[tiab] OR F1174C[tiab] OR D1203N[tiab] OR G1269A[tiab] OR G1123S*[tiab] OR ((crizotinib*[tiab] OR ceritinib*[tiab] OR alectinib*[tiab] OR “alk tki”[tiab] OR alktki[tiab] OR alki[tiab]) AND (experienced[tiab] OR treated[tiab] OR pretreated[tiab] OR “pre treated”[tiab] OR “previously treated”[tiab] OR “treated previously”[tiab] OR resistan*[tiab] OR refractory[tiab] OR naïve[tiab])))	708
#4	Search (#2 OR #3)	6713
#5	Search ("ceritinib" [Supplementary Concept] OR "CH5424802" [Supplementary Concept] OR "AP26113" [Supplementary Concept] OR "CM-118" [Supplementary Concept] OR “ALK TKI”[tiab] OR ALKTKI[tiab] OR (ALK[tiab] AND (inhibitor[tiab] OR inhibitors[tiab])) OR ((anaplastic[tiab] AND lymphoma[tiab] AND kinase[tiab]) AND (inhibitor[tiab] OR inhibitors[tiab])) OR alectinib*[tiab] OR “af 802”[tiab] OR af802[tiab] OR “ch 5424802”[tiab] OR ch5424802[tiab] OR RO5424802[tiab] OR RG7853[tiab] OR Alecensa[tiab] OR crizotinib*[tiab] OR “pf 02341066”[tiab] OR pf02341066[tiab] OR “pf 1066”[tiab] OR pf1066[tiab] OR “pf 2341066”[tiab] OR pf2341066[tiab] OR xalkori[tiab] OR ceritinib*[tiab] OR “ldk 378”[tiab] OR ldk378[tiab] OR “nvp ldk 378”[tiab] OR “nvp ldk378”[tiab] OR “nvp ldk378nx”[tiab] OR zykadia[tiab] OR entrectinib*[tiab] OR “nms e 628”[tiab] OR “nms e628”[tiab] OR “rxdx 101”[tiab] OR rxdx101[tiab] OR brigatinib*[tiab] OR “ap 26113”[tiab] OR ap26113[tiab] OR lorlatinib*[tiab] OR “pf 06463922”[tiab] OR pf06463922[tiab] OR “tsr 011”[tiab] OR tsr011[tiab] OR “asp 3026”[tiab] OR asp3026[tiab] OR “CEP 37440”[tiab] OR CEP37440[tiab] OR “X 396”[tiab] OR X396[tiab] OR “X 276”[tiab] OR X276[tiab] OR “asp 3026”[tiab] OR asp3026[tiab] OR “nvp tae 684”[tiab] OR “nvp tae684”[tiab] OR “tae 684”[tiab] OR tae684[tiab] OR “CEP 28122”[tiab] OR CEP28122[tiab] OR “CEP 14083”[tiab] OR CEP14083[tiab] OR “CEP 14513”[tiab] OR CEP14513[tiab] OR “GSK 1838705A”[tiab] OR GSK1838705A[tiab] OR CM118[tiab] OR “CM 118”[tiab])	2338
#6	Search ("HSP90 Heat-Shock Proteins"[mh] OR “hsp 90 inhibitor”[tiab] OR “hsp90 inhibitor”[tiab] OR luminespib*[tiab] OR “auy 922”[tiab] OR auy922[tiab] OR “nvp auy 922”[tiab] OR “nvp auy922”[tiab] OR “ver 52296”[tiab] OR ver52296[tiab] OR ganetespib*[tiab] OR “sta 9090”[tiab] OR sta9090[tiab] OR onalespib*[tiab] OR “AT 13387”[tiab] OR AT13387[tiab] OR ribociclib*[tiab] OR “lee 011”[tiab] OR lee011[tiab] OR “IPI 504”[tiab] OR IPI504[tiab] OR retaspimycin[tiab] OR tanespimycin*[tiab] OR “kos 953”[tiab] OR kos953[tiab] OR “nsc 330507”[tiab] OR nsc330507[tiab] OR	7766

	geldanamycin*[tiab] OR “nsc 122750”[tiab] OR nsc122750[tiab] OR gamendazole*[tiab] OR gambogic*[tiab] OR “beta guttiferin”[tiab] OR “guttic acid”[tiab] OR celastrol*[tiab] OR tripterin[tiab] OR “biib 028”[tiab] OR biib028[tiab] OR alvespimycin[tiab] OR “bms 826476”[tiab] OR bms826476[tiab] OR “kos 1022”[tiab] OR kos1022[tiab] OR “nsc 707545”[tiab] OR nsc707545[tiab] OR Debio0932[tiab] OR “debio 0932”[tiab])	
#7	Search ("Proto-Oncogene Proteins c-akt"[mh] OR “AKT1 protein, human” [Supplementary Concept] OR "AKT2 protein, human" [Supplementary Concept] OR "AKT3 protein, human" [Supplementary Concept] OR ((Akt[tiab] OR “c akt”[tiab]) AND (kinase[tiab] OR protein[tiab] OR proteins[tiab])))	53,287
#8	Search (“standard of care”[mh] OR ((gold[tiab] OR golden[tiab]) AND standard[tiab]) OR “best supportive care”[tiab] OR “standard of care”[tiab] OR (BSC[tiab] AND (best[tiab] OR supportive[tiab] OR care[tiab])) OR (SOC[tiab] AND (standard[tiab] OR care[tiab])))	74,023
#9	Search (“placebos”[mh] OR placebo*[tiab])	196,068
#10	Search ("docetaxel"[Supplementary Concept] OR "Paclitaxel"[mh] OR daxotel[tiab] OR dexotel[tiab] OR docefrez[tiab] OR docetaxel*[tiab] OR “lit 976”[tiab] OR lit976[tiab] OR deacetyltaxol[tiab] OR “nsc 628503”[tiab] OR nsc628503[tiab] OR oncodocel[tiab] OR “rp 56976”[tiab] OR rp56976[tiab] OR taxoter[tiab] OR taxotere*[tiab] OR texot[tiab] OR taxespira[tiab] OR “abi 007”[tiab] OR abi007[tiab] OR abraxane[tiab] OR anzatax[tiab] OR asotax[tiab] OR biotax[tiab] OR “bms 181339”[tiab] OR bms181339[tiab] OR bristaxol[tiab] OR britaxol[tiab] OR coroxane[tiab] OR formoxol[tiab] OR genexol[tiab] OR “genexol pm”[tiab] OR hunxol[tiab] OR ifaxol[tiab] OR infinnium[tiab] OR intaxel[tiab] OR “mbt 0206”[tiab] OR mbt0206[tiab] OR medixel[tiab] OR mitotax[tiab] OR “nab paclitaxel”[tiab] OR “nsc 125973”[tiab] OR nsc125973[tiab] OR oncogel[tiab] OR onxol[tiab] OR pacitaxel[tiab] OR paclitaxel*[tiab] OR “paclitaxel nab”[tiab] OR pacxel[tiab] OR padexol[tiab] OR parexel[tiab] OR paxceed[tiab] OR paxene[tiab] OR paxus[tiab] OR praxel[tiab] OR taxocris[tiab] OR taxol[tiab] OR taxus[tiab] OR taycovit[tiab] OR yewtaxan[tiab])	42,194
#11	Search ("Pemetrexed"[mh] OR “carboplatin”[mh] OR “cisplatin”[mh] OR "gemcitabine" [Supplementary Concept] OR "vinorelbine" [Supplementary Concept] OR pemetrexed*[tiab] OR alimta*[tiab] OR ciambra[tiab] OR elimta[tiab] OR “ly 231514”[tiab] OR ly231514[tiab] OR blastocarb[tiab] OR boplatex[tiab] OR carboplat[tiab] OR carboplatin*[tiab] OR carbosin[tiab] OR “carbosin lundbeck”[tiab] OR carbotec[tiab] OR carplan[tiab] OR CBDCA[tiab] OR cycloplatin[tiab] OR “delta west carboplatin”[tiab] OR erbakar[tiab] OR ercar[tiab] OR ifacap[tiab] OR “jm 8”[tiab] OR kemocarb[tiab] OR “nsc 241240”[tiab] OR oncocarbin[tiab] OR paraplatin*[tiab] OR platinum*[tiab] OR abiplatin[tiab] OR biocisplatinum[tiab] OR biocysplatinum[tiab] OR blastolem[tiab] OR briplatin[tiab] OR “cddp ti”[tiab] OR “cis ddp”[tiab] OR “cis diamine dichloroplatinum”[tiab] OR “cis diaminechloroplatinum”[tiab] OR “cis diaminedichloroplatinum”[tiab] OR “cis diammine dichloroplatinum”[tiab] OR “cis diamminedichloroplatinum”[tiab] OR “cis dichloridiammineplatinum”[tiab] OR “cis dichloroadiamine platinum”[tiab] OR “cis dichlorodiamine platinum”[tiab] OR “cis dichlorodiammineplatinum”[tiab] OR “cis platinous diamino dichloride”[tiab] OR “cis platinum”[tiab] OR (cis[tiab] AND platinum*[tiab]) OR cisplatin*[tiab] OR cisplatyl[tiab] OR citoplatino[tiab] OR cytoplatin[tiab] OR cytosplat[tiab] OR “diamine dichloroplatinum”[tiab] OR diaminodichloroplatinum[tiab] OR diamminedichloroplatinum[tiab] OR “dichlorodiamine platinum”[tiab] OR dichlorodiammineplatinum[tiab] OR docistin[tiab] OR elvecis[tiab] OR kemoplat[tiab] OR lederplatin[tiab] OR lipoplatin[tiab] OR “liposomal cisplatin”[tiab] OR “mpi 5010”[tiab] OR mpi5010[tiab] OR neoplatin[tiab] OR niyaplat[tiab] OR “nk 801”[tiab] OR noveldexis[tiab] OR “nsc 119875”[tiab] OR platamine[tiab] OR “platamine rtu”[tiab] OR platiblastin[tiab] OR platidiam[tiab] OR platimine[tiab] OR platinex[tiab] OR platinil[tiab] OR platinol*[tiab] OR platinoxan[tiab] OR platiran[tiab] OR platistil[tiab] OR platistin[tiab] OR platosin[tiab] OR randa[tiab] OR romcis[tiab] OR sicatem[tiab] OR “spi 077”[tiab] OR tecnoplatin[tiab] OR gemcitabine*[tiab] OR gemzar*[tiab] OR difluorodeoxycytidine[tiab] OR gemcite[tiab] OR “ly 188011”[tiab] OR ly188011[tiab] OR vinorelbine*[tiab] OR noranhydrovinblastine[tiab] OR anhydrovinblastine[tiab] OR “anx 530”[tiab] OR anx530[tiab] OR eunades[tiab] OR exelbine[tiab] OR “kw 2307”[tiab] OR kw2307[tiab] OR navelbin[tiab] OR navirel[tiab] OR vinbine[tiab] OR vinelbine[tiab])	106,752
#12	Search ("Programmed Cell Death 1 Ligand 2 Protein"[mh] OR "nivolumab" [Supplementary Concept] OR "pembrolizumab" [Supplementary Concept] OR "avelumab" [Supplementary Concept] OR "atezolizumab" [Supplementary Concept] OR "tremelimumab" [Supplementary Concept] OR “PD	7622

	L1”[tiab] OR PDL1[tiab] OR “PD 1”[tiab] OR PD1[tiab] OR nivolumab*[tiab] OR “bms 936558”[tiab] OR bms936558[tiab] OR “mdx 1106”[tiab] OR mdx1106[tiab] OR “ono 4538”[tiab] OR ono4538[tiab] OR opdivo[tiab] OR pembrolizumab*[tiab] OR keytruda[tiab] OR lambrolizumab[tiab] OR “mk 3475”[tiab] OR mk3475[tiab] OR avelumab*[tiab] OR “msb 0010718c”[tiab] OR msb0010718c[tiab] OR atezolizumab*[tiab] OR “mpdl 3280a”[tiab] OR mpdl3280a[tiab] OR “mpdl 3280a”[tiab] OR mpdl3280a[tiab] OR “rg 7446”[tiab] OR rg7446[tiab] OR durvalumab*[tiab] OR medi4736[tiab] OR “medi 4736”[tiab] OR ticilimumab*[tiab] OR tremelimumab*[tiab] OR “cp 675 206”[tiab] OR “cp 675, 206”[tiab] OR “cp 675206”[tiab] OR “cp675 206”[tiab] OR “cp675, 206”[tiab] OR cp675206[tiab])	
#13	Search (rabusertib*[tiab] OR LY2603618[tiab] OR “LY 2603618”[tiab] OR prexasertib*[tiab] OR “ly 2606368”[tiab] OR ly2606368[tiab] OR ((“CHK 1”[tiab] OR CHK1[tiab]) AND inhibitor*[tiab]))	1015
#14	Search ("Insulin-Like Growth Factor I"[mh] OR "figitumumab" [Supplementary Concept] OR figitumumab*[tiab] OR “cp 751871”[tiab] OR cp751871[tiab] OR “insulin like growth factor”[tiab] OR “IGF type 1”[tiab] OR “IGF 1r”[tiab] OR IGF1R[tiab] OR “IGF 1 receptor”[tiab])	50,057
#15	Search ("afatinib" [Supplementary Concept] OR "Canertinib" [Supplementary Concept] OR "PF 00299804" [Supplementary Concept] OR "Erlotinib Hydrochloride"[mh] OR "gefitinib" [Supplementary Concept] OR "Genistein"[mh] OR "icotinib" [Supplementary Concept] OR "lapatinib" [Supplementary Concept] OR "N-(4-(3-chloro-4-(2-pyridinylmethoxy)anilino)-3-cyano-7-ethoxy-6-quinolyl)-4-(dimethylamino)-2-butenamide" [Supplementary Concept] OR "osimertinib" [Supplementary Concept] OR "EKB 569" [Supplementary Concept] OR "HM781-36B" [Supplementary Concept] OR "rociletinib" [Supplementary Concept] OR afatinib[tiab] OR canertinib[tiab] OR dacomitinib[tiab] OR erlotinib[tiab] OR gefitinib[tiab] OR genistein[tiab] OR icotinib[tiab] OR lapatinib[tiab] OR naquotinib[tiab] OR nazartinib[tiab] OR neratinib[tiab] OR olmutinib[tiab] OR osimertinib[tiab] OR pelitinib[tiab] OR poziotinib[tiab] OR rociletinib[tiab] OR sapitinib[tiab] OR tarloxotinib[tiab] OR varlitinib[tiab] OR ((“EGF receptor”[tiab] OR “epidermal growth factor receptor”[tiab]) AND inhibit*[tiab]))	34,979
#16	Search ("Bevacizumab"[mh] OR bevacizumab*[tiab] OR altuzan[tiab] OR avastin[tiab] OR “nsc 704865”[tiab] OR nsc704865[tiab])	13,625
#17	Search ("Antineoplastic Agents"[mh] OR "Antineoplastic Agents"[Pharmacological Action] OR “immunotherapy”[mh] OR “drug therapy”[mh] OR "Protein-Tyrosine Kinases"[mh])	2,257,283
#18	Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	2,579,793
#19	Search ((“Review”[pt] OR “meta-analysis”[pt] OR “Network Meta-Analysis”[mh] OR metaanalysis[tiab] OR “meta analysis”[tiab] OR “systematic review”[tiab] OR “adjusted indirect comparison”[tiab] OR (systematic*[tiab] AND review*[tiab]) OR ((mixed[tiab] OR indirect[tiab]) AND treatment*[tiab] AND comparison*[tiab]) OR (simulated[tiab] AND (treatment*[tiab] OR tx[tiab]) AND comparison*[tiab]) OR (match*[tiab] AND adjust*[tiab] AND (indirect[tiab] OR comparison*[tiab])) OR (nma[tiab] AND (network[tiab] OR metaanalysis[tiab] OR “meta analysis”[tiab])) OR (itc[tiab] AND (indirect[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (mtc[tiab] AND (mixed[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (maic[tiab] AND (match*[tiab] OR adjust*[tiab] OR indirect[tiab] OR comparison*[tiab])) OR (stc[tiab] AND (simulated[tiab] OR treatment*[tiab] OR comparison*[tiab])) OR (NMA[tiab] AND (FP[tiab] OR “fractional polynomial”[tiab]))))) AND ("2012/01/01"[Date - Publication] : "3000"[Date - Publication])	578,004
#20	Search (“controlled clinical trial”[mh] OR “controlled clinical trial”[pt] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR placebo*[tiab] OR trial[tiab])	1,121,737
#21	Search (((“single arm”[tiab] OR “single agent”[tiab]) AND (trial[tiab] OR study[tiab])) OR (historical*[tiab] AND control*[tiab]) OR (“case series”[tiab] AND prospective*[tiab]))	35,699
#22	Search ("Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR	605,119

	"Product Surveillance, Postmarketing"[mh] OR bayesian[tiab] OR “expanded access”[tiab] OR ((postmarketing[tiab] OR “post marketing”[tiab]) AND surveillance[tiab]) OR ((“2 arm”[tiab] OR “3 arm”[tiab] OR “4 arm”[tiab] OR “non inferiority”[tiab] OR superiority[tiab] OR “proof of concept”[tiab] OR “proof of principle”[tiab] OR “proof of correlation”[tiab] OR “phase 1 2”[tiab] OR “phase1 2”[tiab] OR “phase i ii”[tiab] OR “phasei ii”[tiab] OR “phase ii”[tiab] OR “phaseii”[tiab] OR “phase 2”[tiab] OR “phase2”[tiab] OR “ph ii”[tiab] OR phii*[tiab] OR “ph 2”[tiab] OR ph2*[tiab] OR “phase 2 3”[tiab] OR “phase2 3”[tiab] OR “phase ii iii”[tiab] OR “phaseii iii”[tiab] OR “phase iii”[tiab] OR phaseiii*[tiab] OR “phase 3”[tiab] OR phase3*[tiab] OR “ph 3”[tiab] OR ph3*[tiab] OR “ph iii”[tiab] OR phiii*[tiab] OR “phase iv”[tiab] OR phaseiv*[tiab] OR “phase 4”[tiab] OR phase4*[tiab] OR “ph 4”[tiab] OR ph4*[tiab] OR “ph iv”[tiab] OR phiv*[tiab] OR pivotal[tiab] OR efficacy[tiab] OR adaptive[tiab]) AND (trial[tiab] OR study[tiab] OR design[tiab])) OR (extension[tiab] AND (trial[tiab] OR study[tiab] OR phase[tiab])) OR (control*[tiab] AND (“clinical trial”[tiab] OR “clinical study”[tiab])))	
#23	Search (#20 OR #21 OR #22)	1,512,299
#24	Search (((“phase 1”[title] OR “phase i”[title] OR “phase 1a”[title] OR “phase 1b”[title] OR “phase Ia”[title] OR “phase Ib”[title] OR phase1[title] OR phasei[title]) NOT (“phase 1 2”[title] OR “phase 1b 2”[title] OR “phase 1b 2a”[title] OR “phase 1 2a”[title] OR “phase I II”[title] OR “phase Ib II”[title] OR “phase Ib IIa”[title] OR “phase I IIa”[title] OR “phase1 2”[title] OR “phase1b 2”[title] OR “phase1b 2a”[title] OR “phase 1 2a”[title] OR “phaseI II”[title] OR “phaseIb II”[title] OR “phaseIb IIa”[title] OR “phaseI IIa”[title] OR “phase 1 and 2”[title] OR “phase I and II”[title]))	11,576
#25	Search (#23 NOT #24)	1,504,232
#26	Search (#19 OR #25)	2,015,137
#27	Search (#1 AND #4 AND #18 AND #26)	733
#28	Search (#27) AND (pubstatusaheadofprint OR inprocess[sb])	104

Database: Cochrane Library

Platform: Wiley

URL: http://onlinelibrary.wiley.com/cochranelibrary/search/

Date searched: 2nd February 2017 at 14:00 GMT

Hits: 92

Cochrane Database of Systematic Reviews (CDSR) Issue 2 of 12, February 2017: 0

Database of Abstracts of Reviews of Effect (DARE) Issue 2 of 4, April 2015: 0

Cochrane Central Register of Controlled Trials (CENTRAL) Issue 1 of 12, January 2017: 92

No.	Query	Results
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	2918
#2	MeSH descriptor: [Central Nervous System Neoplasms] explode all trees	1820
#3	(((lung or poumon) near/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or blastoma* or microcytic* or carcinogenesis or tumour* or tumor* or metasta* or métastasé or métastatique or avancé or "progression localisée")) or NSCLC* or mNSCLC* or "m NSCLC" or aNSCLC* or "a NSCLC" or msqNSCLC* or "msq NSCLC" or nonsqNSCLC or "non sqNSCLC" or "non sq NSCLC" or SqCLC* or "ns NSCLC" or nsNSCLC* or "n s NSCLC" or "la NSCLC" or laNSCLC* or CPNPC* or (LAC near/3 (lung or adenocarcinoma))	14,182

	or ((SCC near/3 "squamous cell carcinoma") and lung) or (non near/3 small near/3 cell near/3 lung near/3 (cancer* or carcinoma*)) or (("non small" or nonsmall) near/3 lung near/3 cell near/3 (cancer* or carcinoma*)) or (("non small" or nonsmall) near/3 cell near/3 lung near/3 (cancer* or carcinoma*)) or (bronchial near/3 ("non small" or nonsmall) near/3 cell near/3 (cancer* or carcinoma*)) or ("non small cell" near/3 (lung or bronchial or pulmonary or bronchopulmonary or bronchus) near/3 (cancer* or carcinoma*)) or ("non small" near/3 cell near/3 (cancer* or carcinoma*) near/3 lung*) or (pulmonary near/3 "non small cell" near/3 (cancer* or carcinoma*)) or (large near/3 cell near/3 lung near/3 (cancer* or carcinoma*)) or ((squamous or non-squamous or "non squamous") near/5 (cell or "non small cell") near/3 lung near/3 (cancer* or carcinoma*)) or (bronchus near/3 squamous near/3 cell near/3 (cancer* or carcinoma*)) or (lung near/3 epidermoid near/3 (cancer* or carcinoma*)) or (lung near/3 squamous near/3 cell near/3 (cancer* or carcinoma*)) or ((lung or poumon) and (NSCLC* or CPNPC* or "non small" or nonsmall or large or squamous or "non squamous" or non-squamous or "non à petites cellules")) or ((adenocancer or adenocarcinoma) near/3 (lung or pulmonary)) or (((cancer or tumeur) near/3 (poumon or bronchique)) and ("non à petites cellules" or "non-lié à de petites cellules")) or ((brain or CNS or "central nervous system" or cerebral) near/3 (metastasis or metastases or metastatic))):ti,ab,kw	
#4	#1 or #2 or #3	15,643
#5	(ALK or ALKfusion or EML4ALK* or (anaplastic near/3 lymphoma near/3 kinase*) or (ALK* and (anaplastic or lymphoma or kinase))):ti,ab,kw	618
#6	(L1196M or G1269A or C1156Y or L1152* or 1151Tins or G1202R or V118L or I1171T or S1206Y or F1174C or D1203N or G1269A or G1123S* or ((crizotinib* or ceritinib* or alectinib* or "alk tki" or alktki or ALKi) near/3 (experienced or treated or pretreated or "pre treated" or "previously treated" or "treated previously" or resistan* or refractory or naïve))):ti,ab,kw	12
#7	#5 or #6	619
#8	("ALK TKI" or ALKTKI or (ALK near/3 (inhibitor or inhibitors)) or ((anaplastic near/3 lymphoma near/3 kinase) and (inhibitor or inhibitors)) or alectinib* or "af 802" or af802 or "ch 5424802" or ch5424802 or RO5424802 or RG7853 or Alecensa or crizotinib* or "pf 02341066" or pf02341066 or "pf 1066" or pf1066 or "pf 2341066" or pf2341066 or xalkori or ceritinib* or "ldk 378" or ldk378 or "nvp ldk 378" or "nvp ldk378" or "nvp ldk378nx" or zykadia or entrectinib* or "nms e 628" or "nms e628" or "rxdx 101" or rxdx101 or brigatinib* or "ap 26113" or ap26113 or lorlatinib* or "pf 06463922" or pf06463922 or "tsr 011" or tsr011 or "asp 3026" or asp3026 or "CEP 37440" or CEP37440 or "X 396" or X396 or "X 276" or X276 or "asp 3026" or asp3026 or "nvp tae 684" or "nvp tae684" or "tae 684" or tae684 or "CEP 28122" or CEP28122 or "CEP 14083" or CEP14083 or "CEP 14513" or CEP14513 or "GSK 1838705A" or GSK1838705A or CM118 or "CM 118"):ti,ab,kw	76
#9	MeSH descriptor: [HSP90 Heat-Shock Proteins] explode all trees	9
#10	("hsp 90 inhibitor" or "hsp90 inhibitor" or luminespib* or "auy 922" or auy922 or "nvp auy 922" or "nvp auy922" or "ver 52296" or ver52296 or ganetespib* or "sta 9090" or sta9090 or onalespib* or "AT 13387" or AT13387 or ribociclib* or "lee 011" or lee011 or "IPI 504" or IPI504 or retaspimycin or tanespimycin* or "kos 953" or kos953 or "nsc 330507" or nsc330507 or geldanamycin* or "nsc 122750" or nsc122750 or gamendazole* or gambogic* or "beta guttiferin" or "guttic acid" or celastrol* or tripterin or "biib 028" or biib028 or alvespimycin or "bms 826476" or bms826476 or "kos 1022" or kos1022 or "nsc 707545" or nsc707545 or Debio0932 or "debio 0932"):ti,ab,kw	29
#11	MeSH descriptor: [Proto-Oncogene Proteins c-akt] explode all trees	81
#12	((Akt or "c akt") near/3 (kinase or protein or proteins)):ti,ab,kw	159
#13	MeSH descriptor: [Standard of Care] explode all trees	164
#14	((((gold or golden) near/3 standard) or "best supportive care" or "standard of care" or (BSC near/3 (best or supportive or care)) or (SOC near/3 (standard or care))):ti,ab,kw	7249

#15	MeSH descriptor: [Placebos] explode all trees	23,137
#16	placebo*:ti,ab,kw	188,991
#17	MeSH descriptor: [Taxoids] explode all trees	2784
#18	(daxotel or dexotel or docefrez or docetaxel* or "lit 976" or lit976 or deacetyltaxol or "nsc 628503" or nsc628503 or oncodocel or "rp 56976" or rp56976 or taxoter or taxotere* or texot or taxespira or "abi 007" or abi007 or abraxane or anzatax or asotax or biotax or "bms 181339" or bms181339 or bristaxol or britaxol or coroxane or formoxol or genexol or "genexol pm" or hunxol or ifaxol or infinnium or intaxel or "mbt 0206" or mbt0206 or medixel or mitotax or "nab paclitaxel" or "nsc 125973" or nsc125973 or oncogel or onxol or pacitaxel or paclitaxel* or "paclitaxel nab" or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan):ti,ab,kw	7728
#19	MeSH descriptor: [Pemetrexed] explode all trees	188
#20	MeSH descriptor: [Carboplatin] explode all trees	1162
#21	MeSH descriptor: [Cisplatin] explode all trees	3646
#22	(pemetrexed* or alimta* or ciambra or elimta or "ly 231514" or ly231514 or blastocarb or boplatex or carboplat or carboplatin* or carbosin or "carbosin lundbeck" or carbotec or carplan or CBDCA or cycloplatin or "delta west carboplatin" or erbakar or ercar or ifacap or "jm 8" or kemocarb or "nsc 241240" or oncocarbin or paraplatin* or platinum* or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or "cddp ti" or "cis ddp" or "cis diamine dichloroplatinum" or "cis diaminechloroplatinum" or "cis diaminedichloroplatinum" or "cis diammine dichloroplatinum" or "cis diamminedichloroplatinum" or "cis dichloridiammineplatinum" or "cis dichloroadiamine platinum" or "cis dichlorodiamine platinum" or "cis dichlorodiammineplatinum" or "cis platinous diamino dichloride" or "cis platinum" or (cis* near/3 platinum*) or cisplatin* or cisplatyl or citoplatino or cytoplatin or cytosplat or "diamine dichloroplatinum" or diaminodichloroplatinum or diamminedichloroplatinum or "dichlorodiamine platinum" or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or "liposomal cisplatin" or "mpi 5010" or mpi5010 or neoplatin or niyaplat or "nk 801" or noveldexis or "nsc 119875" or platamine or "platamine rtu" or platiblastin or platidiam or platimine or platinex or platinil or platinol* or platinoxan or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin or gemcitabine* or gemzar* or difluorodeoxycytidine or gemcite or "ly 188011" or ly188011 or vinorelbine* or noranhydrovinblastine or anhydrovinblastine or "anx 530" or anx530 or eunades or exelbine or "kw 2307" or kw2307 or navelbin or navirel or vinbine or vinelbine):ti,ab,kw	14,225
#23	("PD L1" or PDL1 or "PD 1" or PD1 or nivolumab* or "bms 936558" or bms936558 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538 or opdivo or pembrolizumab* or keytruda or lambrolizumab or "mk 3475" or mk3475 or avelumab* or "msb 0010718c" or msb0010718c or atezolizumab* or "mpdl 3280a" or mpdl3280a or "mpdl 3280a" or mpdl3280a or "rg 7446" or rg7446 or durvalumab* or medi4736 or "medi 4736" or ticilimumab* or tremelimumab* or "cp 675 206" or "cp 675, 206" or "cp 675206" or "cp675 206" or "cp675, 206" or cp675206):ti,ab,kw	409
#24	(rabusertib* or LY2603618 or "LY 2603618" or prexasertib* or "ly 2606368" or ly2606368 or (("CHK 1" or CHK1) near/3 inhibitor*)):ti,ab,kw	8
#25	MeSH descriptor: [Insulin-Like Growth Factor I] explode all trees	1536
#26	MeSH descriptor: [Receptor, IGF Type 1] explode all trees	24
#27	(figitumumab* or "cp 751871" or cp751871 or "insulin like growth factor" or "IGF type 1" or "IGF 1r" or IGF1R or "IGF 1 receptor"):ti,ab,kw	2358
#28	MeSH descriptor: [Receptor, Epidermal Growth Factor] explode all trees	538
#29	(afatinib or canertinib or dacomitinib or erlotinib or gefitinib or genistein or icotinib or lapatinib or naquotinib or nazartinib or neratinib or olmutinib or osimertinib or pelitinib or poziotinib or rociletinib or sapitinib or tarloxotinib or varlitinib or (("EGF receptor" or "epidermal growth factor receptor") near/3 inhibit*)):ti,ab,kw	1927

#30	MeSH descriptor: [Bevacizumab] explode all trees	680
#31	(bevacizumab* or altuzan or avastin or "nsc 704865" or nsc704865):ti,ab,kw	2423
#32	MeSH descriptor: [Antineoplastic Agents] explode all trees	11,910
#33	MeSH descriptor: [Immunotherapy] explode all trees	7784
#34	MeSH descriptor: [Drug Therapy] explode all trees	131,020
#35	MeSH descriptor: [Protein Kinase Inhibitors] explode all trees	673
#36	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35	309,094
#37	MeSH descriptor: [Review] explode all trees	55
#38	MeSH descriptor: [Meta-Analysis] explode all trees	166
#39	(metaanalysis or "meta analysis" or "systematic review" or "adjusted indirect comparison" or (systematic* near/3 review*) or ((mixed or indirect) near/3 treatment* near/3 comparison*) or (simulated near/3 (treatment* or tx) near/3 comparison*) or (match* near/4 adjust* near/3 (indirect or comparison*)) or (nma near/3 (network or metaanalysis or "meta analysis")) or (itc near/3 (indirect or treatment* or comparison*)) or (mtc near/3 (mixed or treatment* or comparison*)) or (maic near/4 (match* or adjust* or indirect or comparison*)) or (stc near/3 (simulated or treatment* or comparison*)) or (NMA near/3 (FP or "fractional polynomial"))):ti,ab,kw	45,571
#40	#37 or #38 or #39 Publication Year from 2012 to 2017	22,171
#41	MeSH descriptor: [Controlled Clinical Trial] explode all trees	170
#42	(randomized or randomised or randomly or placebo or trial):ti,ab,kw	670,855
#43	MeSH descriptor: [Case Reports] explode all trees	1
#44	((("single arm" or "single agent") near/3 (trial or study)) or (historical* near/3 control*) or ("case series" and prospective*)):ti,ab,kw	2268
#45	MeSH descriptor: [Clinical Trial, Phase II] explode all trees	0
#46	MeSH descriptor: [Clinical Trial, Phase III] explode all trees	1
#47	MeSH descriptor: [Clinical Trial, Phase IV] explode all trees	0
#48	MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees	242
#49	(bayesian or "expanded access" or ((postmarketing or "post marketing") near/2 surveillance) or (("2 arm" or "3 arm" or "4 arm" or "non inferiority" or superiority or "proof of concept" or "proof of principle" or "proof of correlation" or "phase 1 2" or "phase1 2" or "phase i ii" or "phasei ii" or "phase ii" or "phaseii" or "phase 2" or "phase2" or "ph ii" or phii* or "ph 2" or ph2* or "phase 2 3" or "phase2 3" or "phase ii iii" or "phaseii iii" or "phase iii" or phaseiii* or "phase 3" or phase3* or "ph 3" or ph3* or "ph iii" or phiii* or "phase iv" or phaseiv* or "phase 4" or phase4* or "ph 4" or ph4* or "ph iv" or phiv* or pivotal or efficacy or adaptive) near/5 (trial or study or design)) or (extension near/3 (trial or study or phase)) or (control* near/3 ("clinical trial" or "clinical study"))):ti,ab,kw	182,498
#50	#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49	678,501
#51	(("phase 1" or "phase i" or "phase 1a" or "phase 1b" or "phase Ia" or "phase Ib" or phase1 or phasei) not ("phase 1 2" or "phase 1b 2" or "phase 1b 2a" or "phase 1 2a" or "phase I II" or "phase Ib II" or "phase Ib IIa" or "phase I IIa" or "phase1 2" or "phase1b 2" or "phase1b 2a" or "phase 1 2a" or "phaseI II" or "phaseIb II" or "phaseIb IIa" or "phaseI IIa" or "phase 1 and 2" or "phase I and II")):ti	3338
#52	#50 not #51	675,858

#53	#40 or #52	688,831
#54	#4 and #7 and #36 and #53	92
#55	#54 in Cochrane Reviews (reviews and protocols), other reviews and trials	92

Abbreviation: MesH=Medical Subject Headings.

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A10. Overview of guidelines

Name of society/organisation issuing guidelines	Date of issue	Countries to which guideline applies	Summary of recommendations (level of evidence/grade of recommendation for the indication under assessment)
European Society for Medical Oncology [8]	2016	European Union members	For patients with *ALK*-positive metastatic NSCLC, crizotinib as first-line treatment is the preferred option (level of evidence: evidence from at least one large randomised controlled trial of good methodological quality [low potential for bias] or meta-analyses of well-conducted randomised trials without heterogeneity; grade of recommendation: strongly recommended). Ceritinib and alectinib ('currently in clinical development' at the time of the last update of this guideline) are recommended for *ALK*-positive NSCLC patients whose disease progresses while they are receiving treatment with crizotinib (level of evidence: prospective cohort studies; grade of recommendation: strongly recommended). For the treatment of CNS metastases, next-generation TKIs are recommended to restore control of brain disease and delay cranial radiotherapy in patients with a druggable oncogene driver and clinically asymptomatic brain metastases (level of evidence: prospective cohort studies; grade of recommendation: strongly recommended). For *ALK*-positive patients whose disease progresses while they are receiving crizotinib, ceritinib or alectinib is recommended because of their activity against CNS disease (level of evidence: prospective cohort studies; grade of recommendation: strongly recommended)
American Society of Clinical Oncology	2017	United States	If patients have stage IV NSCLC and *ALK* rearrangements, first-line crizotinib therapy is recommended (type: evidence based; benefits outweigh harms evidence quality: intermediate strength of recommendation: moderate)
National Comprehensive Cancer Network	2017 (version 9)	United States	Alectinib, crizotinib and ceritinib are all considered as category 1 agents (based on high-level evidence, there is uniform National Comprehensive Cancer Network consensus that the intervention is appropriate) first-line therapy after detection of *ALK*-positive NSCLC, but alectinib has been awarded category 1 'preferred' status. If the *ALK* rearrangement is discovered during first-line chemotherapy, the chemotherapy should be interrupted or completed and treatment with alectinib, crizotinib or ceritinib should be initiated

College of American Pathologists, the International Association for the Study of LungCancer and the Association for Molecular Pathology [49]	2014	United States	Recommendation: Laboratories should use an ALK FISH assay using dual-labelled break-apart probes for selection of patients for ALK TKI therapy; ALK IHC, if carefully validated, may be considered as a screening method to select specimens for ALK FISH testing Recommendation: RT-PCR is not recommended as an alternative to FISH for selection of patients for ALK inhibitor therapy Expert consensus opinion: A pathologist should be involved in the selection of sections for ALK FISH testing, by assessing tumour architecture, cytological aspects and specimen quality Expert consensus opinion: A pathologist should participate in the interpretation of ALK FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialised training in solid tumour FISH analysis Expert consensus opinion: Testing for secondary mutations in *ALK* associated with acquired resistance to ALK inhibitors is not currently required for clinical management

Abbreviations: ALK=anaplastic lymphoma kinase; CNS=central nervous system; FISH=fluorescence in situ hybridisation; IHC=immumohistochemistry; NSCLC=non-small cell lung cancer; RT-PCR=reverse transcription polymerase chain reaction; TKI=tyrosine kinase inhibitor.

Table A11. Estimated treatment population in absolute numbers in 2017, (%)

	France	Germany	Italy	Spain	United Kingdom
Total lung cancer incident population	45,222 (100)	56,099 (100)	41,300 (100)	27,696 (100)	46,403 (100)
NSCLC incident population	37,263 (82.4)	47,469 (84.6)	35,105 (85.0)	23,899 (86-3)	NA
De novo advanced/metastatic (stage IIIB/IV) disease patients[a]	30,108 (66.6)	38,452 (68.6)	29,839 (72.3)	19,525 (70.5)	NA
Total *ALK*-positive NSCLC patients eligible for first-line treatment	NA	1,923 (3.4)	NA	976 (3.5)	NA
Total *ALK*-positive NSCLC patients who received first-line treatment[b]	626 (1.4)	661 (1.2)	492 (1.2)	400 (1.4)	429 (0.9)

Abbreviations: NA=not applicable; NSCLC=non-small cell lung cancer

[a]Recurrent patients from early stages plus de novo advanced/metastatic disease patients.

[b]*ALK* positivity rate is assumed to be 5%; however, there is expected to be variation in this rate across Europe and testing rates may differ between squamous and non-squamous NSCLC patients. Tissue availability, testing rate, direct treatment rate and exclusion of patients in clinical trials (for 2017) need to be considered to reach the total number of treated patients. The rates are expected to differ across France, Italy, Germany, Spain and the United Kingdom.

Source: [17]

The target population of treatment-naïve adult patients with *ALK*-positive advanced NSCLC was estimated from epidemiology data from five countries (France, Italy, Germany, Spain, United Kingdom) provided by the MAH in the submission file. From the absolute numbers provided, the respective percentages were calculated for each country based on the total lung cancer incident population. These probabilities were then applied to calculate a range for the overall numbers in Europe based on the total lung cancer incident population by GLOBOCAN [54].

Evidence tables of individual studies included for clinical effectiveness and safety

Table A12. Summary of efficacy for the ALEX trial

Title: A randomized, multicentre, Phase III, open-label study of alectinib versus crizotinib in treatment-naïve ALK-positive advanced NSCLC				
Study identifier		BO28984		
Design		Open-label, randomised, comparative study		
Duration of main phase:				
Hypothesis		Superiority		
Treatments groups	Alectinib	600 mg BID alectinib, orally continuously (cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 152 patients		
Crizotinib		250 mg crizotinib BID, orally continuously (Cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 151 patients		
Endpoints and definitions	Primary endpoint	PFS by INV	Progression-free survival	
Key secondary endpoint	PFS by IRC	Progression-free survival		
Title: A randomized, multicentre, Phase III, open-label study of alectinib versus crizotinib in treatment-naïve ALK-positive advanced NSCLC				
Study identifier		BO28984		
Design		Open-label, randomised, comparative study		
Duration of main phase:				
Hypothesis		Superiority		
Treatments groups	Alectinib	600 mg BID alectinib, orally continuously (cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 152 patients		
Crizotinib		250 mg crizotinib BID, orally continuously (Cycles of 28 days) until disease progression, death, or withdrawal, number randomized: 151 patients		
Endpoints and definitions	Primary endpoint	PFS by INV	Progression-free survival	
Key secondary endpoint	PFS by IRC	Progression-free survival		
Assessment report EMA/CHMP/833519/2017 Page 42/77 Secondary endpoints other	Time to CNS progression (IRC) ORR (INV) OS DoR (INV) CNS ORR CNS DoR	Overall response rates Overall survival Duration of response CNS Overall response rates by IRC CNS Duration of response by IRC		
Database lock		31 March 2017		
Results and Analysis				
Analysis description		**Primary Analysis**		
Analysis population and time point description		Intent to treat		

Descriptive statistics and estimate variability	Treatment group	Crizotinib	Alectinib	Hazard ratio
Number of subjects	n=151	n=152	NA	
PFS (INV) (Months)	11.1	NE	0.47	
95% CI	[9.1-13.1]	[17.7-NE]	[0.34-0.65]	
PFS (IRC) (Months) 95% CI	10.4 [7.7-14.6]	25.7 [19.9-NE]	0.50 [0.36-0.70]	
OS (Months)	NR	NR	NA	
ORR (%)	76 %	83 %	NA	
95% CI	[67.8-82.1]	[76.0-88.5]	NA	
DOR (Months)	11.1	NE		
95% CI	[7.9-13.0]	NE		

Abbreviations: INV=investigator IRC=independent review committee; CI=confidence interval; HR=hazard ratio; NE=not estimable; ORR=objective response rate; OS=overall survival; DOR=duration of response; PFS=progression-free survival
Source: Alecensa EPAR variation II/0001, Table 17

Table A13. Summary of efficacy for the ASCEND-4 trial

Title: A phase III multicenter, randomized study of oral LDK378 versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer				
Study identifier	CLDK378A2301 (ASCEND-4)			
Design	Open-label, randomised vs. chemotherapy in first line			
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		Study ongoing	
Hypothesis	Superiority			
Treatments groups	Ceritinib		Ceritinib 750 mg once daily. 189 patients	
	Chemotherapy		Pemetrexed (500 mg/m^2 IV every 21 days) plus cisplatin (75mg/m² IV every 21 days) *or* pemetrexed (500 mg/m^2 IV every 21 days) plus carboplatin (AUC 5-6 IV every 21 days) for four cycles of treatment (induction) followed by pemetrexed alone as a single agent (maintenance) every 21 days in patients without progressive disease after induction chemotherapy. 187 patients	
			Treatment with ceritinib or chemotherapy was continued until the patient experienced progressive disease, unacceptable toxicity, pregnancy or start of a new anticancer therapy or discontinued treatment at the discretion of the patient or investigator, was lost to follow-up or died or the study was terminated by sponsor	
Endpoints and definitions	Primary endpoint	PFS by BIRC	Time from the date of randomisation to the date of the first radiologically documented disease progression per BIRC assessment or death from any cause	
	Secondary	OS	Time from date of randomisation to date of death from any cause	
	Secondary	ORR by BIRC	Proportion of patients with a best overall response of complete response or partial response	
Database lock	11th September 2016			
Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Ceritinib	Chemotherapy	
	Number of participants	189	187	
	Median PFS, months	16.6	8.1	
	95% CI, months	12.6–27.2	5.8–11.1	
	Median OS, months	NE	26.2	
	95% CI, months	29.3 to NE	22.8 to NE	
	ORR (%)	72.5	26.7	
	95% CI	65.5–78.7	20.5–33.7	
Effect estimate per comparison	PFS	Comparison groups	Ceritinib vs. chemotherapy	
		HR	0.55	
		95% CI	0.42–0.73	
		p	<0.001	
	OS	Comparison groups	Ceritinib vs. chemotherapy	
		HR	0.73	
		95% CI	0.50–1.08	
		p	0.056	

Notes	The data cutoff date for this primary analysis was 24th June 2016, when 202 PFS events had been documented as per BIRC assessment and 218 PFS events had been documented as per investigator assessment. The analyses are presented with use of data locked on 11th September 2016. The study is ongoing. The median duration between randomisation and the data cutoff date for all patients was 19.7 months

Abbreviations: AUC=area under the curve; BRIC=blinded independent review committee; CI=confidence interval; HR=hazard ratio; IRC=independent review committee; IV=intravenously; NE=not estimable; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Source: Zykadia EPAR variation II/12, Table 23.

Table A14. Summary of efficacy for the PROFILE 1014 trial

Title: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib Versus Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus			
Study identifier	A8081014 (PROFILE 1014)		
Design	Open-label, multicentre, randomised, phase III study		
	Duration of main phase: until disease progression, unacceptable toxicity, death or patient consent withdrawal Duration of run-in phase: not applicable Duration of extension phase: not applicable		
Hypothesis	Superiority		
Treatments groups	Crizotinib		250 mg twice daily, continuous daily dosing schedule, 172 patients randomised
	Chemotherapy		Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV, every 3 weeks Pemetrexed 500 mg/m^2 IV plus carboplatin AUC 5–6 mg mL/min, every 3 weeks Maximum 6 cycles 171 patients randomised
Endpoints and definitions	Primary endpoint	PFS	Time from the date of randomisation to the date of the first documentation of objective tumour progression (by IRR) or death during the study from any cause, whichever occurred first
	Secondary endpoints	OS	Time from randomisation to the date of death from any cause
		ORR	Percentage of patients with CR or PR according to RECIST 1.1, as determined by IRR
		TTR	Time from randomisation to first documentation of objective tumour response (CR or PR), as determined by IRR
		DR	Time from the first documentation of objective tumour response (CR or PR), as determined by IRR, to the first documentation of objective tumour progression or to death from any cause, whichever occurred first
		DCR	Percentage of patients with CR, PR or stable disease at 12 weeks according to RECIST 1.1, as determined by IRR
		TTP	Time from randomisation to first documentation of objective tumour progression, as determined by IRR
		IC-TTP	Time from randomisation to first documentation of objective intracranial disease progression, based on either new brain metastases or progression of existing brain metastases, as determined by IRR

		EC-TTP	Time from randomisation to first documentation of objective extracranial disease progression, based on either new extracranial lesions or progression of existing extracranial lesions, as determined by IRR
		PRO	TTD in pain in chest, dyspnoea and cough as the time from randomisation to the earliest date the patient's scale scores showed a 10 point or greater increase after the baseline in any of these three symptoms
Data cutoff date	30th November 2013		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Full analysis population		
Descriptive statistics and estimate variability	Treatment group	Crizotinib	Chemotherapy
	Number of participants	172	171
	Primary endpoint		
	PFS (IRR) Participants with events, *n* (%)	100 (58.1)	137 (80.1)
	PFS (median), months (95% CI)	10.9 (8.3–13.9)	7.0 (6.8–8.2)
	Stratified hazard ratio (95% CI)	0.45 (0.35–0.60)	
	p (one-sided stratified log-rank test)	<0.0001	
	Secondary endpoints		
	OS Participants with events, *n* (%)	44 (25.6)	46 (26.9)
	OS (median), months	Not reached	Not reached
	Stratified hazard ratio (95% CI)	0.82 (0.54–1.26)	
	p (one-sided stratified log-rank test)	0.18	
	ORR (CR plus PR), *n* (%)	128 (74.4)	77 (45.0)
	Risk ratio, % (95% CI) (two-sided CMH chi-square test stratified)	1.66 (1.38–2.01)	
	p (two-sided Pearson chi-square test)	<0.0001	
	TTR (median), weeks (range)	6.1 (2.7-41.4)	12.1 (5.1-36.7)
	Duration of response (median), weeks (95% CI)	49.0 (35.1–60.0)	22.9 (18.0–25.1)
	DCR (CR plus PR plus SD), *n* (%) 95% CI, months	135 (79) 72–84	117 (68) 61–75

	*p (*two-sided Pearson chi-square test)	0.038	
	TTP, *n* (%) Median, months 95% CI, months	89 (51.7) 13.6 8.5–15.0	132 (77.2) 7.0 6.8–8.3
	Hazard ratio 95% CI *p* (one-sided unstratified log-rank test)	0.44 0.33–0.58 <0.0001	
	IC-TTP *n* (%) Median, months 95% CI, months	25 (14.5) Not reached	26 (15.2) 17.8 (13.9–)
	Hazard ratio (95% CI)	0.59 (0.34–1.05)	
	p (one-sided unstratified log-rank test)	0.034	
	EC-TTP *n* (%) Median, months 95% CI, months	71 (41.3) 15.2 12.6–21.9	119 (69.6) 7.2 6.9–8.5
	Hazard ratio (95% CI)	0.38 (0.29–0.52)	
	p (one-sided unstratified log-rank test)	<0.0001	

Abbreviations: AUC=area under the curve; CI=confidence interval; CMH= Cochran-Mantel-Haenszel; CR=complete response; DCR=disease control rate; DR= duration of response; EC-TTP=extracranial time to progression; IC-TTP= intracranial time to progression; IRR=independent radiological review; IV=intravenously; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; PRO=patient-reported outcome; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; TTD=time to deterioration; TTP=time to progression; TTR=.time to tumour response
Source: Xalkori EPAR variation II/24.

Table A15: Characteristics of other relevant studies

Study reference/ID	Objective	Study design	Key disease-related eligibility criteria	Intervention/comparator (number enrolled)	Primary outcome measure	Key secondary outcome measures
ALEX (BO28984) (NCT02075840)	To evaluate and compare the efficacy of alectinib vs. crizotinib	Phase III, randomised, active-controlled, multicentre, open-label study	Advanced (stage IIIB) or metastatic (stage IV) *ALK*-positive NSCLC *ALK*-positive confirmed by IHC No prior systemic treatment for NSCLC Prior brain or leptomeningeal metastases allowed if asymptomatic ECOG PS ≤2	ALEC 600 mg BID (152) CRZ 250 mg BID (151)	PFS (INV) by RECIST 1.1	ORR (INV), C-TTP (IRC), PFS (IRC), DOR, OS, AEs (%), TTD (EORTC QLQ-C30, QLQ-LC13), HRQoL (EORTC QLQ-C30, QLQ-LC13) Safety endpoints
PROFILE 1014 (NCT01154140)	To evaluate and compare the efficacy of crizotinib vs. chemotherapy	Phase III, randomised, active-controlled multicentre, open-label study	Locally advanced, recurrent or metastatic non-squamous NSCLC *ALK*-positive NSCLC determined by FISH centrally No prior systemic treatment for NSCLC Patients with brain metastases only if treated and neurologically stable with no ongoing requirement for corticosteroids ECOG PS ≤2	CRZ 250 mg BID (172) PEM 500 mg/m^2 plus CIS 75 mg/m^2 or CARB AUC 5–6 mg/mL/min 3-week cycle, maximum of six cycles (171)	PFS (IRC)	ORR, OS, OS at 12 and 18 months, safety, PROs, C-TTP, TTD (chest pain, dyspnoea, cough), C-PD Safety endpoints

Study reference/ID	Objective	Study design	Key disease-related eligibility criteria	Intervention/comparator (number enrolled)	Primary outcome measure	Key secondary outcome measures
PROFILE 1029 (NCT01639001)	To evaluate and compare the efficacy of crizotinib vs. chemotherapy in an East Asian population of China, Hong Kong, Malaysia, Taiwan and Thailand	Phase III, randomised, active-controlled multicentre, open-label study	Locally advanced, recurrent or metastatic non-squamous NSCLC *ALK*-positive NSCLC determined by FISH No prior systemic treatment for NSCLC Patients with brain metastases only if treated and neurologically stable with no ongoing requirement for corticosteroids ECOG PS ≤2	CRZ 250 mg BID (104) PEM 500 mg/m^2 plus CIS 75 mg/m^2 or CARB AUC 5–6 mg/mL/min 3-week cycle, maximum of 6 cycles (103)	PFS (IRC)	ORR, OS, DCR (12 weeks), landmark survival (1 year, 18 months), DOR (IRC), TTP (IRR), C-TTP, extracranial TTP, PROs (QLQ-C30, QLQ-LC13, EQ-5D VAS and index change from baseline), safety endpoints
ASCEND-4 (NCT01828099)	To evaluate and compare the efficacy of ceritinib vs. chemotherapy	Phase III, randomised, parallel assignment, multicentre, open-label study	Locally advanced, recurrent or metastatic non-squamous NSCLC *ALK*-positive NSCLC by IHC No prior systemic treatment for NSCLC Patients with brain metastases only if neurologically stable and who have not required increasing doses of steroids ECOG PS ≤2	Ceritinib (189) Chemotherapy (187)	PFS (IRC) by RECIST 1.1	OS, PFS (INV), ORR, DOR, DCR, time to response (IRC or INV), C-ORR, C-DCR, C-DOR, C-CBR, PROs, safety, ceritinib PK

Abbreviations: AE=adverse event; ALEC=alectinib; AUC=area under the concentration–time curve; BID=twice daily; C30=core 30; CARB=carboplatin; CBR=; C-CBR=central nervous system; C-DCR=central nervous system disease control rate; C-DOR=central nervous system duration of response; CIS=cisplatin; C-ORR central nervous system objective response rate; C-PD=central nervous system progressive disease; CRZ=crizotinib; C-TTP=central nervous system time to progression; DCR=disease control rate; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC=European Organisation for Research and Treatment of Cancer; FISH=fluorescence in situ hybridisation; HRQoL=health-related quality of life; IHC=immunohistochemistry; INV=investigator assessed; IRC=independent review committee; IRR=independent radiological review; L13=lung cancer module; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD=progressive disease; PEM=pemetrexed; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; QLQ=quality-of-life questionnaire; RECIST=Response Evaluation Criteria in Solid Tumors; TTD=time to deterioration; TTP=time to progression; VAS=visual analogue scale.

Source: ClinicalTrials.gov.

Ongoing and planned studies

Table A16. Ongoing studies of alectinib monotherapy for *ALK*-positive non-small cell lung cancer

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
BO39694 - ROP	NA /LPLV Q2 2024	Rollover (ROP)	All	Alectinib	All ROP comparators	*ALK*-positive NSCLC	This is a rollover study for patients with *ALK*-positive or *RET*-positive cancer treated with alectinib or crizotinib. **Primary Objective:** To provide continued treatment with alectinib or crizotinib as applicable to patients with *ALK*-positive or *RET*-positive cancer who were previously enrolled in any Roche-sponsored alectinib study and who are deriving continued clinical benefit from alectinib or crizotinib in the parent trial at the time of parent trial closure **Secondary Objective:** To assess long-term safety of alectinib therapy
NP28673 ACCALIA G second line	Data: Q4 2017, /LPLV Q3 2017	Phase II	153	Alectinib	NA	*ALK*-positive NSCLC	**Objectives:** Part 1 – determination of a phase II recommended dose – dose escalation study **Primary Objectives:** The primary objectives for part 1 of the study are as follows: • To determine the RP2D of RO5424802 to be used in part 2 of the study • To evaluate the safety and tolerability of 600-mg and 900-mg (if 900 mg is reached) doses of RO5424802 administered twice daily to patients with locally advanced (AJCC stage IIIB) NSCLC not amenable to curative therapy or metastatic (AJCC stage IV) NSCLC who have *ALK* rearrangement and in whom prior crizotinib therapy has failed • To characterise DLTs, if any, associated with RO5424802 after 21 days of treatment when administered twice daily at 600- and 900-mg (if 900 mg is reached) doses to patients with locally advanced (AJCC stage IIIB) NSCLC not amenable to curative therapy or metastatic (AJCC stage IV) NSCLC who have *ALK* rearrangement and in whom prior crizotinib therapy has failed • To characterise the PK of RO5424802 and its major metabolites Part 2 – evaluation of safety and efficacy of RO5424802 in *ALK*-positive NSCLC patients with *ALK* rearrangements **Efficacy objectives** **Primary efficacy:**:To evaluate efficacy of RO5424802 by ORR as per

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							central IRC review of radiographs using RECIST 1.1 in the overall population (with and without prior exposure to cytotoxic chemotherapy) **Secondary efficacy:** To evaluate efficacy of RO5424802 by ORR as per central IRC using RECIST 1.1 in patients without prior exposure to cytotoxic chemotherapy. Additional secondary objectives for the overall population of patients with prior exposure to cytotoxic chemotherapy and patients without prior exposure to cytotoxic chemotherapy are as follows: • To evaluate efficacy of RO5424802 by ORR per investigator review of radiographs using RECIST 1.1 • To evaluate DCR of RO5424802 based on IRC and investigator review of radiographs • To assess DOR in patients treated with RO5424802 based on IRC and investigator review of radiographs • To evaluate the PFS in patients treated with RO5424802 based on IRC and investigator review of radiographs • To evaluate C-ORR in patients with CNS metastases who have measurable disease in the CNS at the baseline, based on IRC review of radiographs • To assess C-DOR in patients who have a CNS objective response based on IRC review of radiographs • To assess C-PRs at 3, 6, 9 and 12 months based on cumulative incidence by IRC review of radiographs • To assess OS **Safety Objectives:** The safety objectives for this study are as follows: • To evaluate the safety profile of RO5424802 using NCI CTCAE version 4.03 • To assess the effect of RO5424802 on cardiac repolarisation (QTc) **Pharmacokinetic objectives**: The pharmacokinetic objectives for this study are as follows: • To evaluate the PK of RO5424802 and metabolite(s) in patients with *ALK*-mutated NSCLC o To characterise the PK of RO5424802 and metabolite(s) in Taiwanese and Korean patients (for Taiwan and Korea sites only) o To evaluate the effect of multiple oral dosing of RO5424802 on the PK of a single oral dose of midazolam, an in vivo probe substrate of CYP3A

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							activity in a subset of cancer patients **Exploratory objectives:** The exploratory objectives for this study are as follows: • To evaluate ORR in patients with *EGFR* mutation who have experienced disease progression while receiving RO5424802 alone and who are subsequently treated with a combination of RO5424802 and erlotinib (part 3) • To evaluate the PK of RO5424802 and its major metabolite(s) and erlotinib in patients with *EGFR* mutation who have experienced disease progression while receiving RO5424802 alone and who receive the combination of RO5424802 and erlotinib (part 3) • To evaluate the safety profile of RO5424802 in combination with erlotinib using NCI CTCAE version 4.03 (part 3) • To evaluate the *ALK* mutations in tumour and blood samples and correlate the mutation rate with response to RO5424802 where possible • To evaluate the coexpression of *EGFR* mutation with *ALK* translocation and *ALK* mutation status • To investigate potential bypass mechanisms of ALK inhibition, such as c-MET, KRAS and c-KIT
NP28761 NA3L	Data: Q4 2017 /LPLV Q3 2017	Phase II	134	Alectinib	NA	*ALK*-positive NSCLC	**Phase I portion:** **Primary objective:** To determine the recommended dose of CH5424802/RO5424802 for use in the phase II portion **Secondary objectives:** In patients with locally advanced (AJCC stage IIIB) NSCLC not amenable to curative therapy or metastatic (AJCC stage IV) *ALK*-positive NSCLC: • To measure pharmacokinetic parameters of CH5424802/RO5424802, under fasting and fed conditions, to determine whether CH5424802/RO5424802 should be administered under fasting or fed conditions in the phase II portion • To assess tumour response • To evaluate safety of CH5424802/RO5424802. • To assess the clinical benefit of CH5424802/RO5424802 **Phase II portion:** **Primary objective:** To evaluate efficacy of CH5424802/RO5424802 based on the ORR (RECIST 1.1) as per IRC in patients with locally advanced (AJCC stage IIIB) NSCLC not amenable to curative therapy or metastatic (AJCC stage IV) *ALK*-positive NSCLC in whom

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							crizotinib has failed **Secondary objectives:** • To determine ORR according to RECIST 1.1 based on investigator review of radiographs • To evaluate DCR, DOR PFS according to RECIST 1.1 by IRC and investigator review of radiographs • To evaluate OS • To evaluate the safety of CH5424802/RO5424802 • To characterise the PK of CH5424802/RO5424802 and metabolite(s) • To assess the QoL using EORTC QLQ-C30 and QLQ-LC13 • To evaluate C-ORR in patients with CNS metastases who have measurable disease in the CNS at the baseline, based on IRC review of radiographs by RECIST 1.1 and RANO criteria • To assess C-DOR in patients who have a CNS objective response based on IRC review of radiographs by RECIST 1.1 and RANO criteria • To assess C-PRs at 3, 6, 9 and 12 months based on cumulative incidence by IRC review of radiographs by RECIST 1.1 and RANO criteria **Exploratory objectives:** • To assess blood-based methods to detect point mutations in plasma • To identify molecular determinants of clinical resistance to ALK inhibitors • To identify potential genetic determinants of pharmacokinetic variability and safety parameters (pharmacogenomics research) • To assess CH5424802/RO5424802 CNS penetration by measuring the CSF/plasma concentration ratio
YO29449 ALESIA (APAC) – first line	Data: Q2/Q3 2018, LPLV Q4 2019	Phase III (APAC)	187	Alectinib	Crizotinib	*ALK*-positive NSCLC	**Primary efficacy objective:** To evaluate and compare the efficacy of alectinib and crizotinib in Asian patients with treatment-naïve *ALK*-positive advanced NSCLC, as measured by investigator-assessed PFS. This objective is to reliably determine whether the benefit (in terms of PFS) of administrating alectinib in this study is consistent with the benefit observed in global study BO28984. **Secondary efficacy objectives**: • To evaluate and compare the ORR and DOR • To evaluate and compare the time to disease progression in the CNS on the basis of review of patient radiographs by an IRC with the use of

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							RECIST 1.1 and RANO criteria, as well as to evaluate the C-ORR) in patients with CNS metastases who have measurable disease in the CNS at the baseline • To assess the C-DOR in patients who have a CNS objective response • To assess C-PRs at 6, 12, 18 and 24 months on the basis of cumulative incidence • To evaluate and compare the PFS assessment by an IRC by treatment arm • To evaluate and compare the OS by treatment arm **Safety objective:** The safety objective for this study is to evaluate the safety and tolerability of alectinib compared with crizotinib. **Pharmacokinetic objective***:* The pharmacokinetic objective for this study is to characterise the PK of alectinib (and metabolite[s], if appropriate) **Patient-reported outcome objectives:** The PRO objectives for this study are as follows: • To evaluate and compare the TTD with patient-reported lung cancer symptoms of cough, dyspnoea (single-item and multi-item subscales), chest pain, arm/shoulder pain and fatigue as measured by EORTC QLQ-C30, the supplemental EORTC QLQ-LC13 and a composite of the following three symptoms: cough, dyspnoea and chest pain • To evaluate and compare PROs regarding HRQoL, daily functioning and side effects of treatment as measured by EORTC QLQ-C30 and EORTC QLQ LC13 **Exploratory objectives:** The exploratory objectives for this study are as follows: • To investigate molecular mechanisms of resistance to ALK inhibitors • To investigate detection of mutations in *ALK* and other genes involved in cancer in plasma
MO29750 ALUR	Data: Q1 2017, LPLV Q2 2019	Phase III	120	Alectinib	Chemotherapy	*ALK*-positive NSCLC	**Primary efficacy objective**: To evaluate and compare between treatment groups the efficacy of alectinib therapy vs. chemotherapy in patients with *ALK*-positive advanced NSCLC who were previously treated with chemotherapy and crizotinib (disease progression or intolerant to crizotinib) as measured by investigator-assessed PFS

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Key secondary efficacy objective: To evaluate and compare between treatment groups the C-ORR in patients with measurable CNS metastases at the baseline as assessed by an IRC **Other secondary efficacy objectives:** To evaluate and compare between treatment arms: □ PFS (assessment by IRC) □ ORR, DCR and DOR in all patients according to RECIST 1.1 (assessment by investigator and IRC) □ PFS in patients with baseline CNS metastases (assessment by investigator and IRC) □ Time to CNS progression in all patients, patients with baseline CNS metastases and patients without baseline CNS metastases (assessment by IRC) □ C-DOR, C-DCR and C-ORR for all patients with baseline CNS metastasis (assessment by IRC) □ C-DOR and C-DCR for patients with baseline measurable CNS metastasis (assessment by IRC) □ OS **Pharmacokinetic objective:** The pharmacokinetic objective for this study was to characterise the PK of alectinib and its major metabolites **Safety objective:** The safety objective for this study was to evaluate the safety and tolerability of alectinib compared with chemotherapy in all patients and patients with CNS metastases at the baseline **PRO objectives:** The PRO objectives for this study were as follows: □ To evaluate and compare TTD in patient-reported lung cancer symptoms of cough, chest pain (single item), dyspnoea (single-item and multi-item subscales), pain in arm/shoulder and fatigue as measured by the EORTC QLQ-C30 and QLQ-LC13, as well as by a composite of three symptoms (cough, dyspnoea [multi-item QLQ-LC13 subscales] and chest pain). Analysis was performed for all patients, as well as in the subgroup of patients with CNS metastases □ To evaluate and compare PROs of HRQoL, patient functioning and side effects of treatment as measured by EORTC QLQ-C30, EORTC QLQ-LC13 and the EQ-5D-5L questionnaire. Analysis was performed for all patients, as well as in the subgroup of patients with CNS metastases **Exploratory objectives:** The exploratory objectives for this study were

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							as follows: To evaluate PROs of patients with CNS metastases, as measured by specific questions from the EORTC QLQ-BN20 To assess exploratory biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to *ALK* genetic alterations) and their association with disease status, clinical outcome, efficacy and safety To investigate molecular mechanisms of resistance to ALK inhibitors To develop biomarker or diagnostic assays to detect *ALK* mutations/fusions in plasma/tumour and to establish performance characteristics of these assays
B-FAST BO29554 *ALK*-positive cohort *RET*-positive cohort	*ALK*-positive cohort Data: Q2 2019 LPLV: 2021–2023 *RET*-positive cohort Data: Q3 2020 LPLV: 2021–2023	ALK-positive cohort Phase II/III (cohort phase II) *RET*-positive cohort Phase II/III (cohort phase Ib/II)	*ALK*-positive cohort 78 *RET*-positive cohort 52–62	Alectinib	NA	*ALK*-positive NSCLC • *ALK*-positive advanced or metastatic stage IIIB/IV NSCLC previously untreated	*ALK*-positive cohort **Primary efficacy:** To evaluate the efficacy of alectinib in patients with *ALK*-positive advanced or metastatic NSCLC as determined by the bSMP assay; investigator assessed ORR based on confirmed objective response (indicated by two objective response assessments based on RECIST 1.1 separated by at least 4 weeks) **Secondary efficacy:** Investigator-assessed DOR, CBR, and PFS per RECIST version 1.1; IRF-assessed ORR, DOR, CBR and PFS per RECIST 1.1; OS **Safety objective:** To evaluate the safety and tolerability of alectinib; incidence, type and severity of adverse events (based on NCI CTCAE version 4.0), including SAEs and AEs of special interest; changes in vital signs, physical findings and clinical laboratory results during the following administration of protocol-specified IMPs **PRO objectives:** To evaluate the impact of alectinib on PROs in patients with *ALK*-positive advanced or metastatic NSCLC as determined by the bSMP assay; proportion of patients whose condition improved compared with the baseline in patient-reported lung cancer symptoms of cough, dyspnoea and chest pain as measured by SILC; Mean change from baseline in HRQoL, patient functioning and symptoms as measured by the EORTC QLQ-C30 and SILC, to evaluate and compare patients' health status to generate utility scores for use in economic models for reimbursement; health status as assessed by the EQ-5D-5L questionnaire

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Biomarker objective: To assess prognostic effect and pharmacodynamics of exploratory biomarkers in blood, and their association with disease status, mechanisms of resistance and/or response to alectinib; relationship between circulating biomarkers related to alectinib efficacy **Exploratory objectives:** To explore the antitumour effect of alectinib in patients with CNS disease identified at the baseline, investigator assessed ORR per RECIST 1.1 in patients with CNS disease, Investigator assessed DOR per RECIST 1.1 in patients with CNS disease, investigator assessed CBR per RECIST 1.1 in patients with CNS disease; to evaluate the efficacy of alectinib in patients with *ALK*-positive advanced or metastatic NSCLC as determined by the bSMP assay, investigator-assessed TIR according to RECIST 1.1. <u>*RET*-positive cohort</u> **Primary efficacy**: Investigator-assessed ORR based on confirmed objective response (indicated by two objective response assessments based on RECIST 1.1 separated by at least 4 weeks) **Secondary efficacy:** Investigator-assessed DOR, CBR and PFS per RECIST 1.1; IRF-assessed ORR, DOR, CBR and PFS per RECIST 1.1; OS **Safety objective:** To assess the safety and tolerability of alectinib at increasing dose levels in patients with advanced *RET*-positive NSCLC so as to determine the MTD and the RP2D; DLTs, if any, associated with alectinib at escalating doses. To assess safety and tolerability of alectinib as a single agent in patients with *RET*-positive advanced or metastatic NSCLC at the RP2D, Incidence, type and severity of adverse events (based on NCI CTCAE version 4.0), including SAEs and AEs of special interest; changes in vital signs, physical findings and clinical laboratory results during the following administration of protocol-specified IMPs **Pharmacokinetic objective:** To explore the pharmacokinetic characteristics of alectinib; pharmacokinetic parameters of alectinib, population PK analysis for alectinib, standard pharmacokinetic parameters of alectinib for dose finding

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							PRO objectives: To evaluate the impact of alectinib on PROs in patients with *RET*-positive advanced or metastatic NSCLC as determined by the bSMP assay; proportion of patients whose condition improved compared with the baseline in patient-reported lung cancer symptoms of cough, dyspnoea and chest pain as measured by SILC; TTD in patient-reported lung cancer symptoms of cough, dyspnoea and chest pain as measured by SILC Mean change from the baseline in HRQoL, patient functioning and symptoms as measured by EORTC QLQ-C30 and SILC to evaluate and compare patients' health status to generate utility scores for use in economic models for reimbursement; health status as assessed by the EQ-5D-5Lquestionnaire **Biomarker objective:** To assess the prognostic effect and pharmacodynamics of exploratory biomarkers in blood, and their association with disease status, mechanisms of resistance and/or response to alectinib; relationship between circulating biomarkers related to alectinib efficacy **Exploratory objectives:** To explore the antitumour effect of alectinib in patients with CNS disease identified at the baseline, investigator-assessed ORR per RECIST 1.1 in patients with CNS disease, investigator-assessed DOR per RECIST 1.1 in patients with CNS disease, investigator-assessed CBR per RECIST 1.1 in patients with CNS disease; to evaluate the efficacy of alectinib in patients with *RET*-positive advanced or metastatic NSCLC as determined by the bSMP assay, investigator-assessed TIR according to RECIST 1.1
MO39084 (QoL and resource utilisation)	Data: Q4 2017	RWD	162	N/A	N/A	CNS metastases	QoL and health resource utilisation in CNS mets patients
BO28984	Data: Q3 2019	Phase III	303	Alectinib	Crizotinib	Treatment-naïve *ALK*-	**Primary objectives:** To evaluate and compare the efficacy of alectinib compared with crizotinib in patients with treatment-naïve *ALK*-positive

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
	LPLV Q2 2019					positive advanced NSCLC	advanced NSCLC as measured by investigator-assessed PFS **Secondary objectives:** To evaluate and compare the ORR and DOR; to evaluate and compare the time to progression in the CNS on the basis of IRC review of radiographs by RECIST 1.1 and RANO criteria, as well as: • To evaluate C-ORR in patients with CNS metastases who have measurable disease in the CNS at the baseline • To assess C-DOR in patients who have a CNS objective response • To assess C-PRs at 6, 12, 18 and 24 months on the basis of cumulative incidence • To evaluate and compare the PFS assessment by the IRC To evaluate and compare the OS **Secondary safety objective:** To evaluate the safety and tolerability of alectinib compared with crizotinib. **Secondary pharmacokinetic objective:** To characterise the pharmacokinetics of alectinib and metabolite(s) **Secondary PRO objectives:** • To evaluate and compare TTD in patient-reported lung cancer symptoms of cough, dyspnoea (single-item and multi-item subscales), chest pain, arm and shoulder pain and fatigue as measured by EORTC QLQ-C30 EORTC QLQ-LC13 as well as a composite of three symptoms (cough, dyspnoea and chest pain) • To evaluate and compare PROs of HRQoL, patient functioning and side effects of treatment as measured by EORTC QLQ-C30 and EORTC QLQ-LC13 **Exploratory objectives:**

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							• To evaluate and compare patient's health status as assessed by the EQ-5D-3L questionnaire to generate utility scores for use in economic models for reimbursement • To evaluate and compare the onset of hypogonadism in adult men by measuring total testosterone and free testosterone (either by direct measurement or by calculation using albumin and sex hormone-binding globulin), follicle-stimulating hormone and luteinising hormone levels in blood • To evaluate and compare efficacy in patients with treatment-naïve *ALK*-positive NSCLC as assessed by the Vysis® ALK Break Apart FISH Probe Kit (Abbott) • To evaluate and compare efficacy and safety in patients with treatment-naïve *ALK*-positive NSCLC as assessed by plasma *ALK* assays (PCR and/or sequencing) • To determine the correlation between *ALK* status as assessed by plasma *ALK* PCR and/or plasma *ALK* sequencing tests and *ALK* status obtained with use of the Ventana ALK IHC and Vysis ALK Break Apart FISH Probe Kit (Abbott). • To investigate molecular mechanisms of resistance to ALK inhibitors • To investigate detection of *ALK* mutations/fusions in plasma

Abbreviations: AE=adverse event; AJCC=American Joint Committee on Cancer; ALK=anaplastic lymphoma kinase; APAC=; AUC=area under the curve; bSMP=;CBR=; C-DCR=central nervous system disease control rate; C-DOR=central nervous system duration of response; CNS=central nervous system; C-ORR central nervous system objective response rate; C-PR=central nervous system progression rate; CSF=cerebrospinal fluid; CYP3A=cytochrome P450 3A; DCR=disease control rate: DLT=dose-limiting toxicity; DOR=duration of response, EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-3L=EuroQoL five dimension three level; EQ-5D-5L=EuroQoL five dimension five level; HRQoL=health-related quality of life; IMP=; IRC=independent review committee; IRF=independent review facility; LPLV=; MTD=; NA=; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PCR=polymerase chain reaction; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; Q1=quarter 1; Q2=quarter 2; Q3=quarter 3; Q4=quarter 4; QLQ-BN20=Quality of Life Questionnaire Brain Neoplasm-20; QLQ-C30=Quality-of-Life Questionnaire Core-30; QLQ-LC13=Quality of-Life Questionnaire Lung Cancer-13;QoL=quality of life; QTc=corrected QT interval; RANO=Response Assessment in Neuro-Oncology; RECIST=Response Evaluation Criteria in Solid Tumors; ROP=;RP2D=recommended phase II dose; RWD=; SAE=serious adverse event; SILC=; TIR=; TTD=time to deterioration.
Sources: Roche internal clinical trial management sources.

Table A17. Finished studies of alectinib monotherapy for *ALK*-positive non-small cell lung cancer

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
ALEX	Q1 2017	Phase III	303	Alectinib	Crizotinib	*ALK*-positive advanced NSCLC	**Primary:** To evaluate and compare the efficacy of alectinib compared with crizotinib in patients with treatment-naïve *ALK*-positive advanced NSCLC as measured by investigator-assessed PFS **Secondary efficacy:** To evaluate and compare the ORR and DOR, to evaluate and compare the time to progression in the CNS on the basis of IRC review of radiographs by RECIST 1.1 and RANO criteria and to evaluate C-ORR in patients with CNS metastases who have measurable disease in the CNS at the baseline, to assess C-DOR in patients who have a CNS objective response, to assess C-PRs at 6, 12, 18 and 24 months on the basis of cumulative incidence, to evaluate and compare the PFS assessment by the IRC, to evaluate and compare the OS **Safety objective:** To evaluate the safety and tolerability of alectinib compared with crizotinib **Pharmacokinetic objective:** To characterise the PK of alectinib and metabolite(s) **PRO objectives:** To evaluate and compare TTD in patient-reported lung cancer symptoms of cough, dyspnoea (single-item and multi-item subscales), chest pain, arm and shoulder pain and fatigue as measured by EORTC QLQ-C30 and the supplemental lung cancer module (QLQ-LC13) as well as a composite of three symptoms (cough, dyspnoea and chest pain); to evaluate and compare PROs of HRQoL, patient functioning and side effects of treatment as measured by EORTC QLQ-C30 and EORTC QLQ-LC13 **Exploratory objectives:** The exploratory objectives for this study are to evaluate and compare patient's health status as assessed by the EQ-5D-3L questionnaire to generate utility scores for use in economic models for reimbursement; to evaluate and compare the onset of hypogonadism in adult men by measuring total testosterone and free testosterone (either by direct measurement or by calculation using albumin and sex hormone-binding globulin), follicle-stimulating hormone) and luteinising hormone levels in blood; to evaluate and compare efficacy in patients with treatment-naïve *ALK*-positive NSCLC as assessed by the Vysis® ALK

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Break Apart FISH Probe Kit (Abbott); to evaluate and compare efficacy and safety in patients with treatment-naïve *ALK*-positive NSCLC as assessed by plasma *ALK* assays (PCR and/or sequencing); to determine the correlation between *ALK* status as assessed by plasma *ALK* PCR and/or plasma *ALK* sequencing tests and *ALK* status obtained with use of the Ventana ALK IHC and Vysis ALK Break Apart FISH Probe Kit (Abbott); to investigate molecular mechanisms of resistance to ALK inhibitors; To investigate detection of *ALK* mutations/fusions in plasma
J-ALEX	Q3 2016	Phase III	207	Alectinib	Crizotinib	*ALK*-positive NSCLC	**Primary endpoint:** PFS (assessed by IRF) **Secondary endpoints:** Efficacy: OS, response rate, DOR, time to response, time to progression of brain metastasis in patients with brain metastasis at the baseline, time to onset of brain metastasis in patients without brain metastasis at the baseline and QOL scores based on EORTC QLQ-C30 and QLQ-LC13 Safety PK: Plasma alectinib concentration and plasma CH5468924 concentration **Exploratory endpoints:** ALK genetic mutations, etc., and biomarkers related to efficacy
NP29783 (second-line postapproval commitment)	Data: Q1 2017, /LPLV Q4 2016	Phase I (hepatic Impairment)	28	Alectinib	NA	*ALK*-positive NSCLC	**Primary objectives:** To assess the PK of alectinib in participants with hepatic impairment and in matched healthy participants after a single oral dose **Secondary objectives:** • To assess the PK of the major active metabolite of alectinib, M4, and the combined exposure of alectinib and M4 (alectinib plus M4) in participants with hepatic impairment and in matched healthy participants after a single oral dose • To investigate safety and tolerability of alectinib in participants with hepatic impairment and in matched healthy participants Exploratory: • To evaluate the relationship, if any, between measures of hepatic

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							impairment (e.g., Child–Pugh scores, NCI criteria for hepatic impairment categories, albumin concentration, bilirubin concentration, aspartate aminotransferase concentration, alanine aminotransferase concentration, prothrombin time, etc.) and pharmacokinetic parameters for alectinib and/or M4, as appropriate

Abbreviations: ALK=anaplastic lymphoma kinase; C-DOR=central nervous system duration of response; CNS=central nervous system; C-ORR=central nervous system objective response rate; C-PR=central nervous system progression rate; DOR=duration of response; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-3L=EuroQoL five dimension three level; HRQoL=health-related quality of life; IRC=independent review committee; IRF=independent review facility; LPLV=; NA=; NCI=National Cancer Institute; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PCR=polymerase chain reaction; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; Q1=quarter 1; Q3=quarter 3; Q4=quarter 4; QLQ-C30=Quality of Life Questionnaire − Core; RANO=Revised Assessment in Neuro-Oncology; RECIST=Response Evaluation Criteria in Solid Tumors; TTD=time to deterioration.
Sources: Roche internal clinical trial management sources.

Table A18. Planned studies of alectinib monotherapy for *ALK*-positive non-small cell lung cancer

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
BO40336 Adjuvant	Data: Q2 2023, LPLV Q3 2023	Phase III	255	Alectinib	Chemotherapy	Resected stage IB–IIIA *ALK*-positive NSCLC	**Primary efficacy objective:** To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected stage IB (tumours ³ 4 cm) to stage IIIA, *ALK*-positive NSCLC; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC, as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible) and clinical status or death from any cause, whichever occurs first **Secondary efficacy objective:** To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected stage IB (tumours ³ 4 cm) to stage IIIA *ALK*-positive NSCLC; OS defined as the time from randomisation to death from any cause **Safety objective:** To evaluate the safety and tolerability of alectinib compared with platinum-based chemotherapy in patients with completely resected stage IB (tumours ³ 4 cm) to stage IIIA *ALK*-positive NSCLC; incidence of adverse events, with severity determined through use of NCI

Study identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							CTCAE version 4.0; safety laboratory values; vital signs; electrocardiogram **Pharmacokinetic objective (alectinib arm only):** To characterise the pharmacokinetics of alectinib and its major metabolite(s) in patients with completely resected stage IB (tumours ³ 4 cm) to stage IIIA *ALK*-positive NSCLC; plasma concentrations of alectinib and its major metabolite(s) at specified time points **Exploratory biomarker objective:** To investigate molecular mechanisms of resistance to alectinib in patients with completely resected stage IB (tumours ³ 4 cm) to stage IIIA *ALK*-positive NSCLC; relationship between biomarkers in blood and tumour tissue (listed in Table 2) and efficacy (DFS)

Abbreviations: DFS=disease-free survival; LPLV=; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC=non-small cell lung cancer; OS=overall survival; Q2=quarter 2; Q3=quarter 3.
Sources: Roche internal clinical trial management sources.

Risk of bias tables

Table A19. Risk of bias – study level (randomised controlled trials)

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (patient-reported outcomes, all-cause mortality)	Incomplete outcome assessment	Selective reporting
ALEX [2]	Low	Low	High[a]	High[b]	Low	Low
ASCEND-4 [56]	Low	Low	High[a]	Low	Low	Low
PROFILE 1014 [57]	Low	Low	High[a]	Low	Low	Low
PROFILE 1029	Unclear[c]	Unclear[c]	High[a]	Unclear[c]	Unclear[c]	Low

[a]Open label.
[b]Primary endpoint was investigator-assessed progression-free survival.
[c] study not fully published, only limited information available

Table A20. Risk of bias – outcome level (randomised controlled trials)

Outcome and trial	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
PFS					
ALEX [2]	High[a]	Low	Low	Low	Low
ASCEND-4 [56]	Low	Low	Low	Low	Low
PROFILE 1014 [57]	Low	Low	Low	Unclear[b]	Low
OS					
ALEX	Low	Low	Low	High[c,d]	High
ASCEND-4	Low	Low	Low	High[e]	High
PROFILE 1014	Low	Low	Low	High[b,f]	High
ORR					
ALEX	High[g]	Low	Low	Low	Low[h]
ASCEND-4	Low	Low	Low	Low	Low
PROFILE 1014	Low	Low	Low	Low	Low
Adverse events					
ALEX	High[i]	Low	Low	Low	High
ASCEND-4	High[i]	Low	Low	Low	High
PROFILE 1014	High[i]	Low	Low	Low	High
Time to CNS progression					
ALEX	Low	Low	Low	Low	Low
Patient-reported outcomes					
ALEX	High[i]	High[j]	High[j]	Low	High

Abbreviations: CNS=central nervous system; DOR=duration of response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.
[a]Investigator-assessed PFS was the primary outcome, but the results were consistent with the findings of independent review committee (IRC) assessment of PFS.
[b]The standard of care (i.e., chemotherapy regimen) has changed since the study was initiated; it remains unclear if this affected the results in the control group.

Outcome and trial	**Blinding – outcome assessors**	**ITT principle adequately realised**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
[c]OS was outside the test hierarchy since ORR was not statistically significant and the study will not be powered to demonstrate any statistically significant difference in the secondary endpoint of OS. [d]Even though per protocol crossover between trial groups was not allowed, patients will be treated at the discretion of the investigator according to local practice after disease progression. [e]One hundred and five (72%) of 145 patients received an anaplastic lymphoma kinase inhibitor after discontinuation of chemotherapy. [f]Of the 171 patients randomly assigned to chemotherapy, 120 (70%) subsequently received crizotinib treatment. Of the 172 patients assigned to crizotinib therapy, 21 (12%) subsequently received platinum-based chemotherapy. This analysis was not adjusted for crossover. [g]Systemic responses were investigator assessed, CNS responses were assessed by an IRC. [h]Although it was investigator assessed, objective assessment would most likely only further reduce statistical significance; the results are consistent with IRC assessment. [i]Open label. [j]Low baseline values (~65 % of patients).					

Table A21. Template for GRADE assessment (e.g., using GRADEproGDT)

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alectinib	Crizotinib	Relative HR (95% CI)*	Absolute (95% CI)		
Alectinib vs. crizotinib												
OS (interim analysis)												
1	RCT	Serious limitation[b]	NA	No serious limitation	NA[b]	Serious limitation[c]	152	151	0.76 (0.48–1.20)	1-year survival rate: 84.3% vs. 82.5%	Low	Critical
PFS												
1	RCT	No serious limitation	NA	No serious limitation	No serious limitation	No serious limitation	152	151	0.47 (0.34–0.65)	Median: NE (17.7 months to NE) vs. 11.1 months (9.1–13.1 months)	High	Critical
ORR												
1	RCT	No serious limitation	NA	No serious limitation	No serious limitation	No serious limitation	152	151	—	75.5% (67.8%–82.1%) vs. 82.9% (76.0%–88.5%)	High	Important
Time to CNS progression												

[b] Not adequately powered; after progression treatment at the physician's discretion.

[c] Currently only results of an interim analysis are available.

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alectinib	Crizotinib	Relative HR (95% CI)*	Absolute (95% CI)		
1	RCT	No serious limitation	NA	No serious limitation	No serious limitation	No serious limitation	Rate of events of CNS progression: 18 (of 152)	Rate of events of CNS progression: 68 (of 151)	Cause-specific HR 0.16 (0.10–0.28); *p*<0.0001	18 (12%) vs. 68 (45%)	High	Critical
Total number of patients with ≥1 AE												
1	RCT	Serious limitation[d]	NA	No serious limitation	NA	No serious limitation	152	151	97% vs. 97%	152 vs. 151	Moderate	Critical
Total number of patients with serious AE												
1	RCT	Serious limitation[d]	NA	No serious limitation	NA	No serious limitation	152	151	28% vs. 29%	43 vs. 44	Moderate	Critical
Time to deterioration in EORTC QLQ-30 global health score												
1	RCT	Very serious limitation[d,e]	NA	No serious limitation	Serious limitation[f]	No serious limitation	100	97	0.72 (0.38–1.39)	—	Very low	Critical

Because there are no clear instructions and specific methodological guidance how to proceed with risk of bias and GRADE related to interim outcomes, consensus was made by the authors of this assessment to rate the quality of evidence for OS according to standard GRADE methods and to include it in this assessment, despite uncertainties on the final result.

Abbreviations: CI=confidence interval; EORTC=European Organisation for Research and Treatment of Cancer; HR=hazard ratio; HRQoL=health-related quality of life; NA=not applicable; NE=not estimable; OS=overall survival; ORR=objective response rate; PFS=progression-free survival; RCT=randomised controlled trial.

*HR if not otherwise indicated.

[d]Open label

[e]Low baseline values

[f] Wide confidence intervall

Applicability tables

Table A22. Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The newly licensed indication of alectinib will comprise 'advanced NSCLC', which comprises besides metastatic disease (i.e., according to the TNM system stage IV disease) also stage IIIB disease. In the ALEX trial, only 3%–4% of enrolled patients had stage IIIB disease at the baseline and guidelines state that there is currently no role for targeted agents in stage III NSCLC outside clinical trials [11]. Thus the applicability to these patients is limited. In addition, most patients (>90%) had adenocarcinoma as the histological subtype; even though this represents the most common histological type, applicability to, for example, large cell carcinoma is limited. Also since most patients had an ECOG PS of 1 or less at the baseline, efficacy and safety in frail patients with a lower PS remain uncertain
Intervention	No issues were identified which might affect benefits or harms from alectinib, since the way of administration, dosing and frequency of cycles used for alectinib are consistent with the upcoming approved licensing
Comparators	The appropriateness of crizotinib and ceritinib as comparators is supported by recent clinical practice guidelines [9]
Outcomes	Direct OS outcome data are not mature yet. Because of further therapies at the investigator's discretion after disease progression, OS data will have very limited applicability
Setting	Nearly half of the patients were of Asian origin. However, ethnicity was a stratification factor

Abbreviations: ECOG=Eastern Cooperative Oncology Group; NSCLC=non-small cell lung cancer; OS=overall survival; PS=performance status; TNM=tumour, node, metastasis.
Source: [17]

APPENDIX 3: REGULATORY AND REIMBURSEMENT STATUS

Table A23. Regulatory status

Country/ region	Institution issuing approval	Authorisation status	Verbatim wording of the (anticipated) indication(s)	Date of approval	Type of approval (full, conditional, exceptional)	Launched yes/no	Marketing authorisation number (if available)
Alectinib							
Japan	Pharmaceuticals and Medical Devices Agency		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	4th July 2014		Yes	
Europe	European Medicines Agency		Alectinib as monotherapy is indicated for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib Alectinib as monotherapy is indicated for the first-line treatment of adult patients with *ALK*-positive advanced NSCLC	16th February 2017 21 December 2017	Full	Launched in the majority of European Union countries with the 'crizotinib failure' indication	
United States	US Food and Drug Administration		Alectinib is a kinase inhibitor indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib. This indication is approved under accelerated approval based on tumour response rate and duration of response. Continued approval for this indication may be contingent on verification and description of clinical benefit in confirmatory trials [a] Alectinib as monotherapy is indicated for the first-line treatment of adult patients with *ALK*-positive advanced NSCLC	11th December 2015 6 November 2017	Full	Yes	
Switzerland	Swiss Agency for Therapeutic Products (Swissmedic)		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	26th January 2017		Yes	

			Proposed indication:[b] Alectinib is indicated for the first-line treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC				
Israel	Ministry of Health Pharmacy Department		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	17th April 2016		Yes	
Canada	Health Canada		Alecensaro (alectinib) is indicated as monotherapy for the treatment of patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	29th September 2016		Yes	
South Korea	Ministry of Food and Drug Safety		The treatment of patients with *ALK*-positive locally-advanced or metastatic NSCLC who were previously treated with crizotinib. The efficacy of alectinib was based on response rate and duration of response; there are no available data on increase of duration of survival	26th October 2016		Yes	
Kuwait	Ministry of Health, Drug & Food Control		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	24th November 2016		Yes	
Hong Kong	Drug Office, Department of Health		Alectinib is indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	9th December 2016		Yes	
Taiwan	Taiwan Food and Drug Administration		Alectinib is a kinase inhibitor indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib[c]	27th February 2017		Yes	
Australia	Therapeutics Goods Administration		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib.	14th March 2017		Yes	

			Proposed indication:[d] Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC				
Singapore	Health Sciences Authority		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	24th April 2017		Yes	
India	Central Drugs Standard Control Organization		Alectinib is indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	30th June 2017		Yes	
Thailand	Thai Food and Drug Administration		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	3rd August 2017		Yes	
Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica		Alectinib is indicated for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib[e]	28th August 2017		Yes	
United Arab Emirates	Ministry of Health and Prevention		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	7th September 2017		Yes	
Turkey	Medicines and Medical Devices Agency		Alectinib as monotherapy is indicated until progression for the treatment of adult patients with *ALK*-positive metastatic NSCLC previously treated with crizotinib	14th September 2017		Yes	
Saudi Arabia	Food and Drug Authority		Alectinib is indicated for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	25th September 2017		Yes	
Comparators							
Crizotinib							
United States			Treatment of patients with locally advanced or metastatic NSCLC that is *ALK* positive as detected	August 2011	Accelerated approval		

			by a Food and Drug Administration-approved test				
Canada			As monotherapy for use in patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC	April 2012	Notice of compliance with Conditions		
European Union			Treatment of adults with previously treated *ALK*-positive advanced NSCLC	October 2012	Conditional approval		
Brazil			Treatment of patients with advanced NSCLC whose tumours are *ALK* positive	February 2016			
Ceritinib							
United States			Treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed crizotinib therapy with or who are intolerant of crizotinib Indication in the first-line setting: Treatment of patients with metastatic *ALK*-positive NSCLC	First approval: April 2014 Date of approval in first line: May 2017	Accelerated approval		
Canada			Treatment as monotherapy in patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC whose disease has progressed with crizotinib therapy or who are intolerant of crizotinib	March 2015	Notice of compliance with conditions		
European Union			Indication: As monotherapy for the treatment of adult patients with *ALK*-positive advanced NSCLC previously treated with crizotinib Indication in the first-line setting: As monotherapy for adult patients with *ALK*-positive advanced NSCLC	May 2015 Date of approval in first-line setting: June 2017	Conditional approval		

This table was last updated on 19 January 2018.
Abbreviation: NSCLC=non-small cell lung cancer.
Source: [17]
[a]Priority review granted by US Food and Drug Administration for first-line indication.

[b]Fast track designation granted by Swissmedic for first-line indication.

[c]This indication is approved under accelerated approval based on tumour response rate and duration of response. Continued approval for this indication may be contingent on verification and description of clinical benefit in confirmatory trials.

[d]Priority review granted by Therapeutics Goods Administration for first-line indication.

[e]The present indication is based on the tumour response rate and duration of response. Continued approval of this indication is subject to verification and description of clinical benefits in confirmatory trials.

Table A24. Overview of the reimbursement status of alectinib in the crizotinib-failure indication in selected European countries and the comparators for the approved indication

Country and issuing organisation	Reimbursement status	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Alectinib – second-line treatment of *ALK*-positive NSCLC			
Austria – Hauptverband der österreichischen Sozialversicherung sträger (HVB)	Ongoing		
Belgium – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV-INAMI)	Ongoing		
Bulgaria National Council for Price and Reimbursement of Medicinal Product	Preparing submission		
Croatia – Croatian Health Insurance Fund (Hrvatski zavod za zdravstveno osiguranje; HZZO)	Ongoing		
Czech Republic - State Institute for Drug Control (SUKL)	Not assessed		
Denmark - Danish Medicines Council (Laegemiddelstyrelsen)	Reimbursed		
England – National Institute for Health and Care Excellence, NICE)	Ongoing		
Estonia – Estonian Health Insurance Fund (Eesti Haigekassa)	Ongoing		
Finland – Pharmaceutical Pricing Board (Lääkkeiden hintalautakunta), HILA)	Ongoing		
France - Haute Autorité de Santé (HAS)	Ongoing		
Germany - Gemeinsamer Bundesausschuss (G BA)	Ongoing	Full reimbursement while the assessment is ongoing	

Country and issuing organisation	Reimbursement status	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Greece – National Organisation for Medicines	Ongoing		
Hungary – National Health Insurance Fund of Hungary (OEP)	Ongoing		
Ireland - National Centre for Pharmacoeconomics (NCPE)	Ongoing		
Italy - Agenzia Italiana del Farmaco (AIFA)	Ongoing		
Latvia - State Agency of Medicines (SAM)	Prearing submission		
Lithuania - Compulsory Health Insurance Fund (CHIF)	Preparing submission		
Luxemburg - Ministère de la Sécurité Sociale	Reimbursed		
Netherlands – ZorgInstituut	Reimbursed		
Norway – Norwegian Medicines Agency	Ongoing		
Poland – Ministry of Health (Ministerstwo Zdrowia, MZ)	Ongoing		
Portugal - National Authority of Medicines and Health Products (Autoridade Nacional do Medicamento e Produtos de Saúde, I.P., INFARMED)	Ongoing		
Romania - National Agency of Medicines and Medical Devices	Not yet submitted		
Scotland (Scottish Medicines Consortium, SMC)	Ongoing		
Slovakia - Ministry of Health (Ministervo zdravotníctva)	Preparing submission		

Country and issuing organisation	Reimbursement status	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Slovenia - Health Insurance Institute of Slovenia (Zavod za zdravstveno zavarovanje Slovenije, ZZZS)	Ongoing		
Spain - Ministry of Health, Social Services and Equality (Ministerio de Sanidad, Servicios Sociales e Igualdad)	Ongoing		
Sweden - The Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmåns verket, TLV)	Reimbursed	Remibursement restricted to adult patients with ALK-positive advanced NSCLC previously treated with crizotinib	
Switzerland - Federal Office of public health (Bundesamt für Gesundheit, BAG)	Reimbursed		
Wales – All Wales Medicines Strategy Group, AWMSG))	Ongoing		
Crizotinib - Second line *ALK-positive* NSCLC			
Belgium	Yes		
Bulgaria	Yes		
Croatia	Yes		
Denmark	Yes		
Finland	Yes		
France	Yes		
Germany	Yes		
Greece	Yes		
Ireland	Yes		
Italy	Yes		
Netherlands	Yes		
Poland	Yes		
Portugal	Yes		
Slovenia	Yes		
Sweden	Yes		
Spain	Yes		
Switzerland	Yes		
United Kingdom	Yes		

Country and issuing organisation	Reimbursement status	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Crizotinib – first-line treatment of *ALK*-positive NSCLC			
Croatia	Yes		
Denmark	Yes		
France	Yes		
Germany	Yes		
Greece	Yes		
Ireland	Yes		
Italy	Yes		
Luxembourg	Yes		
Netherlands	Yes		
Norway	Yes		
Slovenia	Yes		
Spain	Yes		
Sweden	Yes		
United kingdom	Yes		
Ceritinib – second-line treatment of *ALK*-positive NSCLC or in the case of crizotinib treatment failure			
Austria	Yes		
Belgium (3L only)	Yes		
Denmark	Yes		
France	Yes		
Germany	Yes		
Greece	Yes		
Ireland	Yes		
Italy	Yes		
Netherlands	Yes		
Slovenia	Yes		
Sweden	Yes		
United Kingdom	Yes		
Ceritinib – first-line treatment of *ALK*-positive NSCLC			
Denmark	Yes		
Germany	Yes		
Greece	Yes		
Netherlands	Yes		
Sweden	Yes		
United Kingdom	Ongoing at NICE		

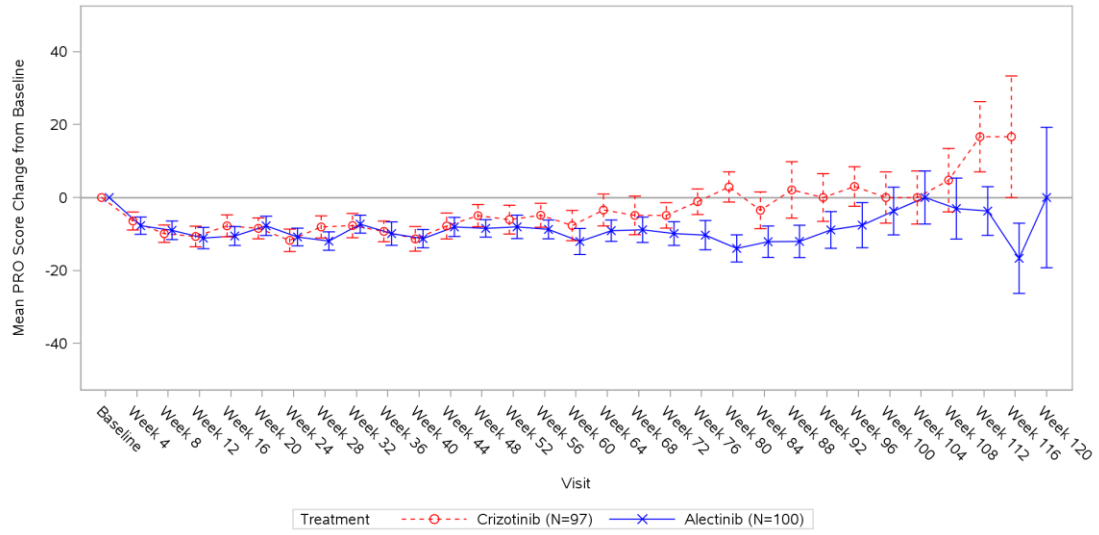
Source: [17] This table was last updated on 19 January 2018

APPENDIX 4: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	**No**
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	**No**
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	**No**
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	**No**
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	**No**
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	**No**
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	**No**
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	**No**

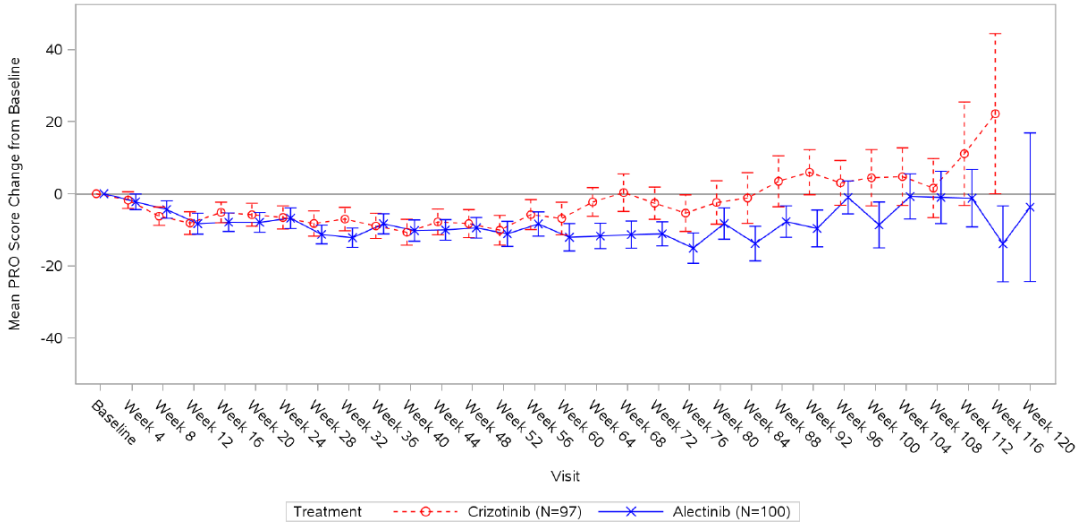
APPENDIX 5. HEALTH-RELATED QUALITY OF LIFE

Figure A9. Mean patient-reported European Organisation for Research and Treatment of Cancer QLQ-LC13 pain in chest score change from the baseline (patient-reported outcome-evaluable population) (ALEX)



Abbreviation: PRO=patient-reported outcome.
Note: Decreases from the baseline correspond to abatement of symptoms. The numbers of patients decrease over time (no imputation for missing data). Patient numbers for crizotinib and alectinib, respectively: baseline *n*=96 and *n*=100; week 48 *n*=47 and *n*=67; week 72 *n*=34 and *n*=54; week 96 *n*=11 and *n*=22.
Source: ALEX clinical study report.

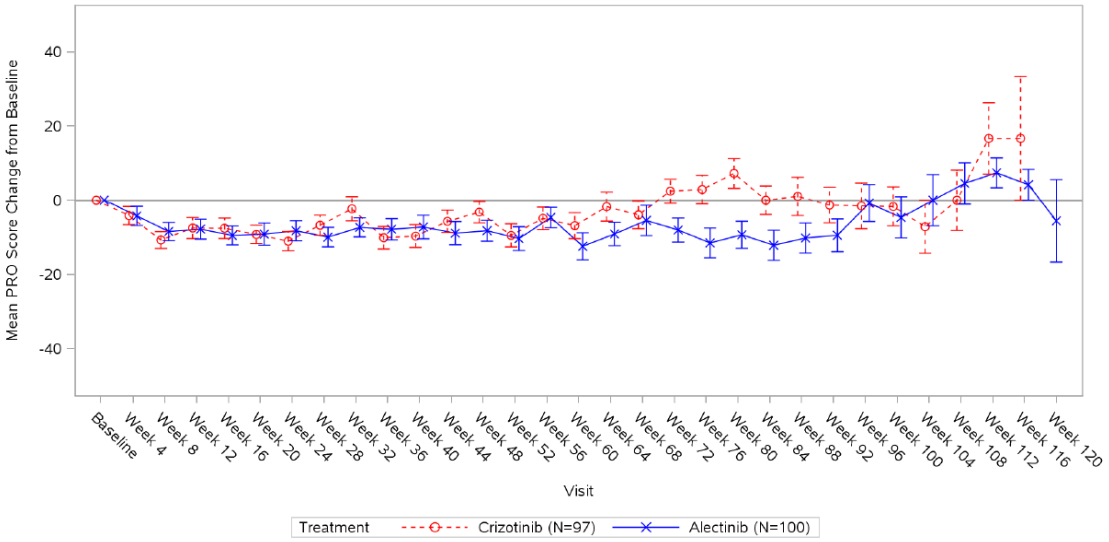
Figure A10. Mean patient-reported Outcome Score European Organisation for Research and Treatment QLQ-C30 fatigue score change from the baseline (patient-reported outcome-evaluable population) (ALEX)



Abbreviation: PRO=patient-reported outcome.

Note: Decreases from the baseline correspond to abatement of symptoms. The numbers of patients decrease over time (no imputation for missing data). Patient numbers for crizotinib and alectinib, respectively: baseline *n*=97 and *n*=100; week 48 *n*=47 and *n*=67; week 72 *n*=34 and *n*=54; week 96 *n*=11 and *n*=22.
Source: ALEX clinical study report.

Figure A11. Mean patient-reported Outcome Score European Organisation for Research and Treatment of Cancer QLQ-C30 pain score change from the baseline (patient-reported outcome-evaluable population) (ALEX)

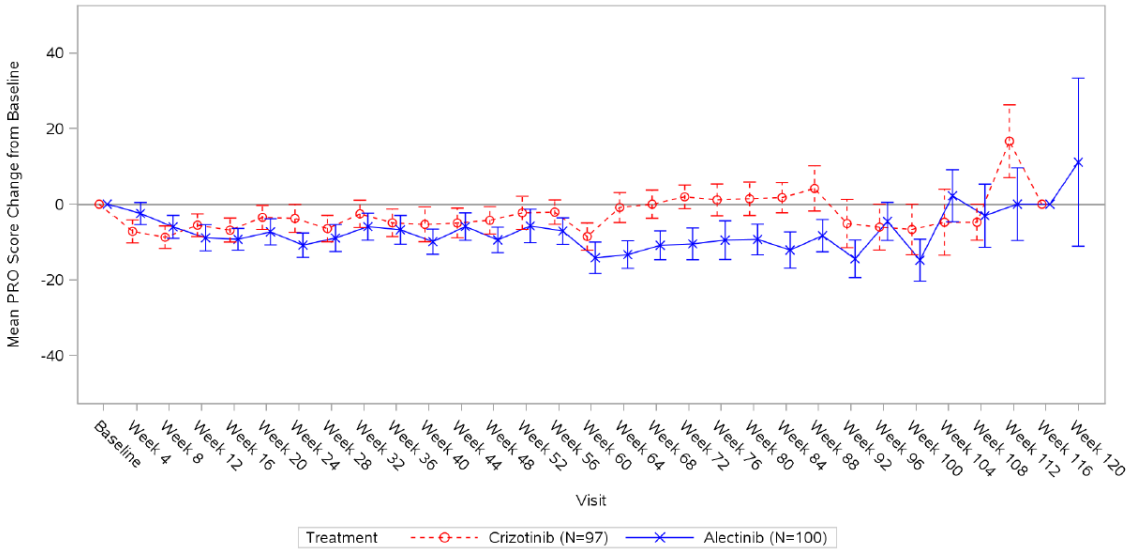


Abbreviation: PRO=patient-reported outcome.

Note: Decreases from the baseline correspond to abatement of symptoms. The numbers of patients decrease over time (no imputation for missing data). Patient numbers for crizotinib and alectinib, respectively: baseline *n*=97 and *n*=100; week 48 *n*=47 and *n*=67; week 72 *n*=34 and *n*=54; week 96 *n*=11 and *n*=22.

Source: ALEX clinical study report.

Figure A12. Mean patient-reported Outcome Score European Organisation for Research and Treatment of Cancer QLQ-LC13 pain in other parts score change from the baseline (patient-reported outcome-evaluable population) (ALEX)



Abbreviation: PRO=patient-reported outcome.

Note: Decreases from the baseline correspond to abatement of symptoms. The numbers of patients decrease over time (no imputation for missing data). Patient numbers for crizotinib and alectinib, respectively: baseline *n*=96 and *n*=100; week 48 *n*=47 and *n*=67; week 72 *n*=34 and *n*=54; week 96 *n*=11 and *n*=22.

Source: ALEX clinical study report.

APPENDIX 6. INDIRECT COMPARISONS – STATISTICAL ASPECTS

General remarks

Included studies
Despite the availability of indirect evidence/NMA, it has to be noted, that in ASCEND-4, four cycles of chemotherapy followed by maintenance therapy were used as a comparator. In contrast, in PROFILE 1014, up to six cycles of the same chemotherapy were allowed, but without maintenance therapy. Given that there was a lack of direct evidence in the comparison of alectinib to ceritinib, a connected network of three trials (ALEX, PROFILE 1014, and ASCEND-4) were used to use indirect evidence to estimate the difference in treatment effect. As with all indirect comparison, there were differences within the three studies that should be noted as the differences may have affected the results of the NMA. Firstly, it has to be noted, that in ASCEND-4, four cycles of chemotherapy followed by maintenance therapy were used as a comparator. In contrast, in PROFILE 2295 1014, up to six cycles of the same chemotherapy were allowed, but without maintenance therapy. The difference between studies in time on treatment was 1.9 months (4.1 months on CHEMO in PROFILE 1014; 6 months on CHEMO in ASCEND-4) and the difference between median PFS in the trials was 1.1 months (median PFS was 7·0 months for CHEMO in PROFILE 1014; median PFS of 8·1 months for CHEMO in ASCEND-4). It is not known whether the difference of 1.1 months in median PFS is due to the maintenance or falls within the range of uncertainty due to other factors or sources of heterogeneity. It is assumed that there is no impact on response endpoints since response should be observed during induction phase (median time to response in CHEMO arm for PROFILE 1014 was 2.8 months compared to 3.1 months in ASCEND-4). There may be an impact on the safety endpoints assuming that more adverse events would occur with longer treatment.

There were higher frequencies in the ALEX study (approximately 40%) compared with less than 30% in PROFILE 1014 and approximately 30% in ASCEND-4. The higher frequency of CNS metastases at baseline observed in the ALEX study may be explained by the requirement for all patients to have CNS imaging at baseline.

Because of these uncertainties involved and possible dependencies regarding the heterogeneity assumptions on the results in the NMA, these results are considered with caution.

Bucher indirect comparison
Indirect comparisons may suffer from the biases of observational studies [18]. Only adjusted instead of unadjusted indirect comparison methods should be used [10]. An adjusted indirect comparison method is the Bucher indirect comparison (Bucher IC), in which relative instead of absolute treatment effects are compared by use of a common comparator [10]. It is an underlying assumption of the Bucher IC that taking into account the common comparator implicitly accounts for differences between studies [63]. In the present case this assumption is not testable; because of the limited number of studies, the heterogeneity between studies cannot be assessed. The results presented for the Bucher IC depend on the validity of this assumption.

Bayesian NMA
In contrast to Bucher IC, in an NMA all the direct and indirect comparisons that can be derived from a complicated network structure are considered simultaneously when the effect estimates are computed.

The base case analysis was performed with a Bayesian fixed effects model. The difference between such a model and a Bayesian random effects model lies in the prior assumption regarding the modelled between-trial heterogeneity. In a Bayesian random effects model a prior distribution is prespecified for the heterogeneity parameter. The Bayesian fixed effects model can be regarded as a special case of a Bayesian random effects model where a priori the whole probability mass of the between-trial heterogeneity is assigned to zero.

Sensitivity regarding heterogeneity assumptions of the Bayesian NMA

The assumption on between-trial heterogeneity in the Bayesian fixed effects NMA is influential in the sense that increasing this parameter implies increasing the total variability of the model, which leads to wider credible intervals. With the exception of the comparison crizotinib versus chemotherapy, where theoretically two studies are available, the comparisons were performed with only a single study. Therefore in the base case the between-trial heterogeneity cannot be derived from the data. Thus the total variability of the model is partly based on an assumption, which cannot be verified empirically.

Similar results in Bucher IC and the Bayesian fixed effects NMA

The results are nearly identical because the network is elementary enough, such that the more complex fixed effects NMA does not use its additional capabilities in processing the data, compared with the simple Bucher method. Thus only the NMA is presented, with focus on the MAH base case fixed effect. *Alectinib versus ceritinib (NMA, indirect comparison).*

Additional results with PROFILE 1029 included

In Table A25 and Table A26, results are presented from the NMA for PFS and OS. In sensitivity analysis 1.2 (fixed effect), results from PROFILE 1029 were included.

Table A25. Network meta-analysis summary treatment effect estimates: progression-free survival by independent review committee, base case (fixed effect), sensitivity analysis 1.2 (fixed effect, including PROFILE 1029) and sensitivity analysis 1.3 (random effect, including PROFILE 1029)

PFS by IRC log hazard ratio		Base case (ALEX, PROFILE 1014, ASCEND-4) Fixed effect NMA					Sensitivity analysis SA1.2 (ALEX, PROFILE 1014, PROFILE 1029, ASCEND-4) Fixed effect NMA					Sensitivity analysis SA1.3 (ALEX, PROFILE 1014, PROFILE 1029, ASCEND-4) Random effect NMA			
Treatment	Vs.	Mean	Median	Lower 95% CrL	Upper 95% CrI		Mean	Median	Lower 95% CrL	Upper 95% CrI		Mean	Median	Lower 95% CrL	Upper 95% CrI
CRZ	CHEMO	-0.801	-0.800	-1.058	-0.546	--	-0.841	-0.840	-1.045	-0.638	--	-0.852	-0.844	-2.147	0.373
CER	CHEMO	-0.600	-0.600	-0.876	-0.330	--	-0.600	-0.600	-0.876	-0.330	--	-0.605	-0.600	-2.450	1.255
ALEC	CHEMO	-1.490	-1.490	-1.911	-1.068	--	-1.530	-1.530	-1.923	-1.138	--	-1.540	-1.524	-3.792	0.668
Hazard ratios															
Treatment	Vs.	Mean	Median	Lower 95% CrI	Upper 95% CrI		Mean	Median	Lower 95% CrI	Upper 95% CrI		Mean	Median	Lower 95% CrI	Upper 95% CrI
CRZ	CHEMO	0.453	0.450	0.347	0.579	--	0.434	0.432	0.352	0.528	--	0.512	0.430	0.117	1.452
CER	CHEMO	0.554	0.549	0.417	0.719	--	0.554	0.549	0.417	0.719	--	0.862	0.549	0.086	3.509
ALEC	CHEMO	0.231	0.225	0.148	0.344	--	0.221	0.217	0.146	0.321	--	0.471	0.218	0.023	1.950
CHEMO	CRZ	2.246	2.224	1.727	2.881	++	2.331	2.317	1.894	2.844	++	2.841	2.326	0.689	8.563
CER	CRZ	1.244	1.222	0.839	1.785		1.292	1.273	0.903	1.789		3.086	1.272	0.146	12.120
ALEC	CRZ	0.509	0.502	0.360	0.702	--	0.509	0.502	0.360	0.702	--	0.807	0.509	0.079	3.160
CHEMO	CER	1.840	1.821	1.391	2.401	++	1.840	1.821	1.391	2.401	++	2.863	1.822	0.285	11.620
CRZ	CER	0.834	0.818	0.560	1.192		0.798	0.786	0.559	1.108		1.740	0.786	0.083	6.883
ALEC	CER	0.424	0.411	0.248	0.674	--	0.406	0.395	0.244	0.634	--	2.502	0.399	0.021	6.559
CHEMO	ALEC	4.541	4.437	2.910	6.762	++	4.713	4.619	3.120	6.846	++	10.800	4.592	0.513	44.340
CRZ	ALEC	2.022	1.993	1.425	2.781	++	2.022	1.993	1.425	2.781	++	3.257	1.965	0.317	12.690
CER	ALEC	2.515	2.432	1.483	4.029	++	2.611	2.534	1.578	4.092	++	15.530	2.510	0.153	47.920

Abbreviations: ALEC=alectinib; CER=ceritinib; CHEMO=chemotherapy; CrI=credible limit; CRZ=crizotinib; IRC=independent review committee; NMA=network meta-analysis; PFS=progression-free survival.

-- significantly lower hazard for treatment versus comparator based on the 95% credible interval; ++ significantly higher hazard for treatment versus comparator based on the 95% credible interval.

Source: MAH NMA report, Table 18.

Table A26. Network meta-analysis summary treatment effect estimates: overall survival unadjusted, base case (fixed effect), sensitivity analysis 1.2 (fixed effect, including PROFILE 1029) and sensitivity analysis 1.3 (random effect, including PROFILE 1029)

OS unadjusted log hazard ratio	Base case (ALEX, PROFILE 1014, ASCEND-4) Fixed effect NMA	Sensitivity analysis 1.2 (ALEX, PROFILE 1014, PROFILE 1029, ASCEND-4) Fixed effect NMA	Sensitivity analysis 1.3 (ALEX, PROFILE 1014, PROFILE 1029, ASCEND-4) Random effect NMA

Treatment	Vs.	Mean	Median	Lower 95% CrI	Upper 95% CrI	Mean	Median	Lower 95% CrI	Upper 95% CrI	Mean	Median	Lower 95% CrI	Upper 95% CrI
CRZ	CHEMO	-0.201	-0.199	-0.617	0.212	-0.162	-0.161	-0.474	0.149	-0.163	-0.156	-1.548	1.189
CER	CHEMO	-0.310	-0.310	-0.685	0.057	-0.310	-0.310	-0.685	0.057	-0.306	-0.305	-2.170	1.611
ALEC	CHEMO	-0.470	-0.469	-1.085	0.140	-0.431	-0.431	-0.979	0.119	-0.441	-0.433	-2.787	1.894
Hazard ratios													
Treatment	**Vs.**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
CRZ	CHEMO	0.836	0.819	0.539	1.237	0.862	0.852	0.623	1.160	1.052	0.855	0.213	3.283
CER	CHEMO	0.746	0.734	0.504	1.058	0.746	0.734	0.504	1.058	1.194	0.737	0.114	5.007
ALEC	CHEMO	0.656	0.625	0.338	1.151	0.676	0.650	0.376	1.126	1.572	0.648	0.062	6.643
CHEMO	CRZ	1.250	1.220	0.809	1.854	1.190	1.174	0.862	1.606	1.473	1.169	0.305	4.705
CER	CRZ	0.933	0.895	0.516	1.570	0.889	0.862	0.530	1.402	2.185	0.859	0.092	9.384
ALEC	CRZ	0.785	0.764	0.487	1.202	0.785	0.764	0.487	1.202	1.239	0.758	0.108	5.088
CHEMO	CER	1.389	1.363	0.945	1.983	1.389	1.363	0.945	1.983	2.202	1.356	0.200	8.758
CRZ	CER	1.161	1.117	0.637	1.939	1.196	1.160	0.714	1.888	2.700	1.164	0.107	10.99
ALEC	CER	0.911	0.853	0.415	1.728	0.938	0.888	0.455	1.707	5.018	0.876	0.042	17.80
CHEMO	ALEC	1.680	1.599	0.869	2.960	1.600	1.538	0.888	2.662	3.981	1.543	0.151	16.23
CRZ	ALEC	1.344	1.310	0.832	2.055	1.344	1.310	0.832	2.055	2.199	1.320	0.197	9.256
CER	ALEC	1.254	1.173	0.579	2.413	1.194	1.126	0.586	2.199	7.274	1.142	0.056	23.81

Abbreviations: ALEC=alectinib; CER=ceritinib; CHEMO=chemotherapy; CrI=credible limit; CRZ=crizotinib; NMA=network meta-analysis; OS=overall survival.

-- significantly lower hazard for treatment versus comparator based on the 95% credible interval; ++ significantly higher hazard for treatment versus comparator based on the 95% credible interval.

Source: MAH NMA report

Table A27. Checklist table

Mark ✓ to indicate that the issue has been addressed satisfactorily, and × if there is any cause for concern for the item. The Comments column should be used to answer the question (YES, NO, NA: not applicable) and/or to spell out the reasons for any concerns, the need for sensitivity analyses, etc.

		Item satisfactory	Comments
A. DEFINITION OF THE DECISION PROBLEM			
A1. Target population for decision			
A1.1	*Has the target patient population for decision been clearly defined?*	✓	*Target population for NMA: ALK-positive NSCLC treatment-naïve patients.*
A2. Comparators			
A2.1	*Decision comparator set: Have all the appropriate treatments in the decision been identified?*	✓	*Yes; alectinib, crizotinib, ceritinib.*
A2.2	*Synthesis comparator set: Are there additional treatments in the synthesis comparator set which are not in the decision comparator set? If so, is this adequately justified?*	✓	*Yes; chemotherapies had to be included as additional treatments in the synthesis comparator set to make a connected network to perform indirect comparisons and the NMA.*
A3. Trial inclusion/exclusion			
A3.1	*Is the search strategy technically adequate and appropriately reported?*	✓	*Systematic literature review included all treatment lines, while NMA included only patients in the first-line setting.* *Search strategy was reported in detail, could be reproduced.*
A3.2	*Have all trials involving at least two of the treatments in the synthesis comparator set been included?*	✓	*See section 2.3 of this report and PRISMA flow chart.*
A3.3	*Have all trials reporting relevant outcomes been included?*	✓	*See section 2.3 of this report and PRISMA flow chart.*
A3.4	*Have additional trials been included? If so, is this adequately justified?*	✓	*No additional trials have been included.*
A4. Treatment definition			
A4.1	*Are all the treatment options restricted to specific doses and cotreatments, or have different doses and cotreatments been 'lumped' together? If the latter, is it adequately justified?*	✓	*In two studies (ASCEND-4 and PROFILE 1014) the comparator was chemotherapy; however, in ASCEND-4 a combination of pemetrexed plus either cisplatin or carboplatin was given for four cycles followed by pemetrexed maintenance therapy, while in PROFILE 1014 it was given for up to six cycles without pemetrexed maintenance therapy.Furthermore, the impact of post-progression cross-over on OS results were identified as a further source of uncertainty related to study treatments.* *The MAH provided the following rationale:*

		Item satisfactory	Comments
			Chemo arms: The difference between studies in time on treatment was 1.9 months (4.1 months on CHEMO in PROFILE 1014; 6 months on CHEMO in ASCEND-4) and the difference between median PFS in the trials was 1.1 months (median PFS was 7·0 months for CHEMO in PROFILE 1014; median PFS of 8·1 months for CHEMO in ASCEND-4). It is not known whether the difference of 1.1 months in median PFS is due to the maintenance or falls within the range of uncertainty due to other factors or sources of heterogeneity. Therefore, it was assumed that studies were "similar enough" to be connected in the evidence network. *OS Rationale: Only PROFILE 1014 report OS data adjusted for treatment cross-over. However, patients could cross over from the CHEMO arm to the ALKi arm in three trials (PROFILE 1014, PROFILE 1029 and ASCEND-4); crossover from CRZ to ALEC was not allowed in the ALEX study. Only available for PROFILE1014 study but not available for the ASCEND-4 study therefore, an unadjusted OS was used within the base case analysis.* *While the identified uncertainties remain, they are considered adequately addressed by the MAH.*
A4.2	*Are there any additional modelling assumptions?*	✓	*No.*
A5. Trial outcomes and scale of measurement chosen for the synthesis			
A5.1	*Where alternative outcomes are available, has the choice of outcome measure used in the synthesis been justified?*	✓	*The MAH conducted a feasibility assessment, including a review of all endpoints within the trials and an evaluation for feasibility to connect the network.*
A5.2	*Have the assumptions behind the choice of scale been justified?*	*NA*	*The endpoints used are standard oncology endpoints.*
A6. Patient population: trials with patients outside the target population			
A6.1	*Do some trials include patients outside the target population? If so, is this adequately justified?*	✓	*No inclusion of patients outside the target population.*
A6.2	*What assumptions are made about the impact, or lack of impact, this may have on the relative treatment effects? Are they adequately justified?*	*NA*	
A6.3	*Has an adjustment been made to account for these differences? If so, comment on the adequacy of the evidence presented in support of this adjustment, and on the need for a sensitivity analysis.*	*NA*	
A7. Patient population: heterogeneity within the target population			

		Item satisfactory	Comments
A7.1	*Has there been a review of the literature concerning potential modifiers of treatment effect?*	✗	*Not provided.*
A7.2	*Are there apparent or potential differences between trials in their patient populations, albeit within the target population? If so, has this been adequately taken into account?*	✗	*The percentage of patients with brain metastases ranges from 26% to 42% between ALEX, ASCEND-4 and PROFILE 1014.* *Previous therapies patients received differ between trials (e.g., previous treatment for CNS metastases differs between ALEX and ASCEND-4 and is not reported for PROFILE 1014).*
A8. Risk of bias			
A8.1	*Is there a discussion of the biases to which these trials, or this ensemble of trials, are vulnerable?*	✓	*Yes.*
A8.2	*If a bias risk was identified, was any adjustment made to the analysis and was this adequately justified?*	✗	*Factors were identified which are not possible to adjust for:* *PROFILE 1029 was identified as having a possible risk of bias because of the study population including Asian patients only; therefore PROFILE 1029 was excluded from the base case analysis of the NMA.* *All trials were open label, which could potentially impact the results.* *Differences in ASCEND-4 include that four cycles of chemotherapy followed by maintenance therapy was used as comparator, whereas in PROFILE 1014 up to six cycles of the same chemotherapy was allowed but without maintenance therapy. The regimen used in ASCEND-4 may be more efficacious than the one used in PROFILE 1014; therefore PFS HR for ceritinib vs. chemotherapy may be underestimated in the NMA, and the PFS HR for crizotinib vs. chemotherapy may be overestimated.*
A9. Presentation of the data			
A9.1	*Is there a clear table or diagram showing which data have been included in the base case analysis?*	✓	*Network diagram and characteristics of included studies was provided.*
A9.2	*Is there a clear table or diagram showing which data have been excluded and why?*	✗	*Not provided.*
B. METHODS OF ANALYSIS AND PRESENTATION OF RESULTS ***B1. Meta-analytic methods***			
B1.1	*Is the statistical model clearly described?*	✓	*Statistical model is adequately described.*
B1.2	*Has the software implementation been documented?*	✓	*Software implementation has been described.*
B2. Heterogeneity in the relative treatment effects			
B2.1	*Have numerical estimates been provided of the degree of heterogeneity in the relative treatment effects?*	✗	*Because all considered comparisons are based on just one relevant study in the base case, the heterogeneity is completely assumption driven. Sensitivity analyses regarding the influence of the heterogeneity assumptions were not presented.*

		Item satisfactory	Comments
B2.2	*Has a justification been given for the choice of random or fixed effect models? Should sensitivity analyses be considered?*	✗	*A decision rule based on the deviance information criteria and the average residual deviance was prespecified, but considering the limited amount of data that can validate heterogeneity assumptions (which constitute the main difference between the fixed effects model and the random effects model), the presentation of extensive sensitivity analyses seems more adequate than deciding between the two extreme cases of absolute certainty about zero heterogeneity (fixed effects model) and high uncertainty regarding heterogeneity (random effects model with vague prior distribution).*
B2.3	*Has there been an adequate response to heterogeneity?*	*NA*	*No observable heterogeneity because of only one trial per comparison, no covariate adjustment.*
B2.4	*Does the extent of unexplained variation in relative treatment effects threaten the robustness of conclusions?*	*NA*	*Limited data; validation of heterogeneity assumptions not possible (see comment on B2.2).*
B2.5	*Has the statistical heterogeneity between baseline arms been discussed?*	✗	*Not provided.*
B3. Baseline model for trial outcomes			
B3.1	*Are baseline effects and relative effects estimated in the same model? If so, has this been justified?*	*NA*	*No baseline model.*
B3.2	*Has the choice of studies to inform the baseline model been explained?*	*NA*	*No baseline model.*
B4. Presentation of results of analyses of trial data			
B4.1	*Are the relative treatment effects (relative to a placebo or 'standard' comparator) tabulated, alongside measures of between-study heterogeneity if a random effects model is used?*	✗	*The relative treatment effects are tabulated, but measures of between-study heterogeneity cannot be extracted from the data.*
B4.2	*Are the absolute effects on each treatment, as they are used in the CEA, reported?*	*NA*	*CEA not done.*
B5. Synthesis in other parts of the natural history model			
B5.1	*Is the choice of data sources to inform the other parameters in the natural history model adequately described and justified?*	*NA*	*No natural history model.*
B5.2	*In the natural history model, can the longer-term differences between treatments be explained by their differences on*	*NA*	*No natural history model.*

		Item satisfactory	Comments
	randomised trial outcomes?		
C. ISSUES SPECIFIC TO NETWORK SYNTHESIS ***C1. Adequacy of information on model specification and software implementation***		✓	*The software implementation is adequate.*
C2. Multiarm trials			
C2.1	*If there are multiarm trials, have the correlations between the relative treatment effects been taken into account?*	*NA*	*No multiarm trials included.*
C3. Connected and disconnected networks			
C3.1	*Is the network of evidence based on randomised trials connected?*	✓	*All included trials are (open-label) phase III RCTs with active control groups.*
C4. Inconsistency			
C4.1	*How many inconsistencies could there be in the network?*	*NA*	*Inconsistencies not possible – no closed loops in the network.*
C4.2	*Are there any a priori reasons for concern that inconsistency might exist because of systematic clinical differences between the patients in trials comparing treatments A and B, and the patients in trials comparing treatments A and C, etc?*	✗	*Yes; percentage of patients with brain metastases ranges from 26% to 42% between ALEX, ASCEND-4 and PROFILE 1014; and previous treatment for CNS metastases differs between ALEX and ASCEND-4 and is not reported for PROFILE 1014.*
C4.3	*Have adequate checks for inconsistency been made?*	*NA*	*Inconsistencies not possible – no closed loops in the network.*
C4.4	*If inconsistency was detected, what adjustments were made to the analysis, and how were these justified?*	*NA*	*Inconsistencies not possible – no closed loops in the network.*
D. EMBEDDING THE SYNTHESIS IN A PROBABILISTIC CEA ***D1. Uncertainty Propagation***			
D1.1	*Has the uncertainty in parameter estimates been propagated through the CEA model?*	*NA*	*No CEA model.*
D2. Correlations			
D2.1	*Are there correlations between parameters? If so, have the correlations been propagated through the CEA model?*	*NA*	*No CEA model.*

Abbreviations: CEA=cost-effectiveness analysis; CNS=central nervous system; HR=hazard ratio; MAH=marketing authorisation holder; NMA network meta-analysis; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT=randomised controlled trial; NA=not applicable.
Source: [17], NMA Report, NMA SAP, NMA FAS.

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