TESIS DOCTORAL

Programa de Doctorado en Biomedicina y Farmacia

Tratamiento de primera línea en cáncer de pulmón no microcítico estadio avanzado con mutación del EGFR: estudio coste-efectividad

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Memoria de investigación realizada por Javier Aguilar Serra para la obtención del grado de Doctor en Biomedicina y Farmacia

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CERTIFICAN

Que la Tesis titulada "Tratamiento de primera línea en cáncer de pulmón no microcítico estadio avanzado con mutación del EGFR: estudio coste-efectividad" presentada por D. Javier Aguilar Serra ha sido realizada en la Universitat de València bajo nuestra dirección y asesoramiento, y en nuestro criterio reúne méritos suficientes para que su autor pueda obtener con ella el grado de Doctor por la Universitat de València,

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Tira los dados

Si vas a intentarlo,
ve hasta el final.
De lo contrario no empieces siquiera.

Tal vez suponga perder novias,
esposas, familia, trabajos
y quizás hasta la cabeza.
Tal vez suponga no comer durante
tres o cuatro días,
tal vez suponga helarte
en el banco de un parque.
Tal vez suponga la cárcel, la humillación,
el desdén y el aislamiento.
Tu aislamiento.

Todo lo demás sólo sirve para poner
a prueba tu resistencia,
tus auténticas ganas de hacerlo.

Y lo harás.

A pesar del rechazo y
de las ínfimas probabilidades,
y será mejor que cualquier cosa
que pudieras imaginar.

Si vas a intentarlo,
ve hasta el final.

No existe una sensación igual.
Estarás sólo con los dioses
y las noches arderán en llamas.

Hazlo, hazlo, hazlo.
Hazlo.
Hasta el final.

Y llevarás las riendas de la vida
hasta la risa perfecta,
es por lo único que vale
la pena luchar.

Charles Bukowski

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ABREVIATURAS

ACB	Análisis coste-beneficio
ACE	Análisis coste-efectividad
ACU	Análisis coste-utilidad
AJCC	American Joint Comission of Cancer
ALT	Alanina aminotransferasa
AS	Análisis de sensibilidad
AVAC	Años de vida ajustados por calidad
AVG	Años de vida ganados
BNM	Beneficio neto monetario
CEM	Coste-efectividad medio
CPCNP	Cáncer de pulmón de células no pequeñas
CPCP	Cáncer de pulmón de células pequeñas
CPM	Cáncer de pulmón microcítico
CPNM	Cáncer de pulmón no microcítico
DIC	Deviance information criterion
DIP	Datos individuales de los pacientes
EGFR	Receptor del factor de crecimiento epidérmico
EMA	Agencia Europea de Medicamentos
ESMO	European Society for Medical Oncology
FDA	Administración de Alimentos y Medicamentos de EEUU
GGT	Gamma glutamil transferasa
GLOBOCAN	Observatorio Global de Cáncer
GRD	Grupos Relacionados con el Diagnóstico
HR	Hazard ratio
IVA	Impuesto del valor añadido
I^2	Índice de heterogeneidad
IALT	International Adjuvant Lung Trial
IASCL	International association for the study of lung cancer
ICER	Incremental cost-effectiveness ratio
IPC	Índice de Precios de Consumo

NCNN	National Comprehensive Cancer Network
NICE	Instituto Nacional de Salud y Excelencia del Reino Unido
OMS	Organización Mundial de la Salud
PET	Tomografía por emisión de positrones
PVL	Precio de venta del laboratorio
RS	Revisión sistemática
RCEI	Ratio coste-efectividad incremental
RCUI	Ratio coste-utilidad incremental
RT	Radioterapia
SBRT	Radioterapia corporal estereotáctica
SG	Supervivencia global
SLP	Supervivencia libre de progresión
SNS	Sistema Nacional de Salud
TC	Tomografía computarizada
TKI	Inhibidores de la tirosina quinasa
TNM	Sistema de estadificación de Tumores, Nódulos y Metástasis
TRO	Tasa de respuesta objetiva
UICC	Union for International Cancer Control
VAN	Valor actualizado neto

PREÁMBULO

La presente memoria de tesis doctoral, presentada en la modalidad de compendio de artículos, tiene como objetivo principal la selección de la terapia más coste-efectiva para el Sistema Nacional de Salud que permita un empleo más eficiente de los recursos en el tratamiento de cáncer de pulmón no microcítico EGFR positivo estadio avanzado mediante la aplicación de modelos farmacoeconómicos previamente validados. Los estudios que conforman la memoria aportan información nueva y valiosa para el diseño de modelos de coste-efectividad que permitan evaluar las ganancias en salud en relación con los costes de las diferentes intervenciones sanitarias, así como para evaluar el impacto de dichas intervenciones sobre los procesos de manejo terapéutico y mejora en la calidad de vida de los pacientes.

Estas publicaciones se detallan a continuación en el orden en que aparecen en esta tesis, así como los índices de impacto de las revistas en las que han sido publicados:

Artículo 1

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Alós-Almiñana M, Cortijo J. **Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis.**

Journal of Comparative Effectiveness Research, 2019.

doi: 10.2217/cer-2019-0029

Factor de impacto: 2,04

Ranking: Q4 (20,64%; 87/109; category: Health Care Sciences & Services)

Artículo 2

Aguilar-Serra J,Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Cortijo J. **Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis.**

Journal of Comparative Effectiveness Research, 2021.

doi: 10.2217/cer-2020-0233

Factor de impacto: 2,04

Ranking: Q4 (20,64%; 87/109; category: Health Care Sciences & Services)

Artículo 3

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. **Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer**

Expert review of pharmacoeconomics & outcomes research, 2022.

doi: 10.1080/14737167.2022.1987220

Factor de impacto: 2,039

Ranking: Q4 (19,72%; 88/109; *Category: Health Care Sciences & Services); Q4 (22,16%; 69/88; Category: Health Policy & Services); Q4 (17,38%; 231/279; Category: Pharmacology & Pharmacy)*

RESUMEN

Los estudios de evaluación económica permiten evaluar conjuntamente los resultados obtenidos y los costes necesarios para su consecución, con el objetivo de derivar los recursos económicos disponibles a la financiación de aquellos tratamientos o intervenciones sanitarias que consigan mejores beneficios terapéuticos a partir de la inversión efectuada. El incremento del gasto sanitario en el Sistema Nacional de Salud español debido al progresivo envejecimiento de la población, la cronificación de las enfermedades antes mortales, la comercialización de nuevos tratamientos más eficaces y costosos, así como el incremento de la demanda de la población por el sistema sanitario, obliga a emplear métodos de evaluación económica conjunta tanto de los resultados obtenidos como de los costes generados por cada fármaco o tecnología sanitaria. El objetivo será, por tanto, derivar los recursos disponibles a la financiación de aquellos tratamientos o tecnologías sanitarias que consigan alcanzar mejores beneficios terapéuticos mediante la inversión realizada.

La tesis doctoral se presenta mediante un compendio de publicaciones que demuestran la contribución de los estudios de evaluación económica en la selección de los fármacos más coste-efectivos para el tratamiento de cáncer de pulmón no microcítico (CPNM) con mutación en el receptor del factor de crecimiento epidérmico (EGFR) estadio avanzado en el contexto del Sistema Nacional de Salud español. Concretamente, se evaluarán los siguientes aspectos:

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, et al. Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2019 Aug;8(11):853-863. doi: 10.2217/cer-2019-0029. Epub 2019 Sep 3.

- El objetivo de este estudio fue evaluar la relación coste-efectividad incremental (RCEI) de osimertinib frente a los inhibidores de la tirosina quinasa (TKI) estándar (erlotinib y gefitinib), para determinar el fármaco de elección en primera línea de tratamiento. Demostramos que osimertinib resultaba ser el fármaco más efectivo en términos de años de vida ajustados por calidad (AVAC) ganados (0,20) en comparación con los TKI estándar. Sin embargo, nuestro

estudio demostró que osimertinib no era coste-efectivo debido a que el RCEI obtenido (273.895,36 €/AVAC) era superior al umbral comúnmente aceptado en España de 24.000 €/AVAC. Además, en nuestro estudio, establecimos que los descuentos superiores al 60% en el coste de adquisición de osimertinib son cruciales para que el fármaco pueda ser considerado una alternativa coste-efectiva.

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, et al. Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2021 Mar;10(4):325-335. doi: 10.2217/cer-2020-0233. Epub 2021 Feb 26.

- Este estudio tiene como objetivo evaluar la relación coste-efectividad incremental del tratamiento en primera línea con dacomitinib en comparación con gefitinib en pacientes recién diagnosticados de CPNM avanzado EGFR-positivo en España. Este estudio demostró que dacomitinib puede ser considerado ligeramente más efectivo en comparación con gefitinib en términos de AVAC ganados (0,06). No obstante, nuestro estudio demostró que dacomitinib no era coste-efectivo en comparación con gefitinib porque el RCEI (111.048 €/AVAC) era superior al umbral comúnmente aceptado en España de 24.000 €/AVAC. Se estableció que descuentos superiores al 25% debían ser aplicados al coste de adquisición de dacomitinib para que pudiera ser considerado como un fármaco coste-efectivo.

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer. Expert Rev Pharmacoecon Outcomes Res. 2022 Jun;22(4):637-646. doi: 10.1080/14737167.2022.1987220. Epub 2021 Oct 11.

- Este estudio tiene como objetivo evaluar la relación coste-efectividad incremental de los tratamientos de primera línea como erlotinib, gefitinib, afatinib, dacomitinib y osimertinib, para los pacientes diagnosticados de CPNM avanzado con mutaciones del EGFR, en el contexto de España. Para ello se realizó un meta-análisis previo empleando el método de las fracciones

polinómicas. El estudio demostró que osimertinib era ligeramente más efectivo en términos de AVAC ganados que gefitinib (0,20), seguido de dacomitinib (0,05), afatinib (0,04) y erlotinib (0,03). Sin embargo, los resultados demostraron que con el umbral actual en España de 24.000 €/AVAC, ninguno de los TKIs resultaba coste-efectivo.

INTRODUCCIÓN

Cáncer de pulmón

Definición. Características generales

Según la Organización Mundial de la Salud (OMS), el cáncer es un grupo de enfermedades iniciadas en casi cualquier tejido y caracterizadas por un crecimiento celular incontrolable que puede invadir también órganos adyacentes o distantes durante la metástasis. En este caso, el cáncer de pulmón podría definirse como un crecimiento maligno de las células que componen los diferentes tejidos del pulmón. Se inicia en las vías respiratorias, que se ramifican a partir de la tráquea para ventilar los pulmones (bronquios), o en los pequeños sacos aéreos del pulmón (alvéolos).

Epidemiologia

En todo el mundo en 2020, según el Observatorio Mundial del Cáncer (GLOBOCAN), se diagnosticaron 2.206.771 nuevos casos de cáncer de pulmón, lo que representa el 11,6% de todos los nuevos casos de cáncer (Figura 1). Asimismo, también resultó ser la principal causa de muerte relacionada con el cáncer, con 1.796.144 muertes en 2020, el 18% de todas las muertes relacionadas con el cáncer en el mundo (Figura 2).

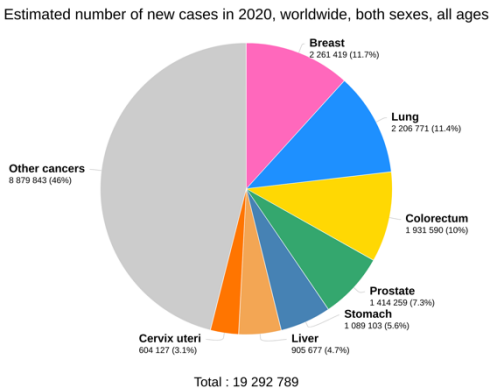

Figura 1. Incidencia de todos los cánceres 2020 (adaptada de Ferlay et al., 2019).

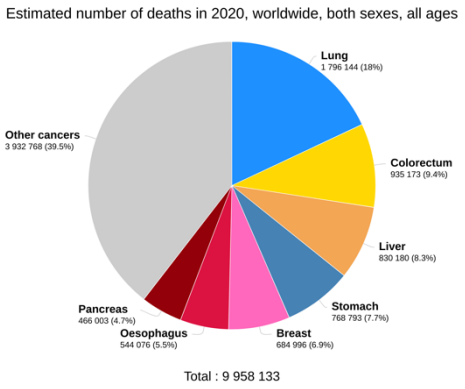

Figura 2. Mortalidad de todos los cánceres 2020 (adaptada de Ferlay et al., 2019).

Desde un punto de vista geográfico, los parámetros de incidencia del cáncer de pulmón son muy variados. Como se observa en la Figura 3, los países que presentan

una mayor tasa de incidencia se encuentran en Europa, Asia oriental y Norteamérica, mientras que los países localizados en las regiones de África central y occidental presentan unas tasas menores, quizás debido a una menor declaración de los casos. Por lo que se refiere a la tasa de mortalidad, su distribución por regiones coincide prácticamente a la observada en las tasas de incidencia (Figura 4).

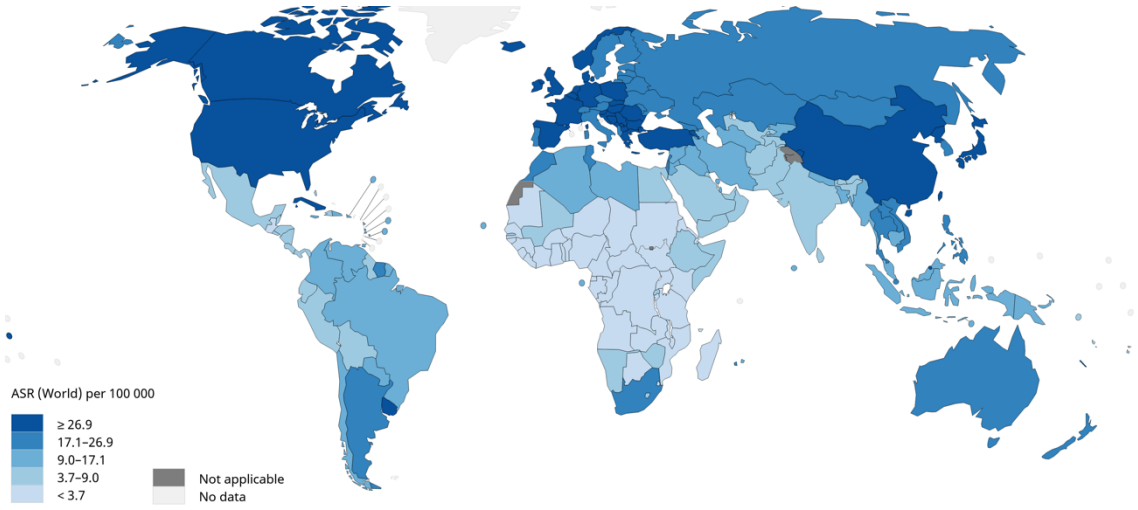

Figura 3. Tasas estimadas de incidencia estandarizadas por edad en 2020, pulmón, ambos sexos, todas las edades. Fuente: GLOBOCAN (http://gco.iarc.fr).

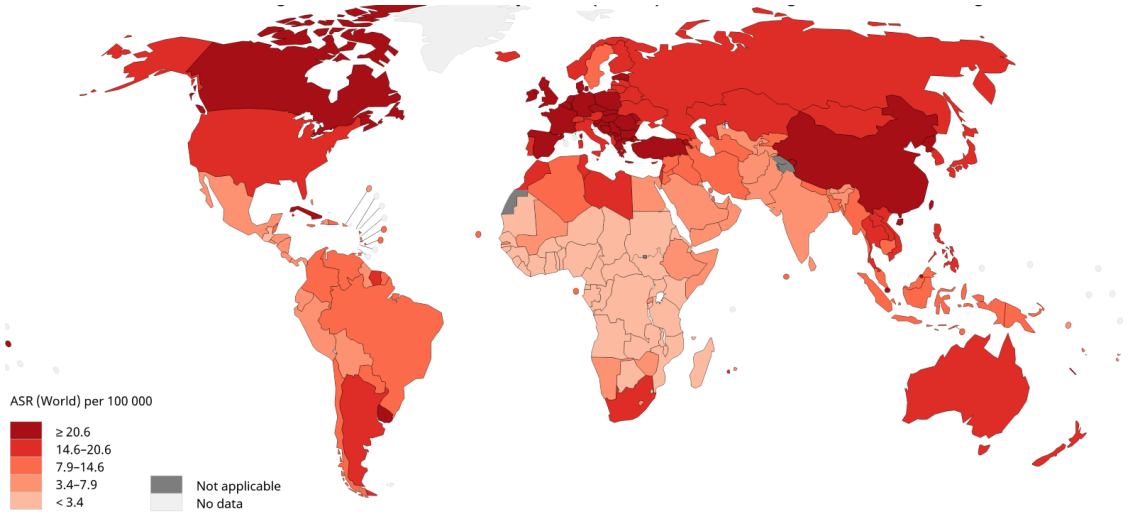

Figura 4. Tasas estimadas de mortalidad estandarizadas por edad en 2020, pulmón, ambos sexos, todas las edades. Fuente: GLOBOCAN (http://gco.iarc.fr).

En España, el cáncer de pulmón fue en 2020 el cuarto cáncer más comúnmente diagnosticado después del cáncer colorrectal, el cáncer de próstata y el cáncer de mama. Además, fue la neoplasia que produjo mayor mortalidad (Ferlay et al., 2019) (Figura 5).

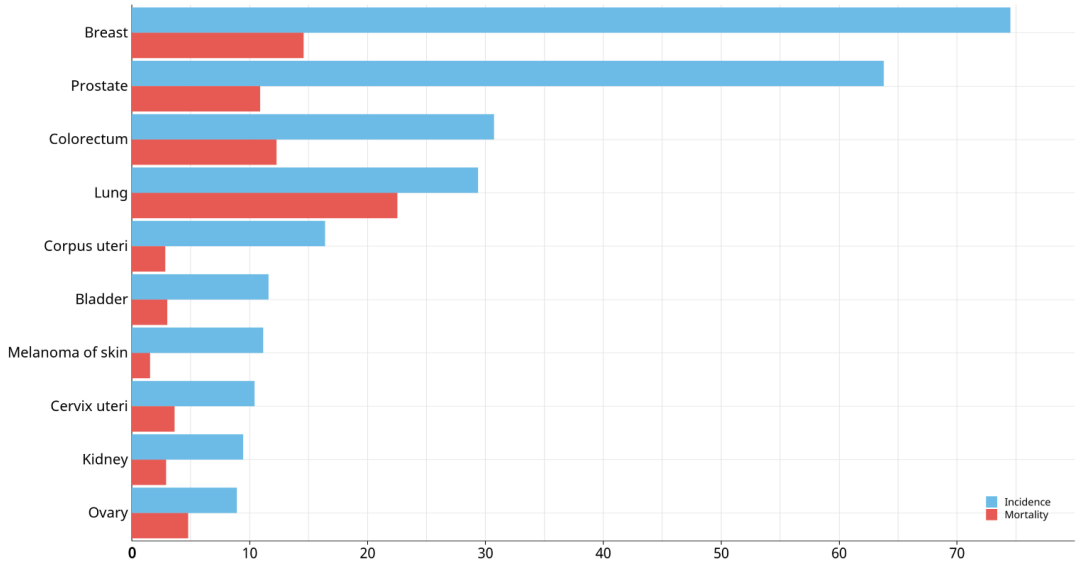

Figura 5. Tasas estimadas de incidencia y mortalidad estandarizadas por edad en 2020, España, ambos sexos, todas las edades (adaptada de Ferlay et al., 2019).

Factores predisponentes y factores de riesgo

- **Tabaco:** es el principal responsable del 80-90% de la incidencia de cáncer de pulmón, con un riesgo 20-30 veces mayor en los fumadores que en los no-fumadores (Alberg & Samet, 2003). Desde los años 50, gracias a diferentes estudios epidemiológicos, se demostró el efecto cancerígeno del humo del tabaco sobre los pulmones (Wynder, 1997). En los últimos 40 años, se ha producido un viraje en las características histológicas, y el adenocarcinoma ha desplazado al carcinoma de células escamosas para constituir el subtipo más común. Se estima que este cambio se debe a la incorporación de los cigarrillos con filtro bajo en alquitrán lo que ha aumentado la exposición del tejido pulmonar periférico a los carcinógenos (Alberg & Samet, 2003). El hábito del tabaquismo influye directamente en la incidencia acumulada de cáncer de pulmón, siendo del 31,7% en hombres y del 15,3% en mujeres fumadores/as, respecto al 0,9% en hombres y 0,5% en mujeres no fumadores/as (Samet et al., 1988). La

duración del hábito tabáquico es un indicador de riesgo más determinante que la cantidad de cigarros que se consume. Esto quiere decir que, un incremento de 3 veces el número de cigarros consumidos se relaciona únicamente con un aumento de 3 veces el riesgo de cáncer de pulmón, en tanto que un incremento de 3 veces en la duración del hábito tabáquico resulta en un aumento de 100 veces el riesgo de desarrollar cáncer de pulmón (de la Cruz et al., 2011).

- **Exposición al humo de otros fumadores:** el tabaquismo pasivo también puede contribuir a aumentar el riesgo de cáncer de pulmón. Diferentes carcinógenos como el benceno, benzo[a]pireno o N-nitrosaminas han sido identificados en el humo del tabaco (de la Cruz et al., 2011). Los no-fumadores que habían estado expuestos al humo del tabaco presentaron un exceso de riesgo de cáncer de pulmón del 24% (IC del 95%: 13%-36%, $p < 0,001$), según un análisis de 37 estudios epidemiológicos (Hackshaw et al., 1997). Además, se estimó que el número de muertes relacionadas con la exposición a carcinógenos en el humo del tabaco era comparable a las producidas por la exposición a radón o amianto (de la Cruz et al., 2011).

- Radón: es un gas radiactivo producido por la descomposición del uranio que se encuentra de forma natural en las rocas, acumulándose en zonas cerradas, como casas o minas, pudiendo llegar incluso a disolverse en las aguas subterráneas. Si bien es químicamente inerte, el radón se descompone en sustancias activas capaces de unirse a las partículas del aire, a través del cual son inhaladas y se adhieren al epitelio pulmonar (Tirmarche et al., 2010). Esta descomposición genera la emisión de radiaciones alfa las cuales dañan directamente el ADN del epitelio respiratorio (Darby et al., 2001). Diferentes estudios epidemiológicos tanto en trabajadores mineros, así como en entornos residenciales, han demostrado una relación directa entre la exposición al radón y el desarrollo de cáncer de pulmón (Laurier et al., 2020; Zhang et al., 2012).

Al margen del tabaquismo, otros factores de riesgo que pueden conducir a la carcinogénesis pulmonar son la exposición a determinadas sustancias como el amianto, el asbesto y la sílice, y a metales como el arsénico, el cromo y el cadmio. Además, también influyen en el desarrollo de tumores a nivel pulmonar los determinantes dietéticos, las radiaciones ionizantes, los factores genéticos y la

contaminación ambiental (Loomis et al., 2018; Secretan et al., 2009). Una lista de los principales factores de riesgo la podemos encontrar en la tabla 1.

Tabla 1. Causas de cáncer de pulmón, estimaciones en riesgo relativo (Kloecker et al., 2020). RR: riesgo relativo

Fumadores	**78% (mujeres) y 92% (hombres) (RR 40)**
Radón	3%-15% (RR 2-10)
Fumadores pasivos	2%-3% (RR 1.7)
Asbestos	1%-2% (RR 1.96)
Dieta pobre en vitaminas	1%-2% (RR 1.3)
Polución del aire	1%-2% (RR 1.3-2.3)
Silicosis	0.5%-1% (RR 1.45)
Factores genéticos	1%-3% (RR 1.3-4.0)

Diagnóstico y estadificación

Diagnóstico

Desde un punto de vista clínico, la mayoría de los casos de cáncer de pulmón se diagnostican en estadios avanzados, puesto que los estadios iniciales de la carcinogénesis suelen ser asintomáticos, además de no existir programas de cribado estatales que puedan extenderse a los pacientes sanos, pero con riesgo de padecer la enfermedad. Como consecuencia, la mayoría de los pacientes con cáncer de pulmón son diagnosticados en un estadio prácticamente irresecable e incluso, en un 20% de ellos, con enfermedad localmente avanzada (Osmani et al., 2018).

Los síntomas pueden ser debidos a los efectos locales del tumor, a la diseminación regional o distante, o a los efectos distantes no relacionados con la metástasis (síndromes paraneoplásicos). Muchos síntomas, a pesar de estar relacionados con el cáncer de pulmón, son en su mayoría inespecíficos. A continuación, se detallan algunos de los síntomas más habituales:

- **Tos:** síntoma más habitual y se encuentra en el 60-75% de todos los pacientes con cáncer de pulmón (Bradley et al., 2019; Kocher et al., 2015).

- Disnea: puede ser debida a un embolismo pulmonar, efusión pleural o neumonía. La incidencia es del 30-50% (Bradley et al., 2019).

- Dolor torácico: suele producirse en la misma región del pecho donde se localiza el tumor primario. Presenta una incidencia del 25-50% (Bradley et al., 2019).

- Hemoptisis: provocado habitualmente por una bronquitis subyacente, la incidencia es del 25-50% (Bradley et al., 2019).

- Ronquera: debido a un tumor que afecta al nervio laríngeo. Presenta una incidencia del 10% (Bradley et al., 2019).

- Pérdida de peso: presenta una incidencia del 30-40% (Bradley et al., 2019).

Si en base a estos síntomas se sospecha de cáncer de pulmón, deben realizarse en primer lugar pruebas radiológicas como la tomografía computarizada (TC) de tórax y de abdomen superior. La adición de la tomografía por emisión de positrones (PET) mejoró su precisión, permitiendo la detección de metástasis localizada en los ganglios linfáticos y la determinación de fibrosis pulmonar (Latimer & Mott, 2015).

Tras la obtención de las imágenes radiológicas, la confirmación del diagnóstico se realiza mediante una biopsia citológica o histológica, que permite, en primer lugar, asegurar que se trata de una lesión cancerígena y, en segundo lugar, diferenciar entre cáncer de pulmón de células pequeñas o cáncer de pulmón microcítico (CPM) y cáncer de pulmón de células no pequeñas o cáncer de pulmón no microcítico (CPNM) (Latimer & Mott, 2015).

En el caso de CPNM, la realización de test para determinar biomarcadores permite identificar si el cáncer de pulmón podría responder a terapias dirigidas o personalizadas que actúan contra estos biomarcadores. Si no existen estos biomarcadores la terapia personalizada no es efectiva. Los principales biomarcadores de CPNM detectados son:

- EGFR (receptor del factor de crecimiento epidérmico):
    - Deleciones del exón 19 o las mutaciones del exón 21 L858R.
    - Inserciones en el exón 20 del EGFR y la mutación T790M.
- ALK (gen de la cinasa del linfoma anaplásico).

- ROS1 (ROS proto-oncogen 1).
- BRAF gen.
- PD-L1 (ligando de muerte programada 1).

Estadificación

Una vez realizadas las pruebas radiológicas se obtiene la información necesaria para determinar si, a parte del pulmón, hay otros órganos afectados. Investigar hasta donde se extiende la carcinogénesis es fundamental para establecer el estadio de la enfermedad. El estadio tiene un papel pronóstico y terapéutico, ya que en función de este (sumado a otros factores) se decide el tratamiento más adecuado.
La nomenclatura estándar de la *American Joint Commission of Cancer* (AJCC) y de la *Union for International Cancer Control* (UICC), sigue siendo el sistema de estadificación de tumores, ganglios y metástasis (TNM) que mayor aceptación internacional ha recibido, y es empleado actualmente para definir con precisión la extensión anatómica del cáncer de pulmón en el ser humano en el momento del diagnóstico. La octava edición del Manual de Estadificación del Cáncer fue revisada por la *International Association for the Study of Lung Cancer* (IASLC) y publicada en enero de 2017, siendo la que actualmente se emplea (Detterbeck et al., 2017).

Este sistema se basa en tres indicadores: T, correspondiente al tamaño del tumor primario (Tx, T0-T4); N, basado en la presencia de ganglios linfáticos locales y regionales afectados (Nx, N0-N3); y M, que define la presencia de metástasis más allá de los ganglios linfáticos regionales (M0-M1c) (Detterbeck et al., 2017). Las tablas 2 y 3 muestran la 8ª edición de la clasificación de los estadios del cáncer de pulmón.

Tabla 2. Estadificación TNM del cáncer de pulmón, 8ª edición. Adaptado de "The IASLC Lung Cancer Staging Project: Propuestas para la revisión de las agrupaciones de estadios TNM en la próxima (octava) edición de la clasificación TNM para el cáncer de pulmón" (Detterbeck et al., 2017).

Tumor Primario	
Tx	El tumor primario no puede ser evaluado, o el tumor se confirma por la presencia de células malignas en el esputo o en los lavados bronquiales, pero no se visualiza mediante imágenes o broncoscopia
T0	No hay evidencia de tumor primario
Tis	Carcinoma *in situ*
T1	Tumor de 3 cm o menos en su mayor dimensión, rodeado de pulmón o pleura visceral, sin evidencia broncoscópica de invasión proximal que el bronquio lobar (es decir, no en el bronquio principal)
T1mi	Adenocarcinoma mínimamente invasivo
T1a	Tumor de 1 cm o menos en su mayor dimensión
T1b	Tumor de más de 1 cm pero no más de 2 cm en su mayor dimensión
T1c	Tumor de más de 2 cm pero no más de 3 cm en su mayor dimensión
T2	Tumor de más de 3 cm pero no más de 5 cm; o tumor con cualquiera de las siguientes características: - Involucra el bronquio principal independientemente de la distancia a la carina, pero sin afectar a la carina. - Invade la pleura visceral. - Se asocia con atelectasia o neumonitis obstructiva que se extiende a la región hiliar que afecta a una parte o a la totalidad del pulmón.
T2a	Tumor de más de 3 cm pero no más de 4 cm en su mayor dimensión.
T2b	Tumor de más de 4 cm pero no más de 5 cm en su mayor dimensión.
T3	Tumor de más de 5 cm pero no más de 7 cm en su mayor dimensión o que invade directamente cualquiera de los siguientes: pleura parietal, pared torácica (incluidos los tumores del surco superior) nervio frénico, pericardio parietal; o nódulo(s) tumoral(es) separado(s) en el mismo lóbulo que el primario.
T4	Tumor de más de 7 cm o de cualquier tamaño que invada alguno de los siguientes elementos: diafragma, mediastino, corazón, grandes vasos, tráquea, nervio laríngeo recurrente, esófago, cuerpo vertebral, carina; nódulo(s)

	tumoral(es) separado(s) en un lóbulo ipsilateral diferente al del primario.
Ganglios linfáticos regionales (N)	
Nx	Los ganglios linfáticos regionales no pueden ser evaluados
N0	No hay metástasis en los ganglios linfáticos regionales
N1	Metástasis en los ganglios linfáticos peribronquiales ipsilaterales y/o hiliares ipsilaterales y en los ganglios intrapulmonares, incluida la afectación por extensión directa.
N2	Metástasis en los ganglios linfáticos mediastínicos y/o subcarinales ipsilaterales.
N3	Metástasis en el mediastino contralateral, hiliar contralateral, escaleno ipsilateral o contralateral, o ganglio(s) linfático(s) supraclavicular(es).
Metástasis a distancia (M)	
M0	No hay metástasis a distancia.
M1	Metástasis a distancia.
M1a	Nódulo(s) tumoral(es) separado(s) en un lóbulo contralateral; tumor con nódulos pleurales o pericárdicos o derrame pleural o pericárdico maligno.
M1b	Metástasis extratorácica única en un solo órgano.
M1c	Metástasis extratorácicas múltiples en uno o varios órganos.

Tabla 3. Estadificación TNM del cáncer de pulmón en función de su evolución, 8ª edición. Adaptado de *"The IASLC Lung Cancer Staging Project: Propuestas para la revisión de las agrupaciones de estadios TNM en la próxima (octava) edición de la clasificación TNM para el cáncer de pulmón"* (Detterbeck et al., 2017).

Carcinoma oculto	TX	N0	M0
Estadio 0	Tis	N0	M0
Estadio IA	T1	N0	M0
Estadio IA1	T1mi T1a	N0 N0	M0 M0

Estadio IA2	T1b	N0	M0
Estadio IA3	T1c	N0	M0
Estadio IB	T2a	N0	M0
Estadio IIA	T2b	N0	M0
Estadio IIB	T1a-c T2a,b T3	N1 N0	M0 M0
Estadio IIIA	T1a-c T2a,b T3 T4	N2 N1 N0, N1	M0 M0 M0
Estadio IIIB	T1 a-c T2a,b T3,T4	N3 N2	M0 M0
Estadio IIIC	T3, T4	N3	M0
Estadio IV	Cualquier T	Cualquier N	M1
Estadio IVA	Cualquier T	Cualquier N	M1a, M1b
Estadio IVB	Cualquier T	Cualquier N	M1c

Clasificación histopatológica

La clasificación histopatológica del cáncer de pulmón está basada en los criterios establecido por la OMS, cuya cuarta edición fue publicada en 2015 (Travis et al., 2015). Según esta clasificación, el cáncer de pulmón se divide en dos tipos principales: cáncer de pulmón de células pequeñas (CPCP) o CPM y cáncer de pulmón de células no pequeñas (CPCNP) o CPNM (Tabla 4).

Tabla 4. Clasificación histológica de cáncer de pulmón. Adaptado de *"Abeloff's Clinical oncology"* (Elaine M. Zeman, 2014).

Tipo	Porcentaje de todos los cánceres de pulmón	Presentación clásica
Cáncer de pulmón no microcítico • Adenocarcinoma • Carcinoma de células escamosas • Carcinoma de células grandes	 40 25 10	Periférico
Cáncer de pulmón de células pequeñas	15	Central, linfoadenopatía masiva, síndromes paraneoplásicos
Otros tipos poco comunes (como carcinoides)	5	Varias

Cáncer de pulmón de células no pequeñas (CPCNP) o cáncer de pulmón no microcítico (CPNM)

El CPNM supone aproximadamente el 85% de todos los casos de cáncer de pulmón. Se subdivide en 3 principales tipos: adenocarcinomas, carcinoma de células escamosas y el carcinoma (indiferenciado) de células grandes del pulmón (Figura 6).

- **Adenocarcinoma**

El adenocarcinoma de pulmón es el tipo de CPNM más común y supone aproximadamente el 40% de todos los cánceres de pulmón (Travis et al., 2015). Estos tumores tienen un origen epitelial y presentan una diferenciación glandular y producción mucinosa (Figura 6C). El 75% de los adenocarcinomas de pulmón presentan marcadores inmunohistoquímicos como TTF-1, napsina A y KRT7 los cuales permiten su diagnóstico diferencial. La clasificación de la OMS de cáncer de pulmón

también considera los estadios iniciales del cáncer de pulmón como adenocarcinoma in situ (lesión pre invasiva con patrón lepídico y diámetro de menos de 3 cm), adenocarcinoma mínimamente invasivo (adenocarcinoma con diámetro mayor de 3 cm) o adenocarcinoma invasivo (Travis et al., 2015). Los factores de exclusión incluyen un tamaño de invasión superior a 5 mm, a pesar de que el tamaño del tumor y el tamaño de la invasión se ajustasen a la definición de adenocarcinoma mínimamente invasivo, y existiese invasión linfovascular, invasión perineural o necrosis tumoral.

- **Carcinoma de células escamosas**

El carcinoma de células escamosas supone del 25% al 30% de todos los casos cáncer de pulmón (Figura 6A). Se desarrolla habitualmente en células localizadas en el epitelio de las vías respiratorias y tiene una mayor relación con los antecedentes de tabaquismo. Suelen estar presentes marcadores inmunohistoquímicos como p40, desmogleína-3, CK5 y CK6 (Takamochi et al., 2016).

- **Carcinoma de células grandes**

Supone del 5% al 10% de todos los casos de cáncer de pulmón y habitualmente se diagnostica por exclusión (Figura 6B). La incidencia de este tipo de carcinoma se considera cada vez menor debido a la nueva subtipificación del carcinoma de pulmón, la cual está permitiendo una mejor clasificación de los carcinomas de células escamosas y los adenocarcinomas peor diferenciados (Girard et al., 2009). Histológicamente, se caracterizan por ser poco diferenciados y estar compuestos por células grandes con abundante citoplasma y grandes nucléolos.

Cáncer de pulmón de células pequeñas (CPCP) o cáncer de pulmón microcítico

El CPCP supone alrededor del 15% de todos los casos de cáncer de pulmón diagnosticados. La mayoría de los pacientes diagnosticados con CPCP son o han sido fumadores (Gazdar et al., 2017). Se caracteriza por ser un tumor epitelial maligno de rápido crecimiento originado a partir de precursores de células neuroendocrinas y localizado alrededor de la parte proximal del árbol bronquial. Morfológicamente, se caracteriza por presentar unos núcleos celulares muy hipercromáticos con forma

elíptica o fusiforme que demuestran un moldeado nuclear y un citoplasma muy escaso (Figura 6D). Su evolución es muy agresiva, y en el momento de la presentación suele esperarse una extensa metástasis, lo que se traduce en una supervivencia a los 5 años del 7-10% (Gazdar et al., 2017).

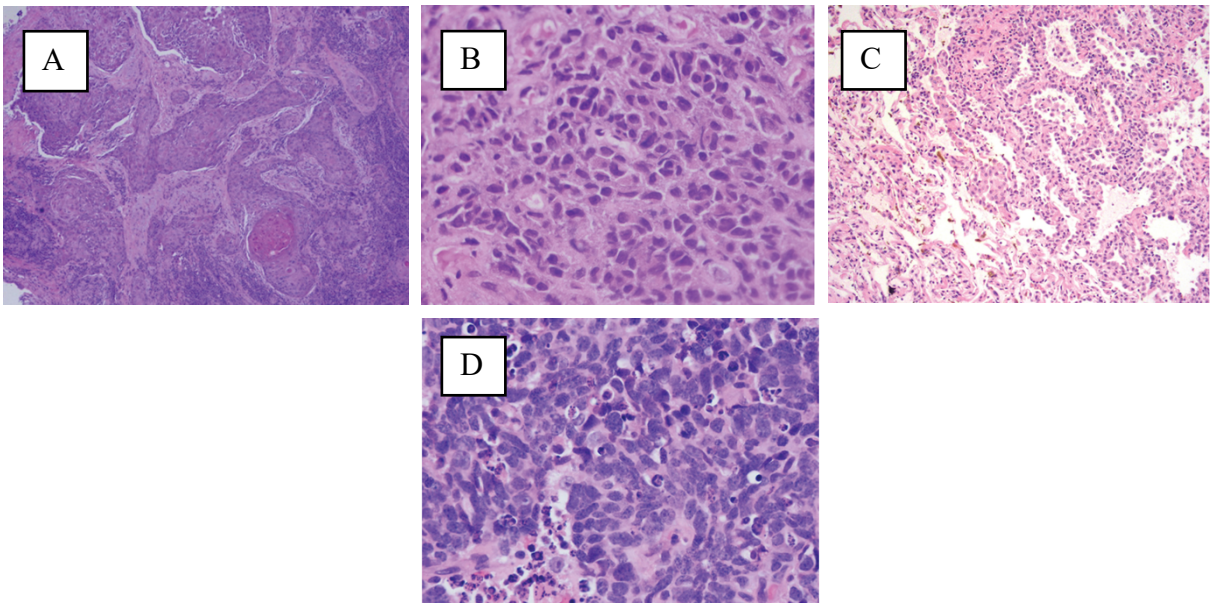

Figura 6. Clasificación histopatológica de cáncer de pulmón. A) Carcinoma de células escamosas, B) carcinoma de células grandes, C) adenocarcinoma y D) cáncer de pulmón de células pequeñas. Adaptado de *"Lung Cancer: Standards of care" (1st Edition)* (adaptada de Kloecker et al., 2020).

Tratamiento de CPNM

El tratamiento de CPNM es específico para cada estadio. A medida que se confirma la estadificación de la patología, los pacientes diagnosticados en estadio I o II deben ser considerados para la resección quirúrgica. En aquellos pacientes en estadios iniciales, pero médicamente inoperables, la radioterapia convencional (RT) ha resultado ser el tratamiento tradicionalmente de elección (Wisnivesky et al., 2005). Sin embargo, las nuevas terapias radiológicas como la radioterapia corporal estereotáctica (SBRT) han demostrado una mejora tanto del control local como de la supervivencia global (SG), estimándose una mejora de la SG a 5 años del 19% al 42% al compararse con la RT (Grutters et al., 2010; Onishi et al., 2007).

Cirugia

La resección quirúrgica de un solo lóbulo, conocida como lobectomía, ha sido ampliamente aceptada como tratamiento de elección en CPNM en fase inicial, siempre y cuando los pacientes sean capaces de tolerar el procedimiento (Howington et al., 2013). Muchos de estos pacientes tienen diversos factores de riesgo como un historial bastante extenso de tabaquismo, lo cual genera diversas comorbilidades médicas pulmonares, que descartan su cirugía. Los factores que determinan la operabilidad del tumor están basados en determinantes tales como la edad avanzada, factores de riesgo cardiovasculares o pulmonares, así como otras comorbilidades coexistentes. En estos casos, sus opciones son una cirugía menos extensa o un tratamiento no quirúrgico basado en radioterapia, citado anteriormente.

Quimioterapia adyuvante

A pesar de la resección completa, muchos de estos pacientes recaen o fallecen. Es por ello que, para eliminar cualquier resto tumoral e incrementar la supervivencia global de estos pacientes, se instauran tratamientos adyuvantes de quimioterapia y/o radioterapia. El tratamiento adyuvante consiste en regímenes combinados a base de cisplatino y está indicado en pacientes con enfermedad en estadio II y IIIA después de la resección quirúrgica. En el estudio llevado a cabo por la International Adjuvant Lung Trial (IALT), 1.867 pacientes en estadio I a IIIA de la enfermedad después de la resección, fueron asignados aleatoriamente a un grupo de control o a un grupo de tratamiento con un régimen de quimioterapia adyuvante basado en un doblete de cisplatino con vinorelbina, etoposido, vinblastina o vindesina. El estudio mostró una mejora significativa en la mediana de supervivencia, la supervivencia libre de progresión (SLP), la supervivencia global a 5 años y la SLP a 5 años con un valor de hazard ratio (HR) de 0,86 para la supervivencia a favor del grupo de pacientes tratado con quimioterapia (Arriagada et al., 2009).

Terapia dirigida: inhibidores de la tirosina quinasa (TKI)

En esta Tesis, nos hemos centrado en un tipo de CPNM caracterizado por la presencia de mutaciones somáticas en el gen que codifica el EGFR. Varios factores demográficos y patológicos están asociados a la prevalencia de la mutación del EGFR. Así pues, la mutación EGFR se diagnostica habitualmente entre los pacientes con adenocarcinoma, los que nunca han fumado y los de etnia asiática oriental. La prevalencia global de las

mutaciones del EGFR entre los pacientes asiáticos es aproximadamente del 30%, entre los pacientes con adenocarcinoma del 47% y entre los pacientes que nunca han fumado del 56%. Sin embargo, la prevalencia media de las mutaciones EGFR entre los pacientes caucásicos es de aproximadamente el 7%, entre los pacientes con adenocarcinoma el 13% y el 35% entre los que nunca han fumado (Sekine et al., 2008). En España, se detectaron mutaciones del EGFR en el 11,6% de los pacientes con CPNM, de los cuales el 17,4% presentaba mutación L858R en el exón 21 y el 82,6% deleciones en el exón 19 (Esteban et al., 2015).

Las guías clínicas actuales, como la National Comprehensive Cancer Network (National Comprehensive Cancer Network (NCCN), 2022) y la European Society for Medical Oncology (ESMO) (Planchard el al., 2018), recomiendan realizar pruebas de detección de mutaciones EGFR en todos los pacientes con CPNM no escamoso avanzado antes de iniciar el tratamiento de primera línea. Esta recomendación se basa en la superioridad que han demostrado los fármacos TKI en pacientes con CPNM en estadio IIIB/IV con mutaciones EGFR, en comparación con quimioterapia (Chen et al., 2013; Mitsudomi et al., 2010; Mok et al., 2017; Rosell et al., 2012; Wu et al., 2014).

Los fármacos TKI se dividen en tres generaciones:

- **Primera generación:** erlotinib y gefitinib.
- **Segunda generación:** afatinib y dacomitinib.
- **Tercera generación:** osimertinib.

Los receptores con actividad tirosina quinasa presentan la estructura básica que ilustra la Figura 7 e incorporan un grupo activo con actividad tirosina quinasa en la región intracelular.

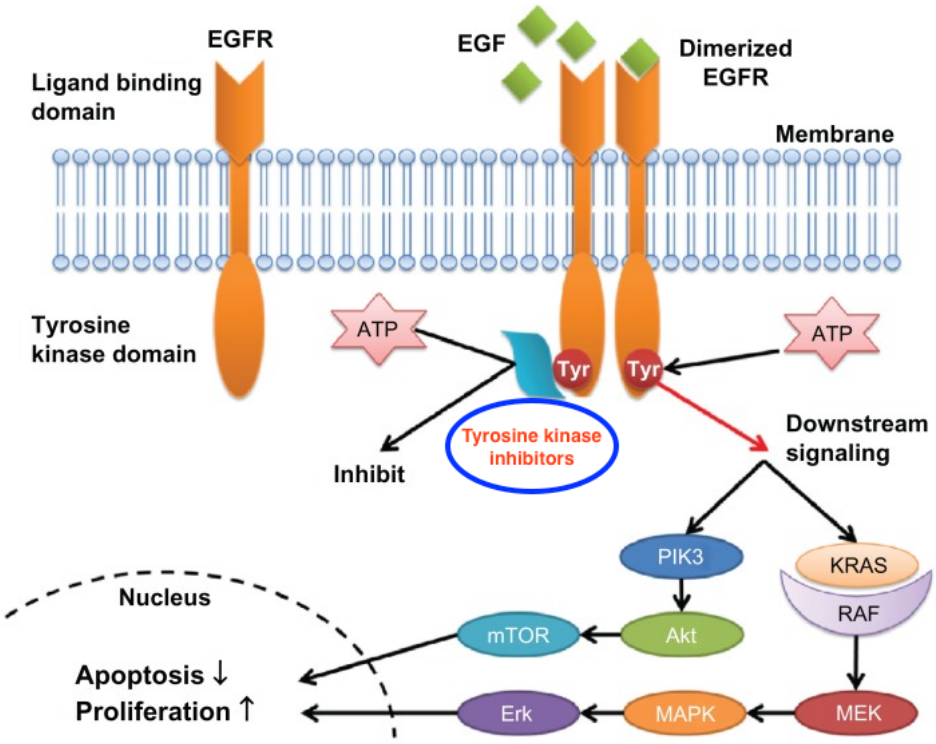

Figura 7. Mecanismo de acción de los fármacos Inhibidores de la tirosina quinasa.

- **Primera generación: erlotinib y gefitinib**

El mecanismo de acción de los TKIs de primera generación consiste en inhibir la fosforilación intracelular del EGFR, mediante el bloqueo reversible del sitio de unión del ATP (ATP-binding sites) de la tirosina quinasa localizada en dicho receptor.

- **Erlotinib**

Erlotinib es un EGFR-TKI reversible administrado por vía oral, el cual recibió la aprobación de la Administración de Alimentos y Medicamentos de los Estados Unidos (FDA, por sus siglas en inglés) como tratamiento de primera línea para pacientes con mutación del EGFR en 2013.

En el ensayo EURTAC, se aleatorizaron 173 pacientes con CPNM EGFR+ en grupos de tratamiento con erlotinib vs quimioterapia (Rosell et al., 2012). La mediana de la SLP fue de 9,7 meses en el grupo de erlotinib comparado con 5,2 meses en el grupo tratado con quimioterapia (HR 0-37, IC 95% 0,25-0,54; p < 0-0001). Por lo que se refiere a la SG, los valores fueron de 22,9 meses en el grupo de erlotinib en

comparación con los 18,8 meses de quimioterapia, comprobándose que no existían diferencias estadísticamente significativas entre ambos subgrupos de tratamiento (HR 0,80; p=0,42). Otro estudio aleatorizado de fase 3 (OPTIMAL) llevado a cabo en China también confirmó la superioridad de erlotinib respecto a la quimioterapia de primera línea en pacientes con CPNM con mutación del EGFR (13,1 frente a 4,6 meses; HR 0,16; IC del 95% 0,10-0,26; p < 0-0001) (Zhou et al., 2011).

La dosis de tratamiento son 150 mg/día. Los principales efectos adversos notificados son diarrea, falta de apetito, erupción cutánea, astenia, tos e incremento de las transaminasas alanina aminotransferasa (ALT) y gamma glutamil transpeptidasa (GGT).

- **Gefitinib**

En 2015, gefitinib fue aprobado por la FDA como tratamiento de primera línea para pacientes con CPNM metastásico con mutaciones activadoras del EGFR (Douillard et al., 2014). El estudio IPASS (Iressa Pan-Asia Study) fue el primer ensayo clínico aleatorizado que comparó un fármaco TKI con quimioterapia habitual en el tratamiento de primera línea del CPNM avanzado con adenocarcinoma (Fukuoka et al., 2011). Los resultados finales obtenidos demostraron un incremento en la SLP en el brazo de gefitinib respecto a la quimioterapia. Sin embargo, la SG no presentaba diferencias al comparar la población general con los pacientes con mutación EGFR positiva [18,8 meses vs 17,4 meses; HR 0,90; IC del 95%, 0,79 a 1,02; p < 0,109]. Curiosamente, el beneficio de la SLP sólo existió en el subgrupo con mutación EGFR positiva (mediana de 9,5 frente a 6,3 meses, HR 0,48 [0,36-0,64], p < 0,001) y no en el subgrupo con mutación EGFR negativa (mediana de 1,5 vs 5,5 meses, HR 2,85 [2,05-3,98], p < 0,001). Los resultados de los ensayos First-SIGNAL, NEJ002 y WJTOG3405 (Han et al., 2012; Inoue et al., 2013; Mitsudomi et al., 2010) fueron similares a los de IPASS en pacientes con CPNM EGFR+ mediante la comparación de gefitinib con la quimioterapia doble como tratamiento de primera línea.

La dosis de tratamiento son 250 mg/día. Erupción cutánea, diarrea y disfunción hepática fueron los efectos adversos más comunes notificados con gefitinib.

- **Segunda generación: afatinib y dacomitinib**

Los inhibidores de segunda generación, afatinib y dacomitinib, son inhibidores irreversibles que se unen covalentemente al EGFR.

- **Afatinib**

Afatinib es un derivado de la anilina-quinazolina con un grupo reactivo de acrilamida que puede modificar residuos de cisteína conservados por adición de Michael dentro de los dominios catalíticos del EGFR, HER2 y ErbB-4. Debido a que la unión covalente irreversible puede inhibir la actividad de la quinasa hasta la síntesis de nuevos receptores, el tiempo de acción de afatinib puede ser más largo que el de los TKIs de primera generación (erlotinib y gefitinib).

Afatinib fue aprobado por la Agencia Europea del Medicamento (EMA) para su uso como primera línea de tratamiento en septiembre de 2013. Los ensayos LUX-Lung 3 y LUX-Lung 6 compararon la eficacia de afatinib frente a pemetrexed más cisplatino (LUX-Lung 3) (Sequist et al., 2013) o gemcitabina más cisplatino (LUX-Lung 6) (Wu et al., 2014) y demostraron su superioridad en cuanto a SLP en comparación con la quimioterapia. El análisis conjunto de LUX-Lung 3 y LUX-Lung 6 (Yang et al., 2015) se realizó para evaluar el efecto de afatinib en la SG de los pacientes con adenocarcinoma de pulmón y mutación del EGFR. En el conjunto de la población, no hubo beneficio de supervivencia con afatinib en comparación con la quimioterapia basada en platino, pero los pacientes con deleción 19 del EGFR obtuvieron un beneficio significativo de la SG en comparación con los portadores de mutaciones del exón 21 L858R. En comparación con los EGFR-TKIs de primera generación, afatinib es el único que presenta un beneficio en la SG en pacientes que albergan la deleción del exón 19 en lugar de las mutaciones L858R respecto a la quimioterapia. Por último, Lux-Lung 7 fue el primer ensayo clínico que comparó de forma directa los EGFR-TKI de primera y segunda generación. Afatinib mejoró significativamente la SLP (11,0 vs 10,9 meses, HR 0,73 (0,57-0,95), p=0,017). Sin embargo, no fue significativamente diferente entre el grupo de afatinib y el de gefitinib (27,9 frente a 24,5 meses, HR 0,86 (0,66-1,12), p=0,2580). Ahora bien, en la práctica clínica diaria el beneficio de 0,1 meses de SLP no influiría demasiado, pero este resultado podría indicar que afatinib tiene un efecto inhibidor más amplio y duradero capaz de prolongar el tiempo de respuesta en comparación con gefitinib.

La dosis de tratamiento son 40 mg/día. Los efectos adversos más comunes relacionados con el tratamiento son diarrea, erupción cutánea, estomatitis y paroniquia.

- **Dacomitinib**

Dacomitinib es un inhibidor pan-ErbB, que inhibe irreversiblemente el EGFR mediante la formación de enlaces covalentes. Esta inhibición irreversible también afecta a otros receptores de la familia ErbB como ErbB2 y ErbB4 (Engelman et al., 2007). Dacomitinib ha sido evaluado en varios ensayos clínicos y, en general, no ha podido demostrar una mayor eficacia clínica significativa que los TKIs de primera generación, además de presentar un mayor número de efectos adversos (Ellis et al., 2014; Ramalingam et al., 2014). En el ensayo ARCHER 1009, se comprobó que dacomitinib tenía una eficacia similar a la de erlotinib como tratamiento de segunda línea en pacientes CPNM EGFR+ (7,44 meses para dacomitinib y erlotinib, HR 0,46 (0,18–1,18), p=0,098) (Ramalingam et al., 2014). En el ensayo clínico ARCHER 1050, se demostró un incremento en la SLP de dacomitinib frente a gefitinib en primera línea de tratamiento en pacientes CPNM EGFR+ (14,7 meses vs 9,2 meses, HR 0,59 (0,47–0,74), p<0,001) (Wu et al., 2017a). Además, los resultados maduros del análisis de la SG en los pacientes del ensayo ARCHER 1050 tras un seguimiento de 30 meses, demostró una mejora significativa de la SG en el grupo de dacomitinib en comparación con gefitinib (HR 0,760, (0,582-0,993), p= 0,0438), con una mediana de la SG de 34,1 meses con dacomitinib y 26,8 meses con gefitinib (Mok et al., 2018). Cabe destacar que este estudio demostró por primera vez una mejora significativa de la SG, comparando un EGFR-TKI de segunda generación con un EGFR-TKI de primera generación.

La dosis de tratamiento de dacomitinib es 45 mg/día. Sin embargo, dacomitinib presenta una mayor probabilidad de desarrollar efectos adversos severos grado 3 tales como dermatitis acneiforme, erupción cutánea, paroniquia y diarrea. Esto se produce porque su modo de unión es irreversible (como fármaco de segunda generación), por lo que tienen un efecto más potente y duradero en el organismo. Por ello, la gestión de dicha toxicidad puede realizarse mediante la reducción de la dosis y la automedicación estándar (Corral et al., 2019).

- **Tercera generación: osimertinib**

La resistencia adquirida a los TKIs de primera y segunda generación se ha asociado al desarrollo de una segunda mutación del EGFR, la mutación puntual p.Thr790Met (T790M) en el exón 20 (también en el dominio quinasa), detectable en el 50-63% de las muestras de biopsia de tejido pulmonar tomadas tras la progresión de la enfermedad (Oxnard et al., 2011; Pao et al., 2005; Yu et al., 2013). Los TKIs de primera generación tienen la desventaja de ser inhibidores reversibles y son ineficaces contra la mutación T790M; mientras que la mutación T790M sólo afecta ligeramente a la unión del gefitinib, éste es superado por el ATP, que presenta una mayor afinidad al sitio de unión del EGFR (Cross et al., 2014; Yun et al., 2008) (Figura 8). Por otro lado, los TKIs de segunda generación tienen una potencia suficiente contra las mutaciones duales L858R/T790M, sin embargo, no puede administrarse a los pacientes en las concentraciones necesarias para superar la resistencia T790M, como se ha visto in vitro (Cross et al., 2014; Li et al., 2008).

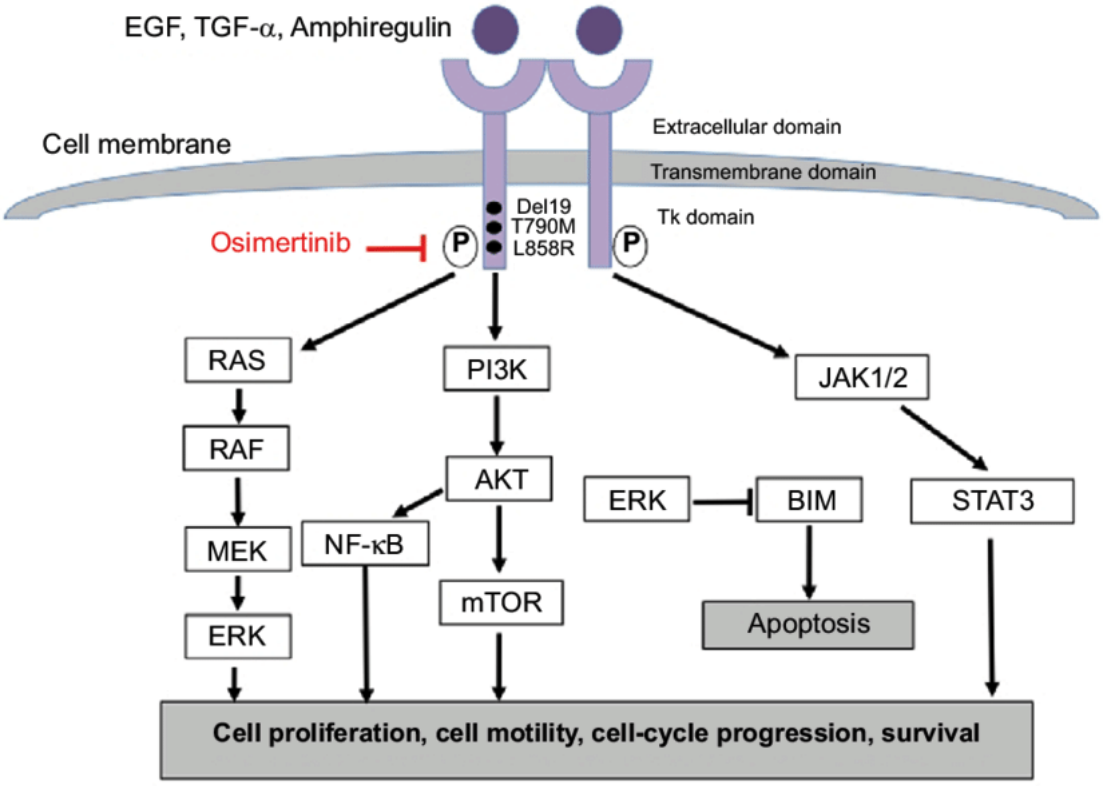

Figura 8. Mecanismo de acción de acción de Osimertinib.

- **Osimertinib:**

Osimertinib fue el primer TKI de tercera generación que recibió la aprobación de la FDA y de la EMA para el tratamiento del CPNM metastásico con mutación EGFR y, además con mutación adquirida T790M que progresa durante o después del tratamiento con un TKI previo (European Medicines Agency (EMA), 2018; U.S. Food and Drug Administration, 2017).

El ensayo AURA3 fue el primer estudio fase III que demostró una mejora significativa de la SLP de osimertinib respecto a quimioterapia (10,1 vs. 4,4 meses; HR 0,30 (0,23 to 0,41) p<0,001) (Mok et al., 2017). En el estudio FLAURA, el objetivo fue examinar dos hipótesis: en primer lugar, si la actividad de osimertinib contra las mutaciones sensibilizadoras comunes era tan sólida como la de los TKIs de primera y segunda generación y, en segundo lugar, si el tratamiento con un inhibidor de la T790M podría retrasar el desarrollo de las mutaciones T790M (Soria et al., 2018a). Se trató de un ensayo de fase III, en el que se inscribieron 556 pacientes con CPNM con mutación EGFR positiva (ex19del o L858R), a los que se administró gefitinib o erlotinib frente a osimertinib en una proporción de 1:1. La mediana de la SLP fue significativamente mayor con osimertinib respecto a los EGFR-TKI estándar (18,9 frente a 10,2 meses; HR 0,46; IC del 95%, 0,37 a 0,57; p<0,001). La duplicación de la duración de la respuesta con osimertinib sugiere que es eficaz para retrasar la aparición de la resistencia adquirida en comparación con erlotinib o gefitinib. Además, el brazo de osimertinib tuvo una menor frecuencia de efectos adversos de grado 3 o superior.

Los actuales intentos de identificar y atacar los mecanismos de resistencia a los TKIs en el CPNM EGFR+ han demostrado ser una estrategia exitosa, que repercute en los resultados de eficacia y en la calidad de vida de los pacientes. Esto es particularmente cierto en el caso de los TKIs de tercera generación, ejemplificado por el osimertinib, que ha demostrado tanto una mayor eficacia como una menor toxicidad que los fármacos de primera y segunda generación. La notable eficacia de osimertinib en el sistema nervioso central ha añadido otra modalidad de tratamiento a la radiación para el control del CPNM con mutación EGFR en el SNC, al ser capaz de atravesar la barrera hematoencefálica (Soria et al., 2018a).

A continuación, se resume de manera cronológica los diferentes descubrimientos alcanzados respecto a la investigación de CPNM EGFR+ y el desarrollo de los fármacos TKIs para su tratamiento (Figura 9).

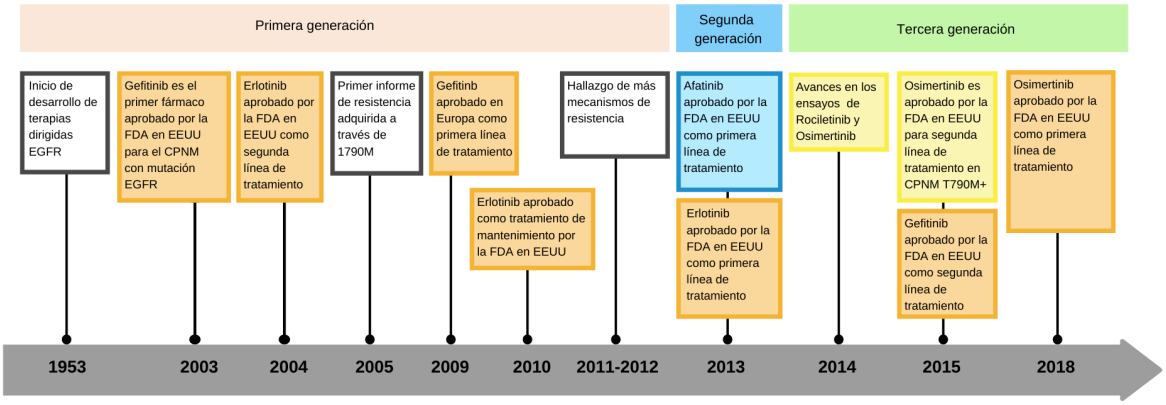

Figura 9. Cronología y desarrollo de las diferentes generaciones de fármacos TKIs.

Manejo de CPNM EGFR+

La determinación del tratamiento más adecuado para cada paciente se debe realizar teniendo en cuenta múltiples factores como la eficacia, la seguridad y la calidad de vida asociadas a cada fármaco TKI.

Los pacientes con CPNM y mutación positiva EGFR deben recibir TKIs de primera línea tales como erlotinib, gefitinib, afatinib o dacomitinib. Ninguno de estos cuatro TKIs está consensuado como opción preferida (Planchard el al., 2018). Sin embargo, actualmente se considera a osimertinib (fármacos de tercera generación) como la opción preferida en primera línea tras los últimos datos obtenidos en supervivencia global (Ramalingam et al., 2020) (Figura 10).

Una vez se haya desarrollado resistencia al tratamiento de primera línea con cualquier TKI, excepto con osimertinib, se deberá realizar la detección de la mutación T790M. Para ello, el método más adecuado es una biopsia líquida, y si el resultado es negativo, debe intentarse una nueva biopsia para confirmar este resultado. Si por el contrario el resultado es positivo a T790M, osimertinib es el tratamiento de elección, siempre y cuando no se haya empleado previamente.

Una vez que se hayan desarrollado resistencias a los TKIs, la última línea de tratamiento es la quimioterapia basada en dobletes de platino.

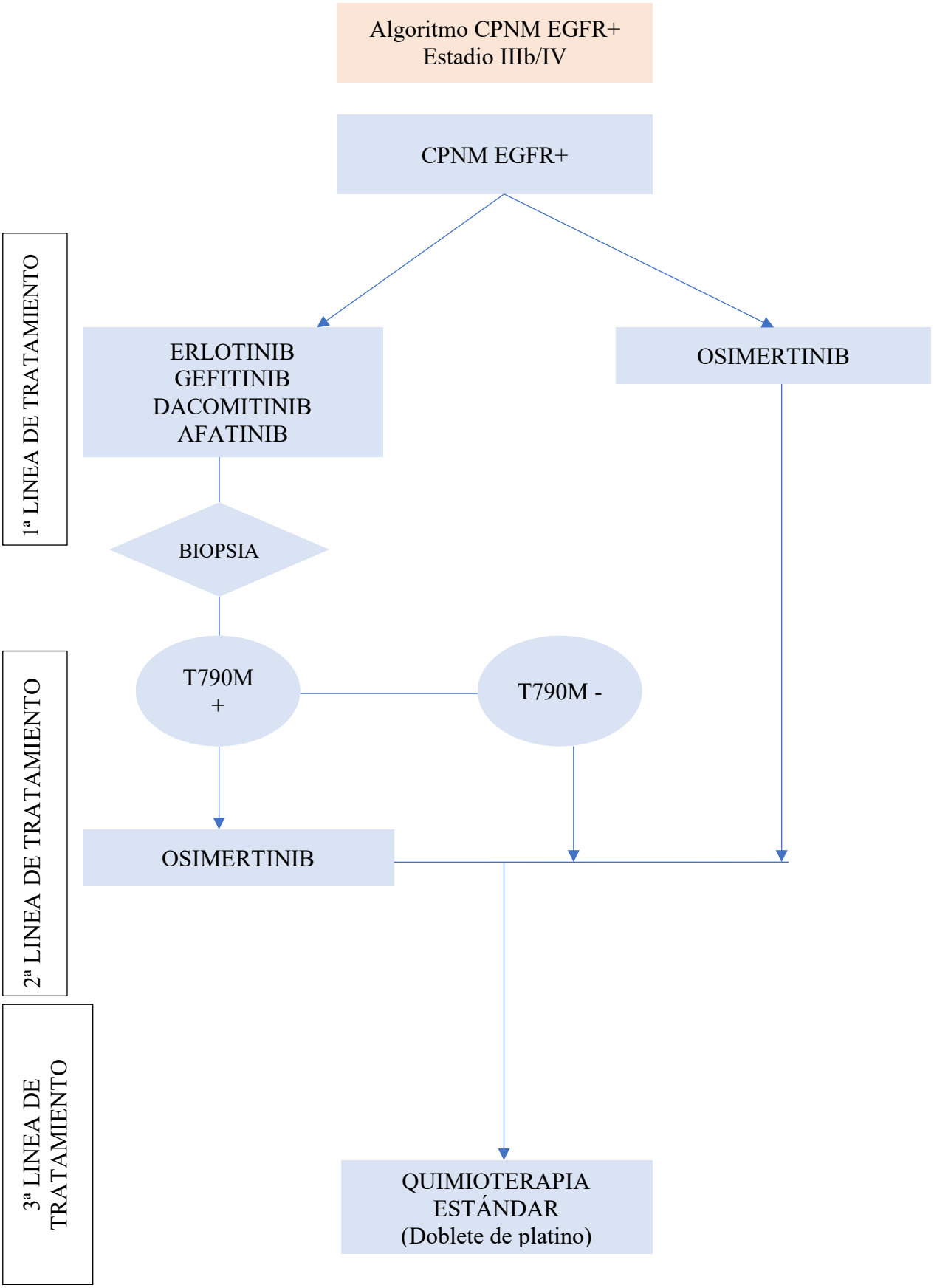

Figura 10. Algoritmo de tratamiento de cáncer de pulmón de células no pequeñas EGFR positivo.

FARMACOECONOMIA

Introducción

Los diferentes sistemas nacionales de salud, tanto en España como en otros países del mundo, se enfrentan actualmente a importantes retos demográficos y sanitarios. El progresivo envejecimiento de la población, la dispersión territorial, la cronificación de muchas enfermedades y el continuo desarrollo de nuevos fármacos, a pesar de aportar un importante nivel de innovación, conllevan un elevado coste económico.

En un contexto como el actual, donde los recursos disponibles son limitados e insuficientes, los distintos sistemas nacionales de salud no solamente deben fijar su atención en la eficacia, seguridad y calidad de los nuevos fármacos y tecnologías sanitarias disponibles, sino también en el coste que éstos suponen. Con el objetivo/reto de mejorar la calidad asistencial y la calidad de vida de los pacientes, así como generar los mayores beneficios terapéuticos para los mismos, la farmacoeconomía se ha establecido como una opción muy valiosa para evaluar los resultados en salud que producen las innovaciones terapéuticas en condiciones de uso de la práctica clínica diaria.

La farmacoeconomía podría definirse como la evaluación de los medicamentos y tecnologías sanitarias aplicando un razonamiento económico. Para ello se recurre a la utilización de métodos y principios propios de la economía de la salud con el objetivo de realizar evaluaciones económicas de los fármacos o tecnologías sanitarias que ayuden a determinar la eficiencia de éstos (Drummond et al., 2015).

Los estudios de farmacoeconomía tratan de fundamentar una serie de decisiones muy diferentes, pero inevitables, en el ámbito de la asistencia sanitaria. Cualquiera que sea el contexto o la decisión concreta, se plantea una pregunta común: ¿estamos convencidos de que los recursos sanitarios adicionales (necesarios para poner el procedimiento, servicio o programa a disposición de quienes podrían beneficiarse de él) deben gastarse de esta manera y no de otras?

Así pues, el objetivo final de la evaluación económica es detectar qué medidas son prioritarias para maximizar el beneficio en salud con los recursos disponibles. Por ello, la utilización de recursos de una forma determinada siempre implica un sacrificio. El "coste de oportunidad" podríamos definirlo como el valor de la mejor opción a la que

se renuncia cuando se realiza una elección. El coste de oportunidad que supone la financiación de medicamentos y otras tecnologías sanitarias es elevado, sin embargo, se consideran económicamente rentables para los financiadores sanitarios, es decir, para los sistemas de salud (Dilla et al., 2009).

Tipos de evaluaciones económicas

Las evaluaciones económicas se dividen en dos grupos:

- **Parciales:** se valoran los resultados en salud y costes por separado.
- **Completas:** los resultados en salud y los costes se evalúan de manera conjunta. Son las que más información aportan, y se dividen en cuatro tipos en función de cómo se valoran los resultados en salud, ya que los costes siempre se miden en unidades monetarias: análisis de minimización de costes, análisis coste-efectividad (ACE), análisis coste-utilidad (ACU) y análisis coste-beneficio (ACB) (Figura 11).

<table>
<tr><th></th><th></th><th colspan="3">¿Se evalúan tanto los costes como los resultados?</th></tr>
<tr><td rowspan="4">¿Existe comparación entre dos o más alternativas?</td><td rowspan="2"></td><td colspan="2">NO</td><td>SI</td></tr>
<tr><td>Valoración de los efectos</td><td>Valoración de los costes</td><td></td></tr>
<tr><td>NO</td><td>Evaluación Parcial
Descripción de los resultados</td><td>Evaluación parcial
Descripción de costes
Estudios de coste de la enfermedad
Análisis de impacto presupuestario</td><td>Evaluación parcial
Análisis coste-consecuencia</td></tr>
<tr><td>SI</td><td>Evaluación Parcial
Evaluación de la eficacia o efectividad</td><td>Evaluación parcial
Análisis de costes</td><td>Evaluación completa
AMC
ACE
ACU
ACB</td></tr>
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Figura 11. Tipos de evaluaciones económicas. AMC: análisis de minimización de costes; ACE: análisis coste-efectividad; ACU: análisis coste-utilidad; ACB: análisis coste-beneficio.

Análisis de minimización de costes (AMC)

Es un tipo de evaluación económica completa de dos o más alternativas, en las que la comparación directa entre ellas considera únicamente el coste, asumiendo la

existencia de equivalencia de resultados en salud (Newby & Hill, 2003). Por tanto, los costes de cada una de las alternativas serán los que determinen la opción más eficiente. También se le denomina análisis de identificación de costes, de reducción de costes o análisis coste-coste.

Deberá emplearse únicamente en el caso que se demuestre que las alternativas son equivalentes en términos terapéuticos. Por ello, se deberá justificar adecuadamente la equivalencia terapéutica, así como que la medida de resultado empleada es la válida y aceptada científicamente (López-Bastida et al., 2010).

Análisis de coste-efectividad (ACE)

Es un tipo de evaluación económica completa que determina de forma numérica cuál es la relación entre los costes de una intervención dada y las consecuencias de ésta, con la particularidad de que dichas consecuencias se expresan en las mismas unidades habitualmente utilizadas en la clínica. Las variables de eficacia clínica pueden ser variables finales (años de vida ganados (AVGs), mortalidad, etc) o variables intermedias (SLP, número de días sin síntomas, reducción de la presión arterial en mm de mercurio, etc). La utilidad de los ACE vendrá mediada por la capacidad de obtener las variables de eficacia en las mismas unidades.

Los resultados del ACE se expresan habitualmente como el cociente que se obtiene al dividir el coste neto de la intervención por su beneficio neto o efectividad. Este cociente se conoce habitualmente como coste-efectividad medio (CEM). Sin embargo, a pesar de que el empleo del CEM se considera correcto, aporta poca información de utilidad como elemento de evaluación para la toma de decisiones, ya que no establece una comparación entre las alternativas disponibles.

Por ello, los ACE emplean otro cociente llamado ratio coste-efectividad incremental (RCEI), a través del cual los costes y efectos de una intervención se comparan con los costes y efectos de otra intervención para una misma patología, expresándose los resultados en las mismas unidades. El resultado se obtiene mediante el cociente entre la diferencia de costes y la diferencia de eficacias de las dos alternativas comparadas, expresando el resultado como coste extra por unidad de beneficio adicional conseguido con una opción respecto a la otra (Prieto et al., 2004).

$$RCEI = \frac{Coste\ Intervención\ B - Coste\ Intervención\ A}{Eficacia\ Intervención\ B - Eficacia\ Intervención\ A}$$

Los diferentes valores obtenidos de RCEI se representan gráficamente mediante el plano coste-efectividad incremental (Figura 12).

Si consideramos *F* como el tratamiento o tecnología sanitaria alternativa empleada como comparación, la figura muestra las diferentes situaciones que puede dar lugar una evaluación económica.

I) Si el valor de RCEI se sitúa en el **cuadrante II** significa que la tecnología sanitaria es más efectiva y menos costosa que la representada por **F**. Podríamos concluir, por tanto, que la tecnología sanitaria evaluada es **dominante** respecto a la comparada.

II) Si el valor de RCEI se sitúa en el **cuadrante IV** significa que la tecnología evaluada presenta unos mayores costes y una efectividad menor que la comparada. Concluiríamos por tanto que la alternativa evaluada se encuentra **dominada** respecto a la comparada.

III) Si el valor de RCEI se sitúa en el **cuadrante III** implica que la nueva tecnología evaluada resulta menos efectiva pero también implique menores costes.

IV) Si el valor RCEI se sitúa en el **cuadrante I** supone que la tecnología evaluada proporciona una mayor efectividad pero también con mayores costes que la tecnología comparada **F**.

En las situaciones I) y II), es decir, las representadas por los **cuadrantes II y IV**, la decisión tomada por parte de los evaluadores no supone ningún inconveniente. Por tanto, si la nueva tecnología evaluada es a la vez más efectiva y menos costosa que la alternativa, su aceptación es inmediata **(cuadrante II)**. Si, por el contrario, el valor de RCEI obtenido concluye que la nueva tecnología supone costes adicionales y proporciona menos beneficios **(cuadrante IV)** queda demostrado claramente que su elección carece de sentido, por lo que debe ser rechazada. De aquí se concluye que en ambos supuestos existe dominancia: en el primer caso, la tecnología nueva domina y en el segundo caso es dominada.

En la situación IV), es decir, que el valor RCEI se sitúe en el **cuadrante I**, la eficiencia del nuevo tratamiento dependerá del valor asignado al umbral de dicho valor RCEI. Por

umbral entendemos el valor máximo que el financiador estaría dispuesto a pagar por ganar una unidad de salud. En España, se realizó una estimación a nivel nacional con el objetivo de determinar el coste que supondría obtener un año de vida ajustado por calidad (AVAC), siendo éste de 20.000-25.000 €/AVAC (Vallejo-Torres et al., 2018).

Finalmente puede suceder que el valor RCEI se sitúe en el **cuadrante III** (situación IV), en el que el nuevo tratamiento sea menos costoso y efectivo que el comparador. Así pues, el hecho de incluir este tratamiento a pesar de resultar eficiente quizás no podría ser considerado éticamente aceptable. Para determinar si esta intervención es eficiente, se recomienda el cálculo del beneficio neto monetario (BNM). Este parámetro determina las ganancias en salud en términos monetarios. Se calcula como:

$$BNM = (\Delta E * \lambda) - \Delta C$$

donde ΔE es el incremento en unidades de eficacia, λ es umbral que está disponible a pagar, y ΔC es el incremento de costes entre las alternativas comparadas. El BNM debe ser positivo para considerar la alternativa coste-efectiva, siendo por tanto más coste-efectivo cuanto mayor sea el valor del BNM obtenido (Drummond et al., 2015).

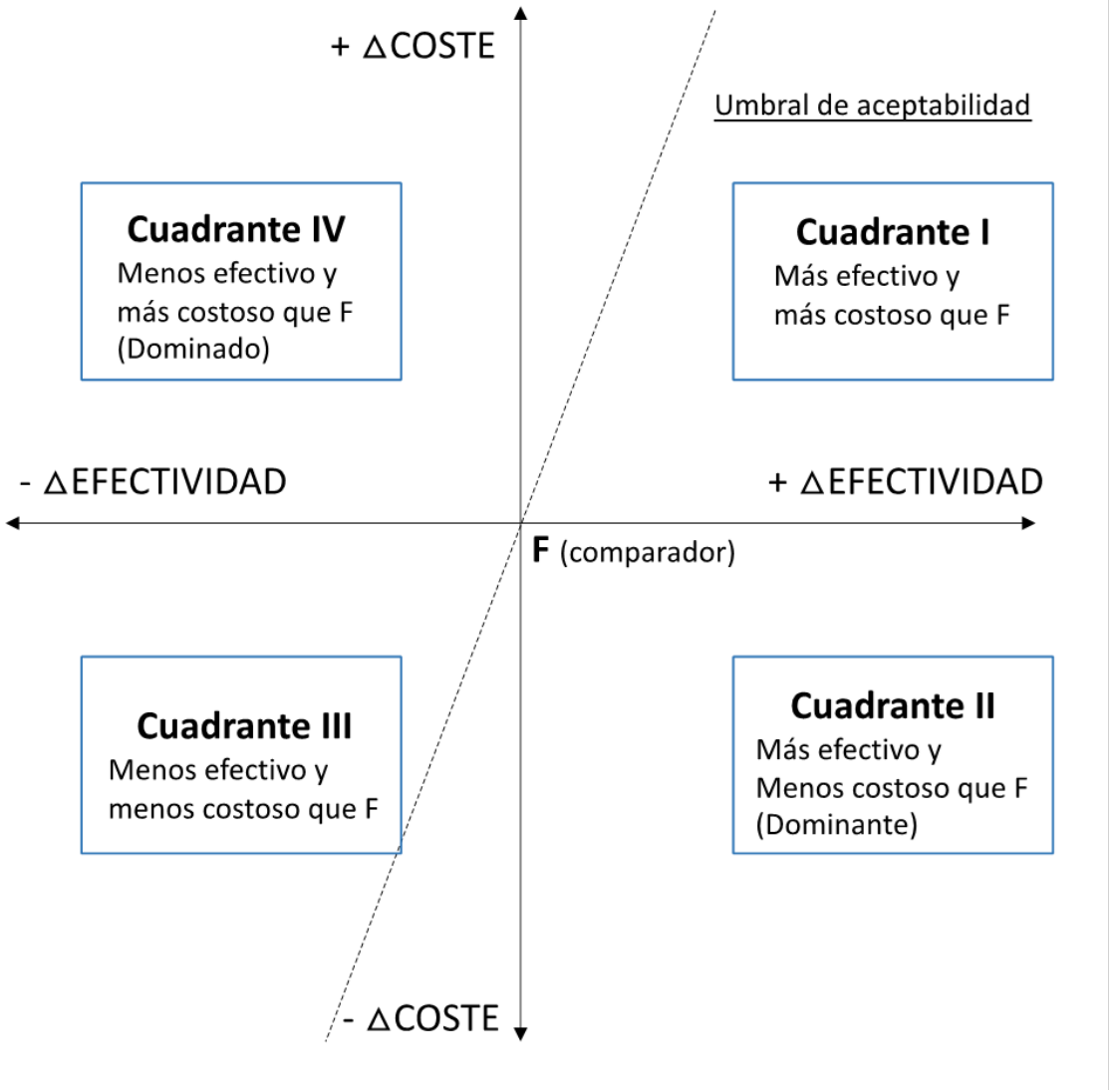

Figura 12. Plano coste-efectividad incremental.

Análisis de coste-utilidad (ACU)

Se trata de un tipo de evaluación económica en la que el parámetro de efectividad se mide en calidad de vida, a diferencia del CEA que se mide en unidades clínicas. Las principales variables empleadas son el AVAC y el año de vida ajustado por discapacidad (AVAD), parámetros donde se combina la cantidad de vida ganada con la calidad de vida. El AVAC es el parámetro más utilizado y podríamos interpretarlo como un año de vida ganado con un estado de salud perfecto. En el caso de un paciente que se somete a un tratamiento, podríamos definirlo como el número de años adicionales que vive

como resultado de ese tratamiento o intervención sanitaria, teniendo en cuenta además la calidad de vida de estos años (Drummond et al., 2015).

La principal ventaja del empleo de AVAC y la consiguiente obtención del ratio coste/AVAC es que permite una mayor comparabilidad entre diferentes estudios. Por tanto, permite generalizar los resultados con el objetivo de comparar intervenciones que se han estudiado para distintas patologías o intervenciones sanitarias, ayudando a la toma de decisiones por parte de los clínicos u otras autoridades financiadoras.

Una vez obtenidos los resultados, éstos se expresan en coste por AVAC ganado (coste/AVAC), y por el ratio coste utilidad incremental (RCUI).

Análisis de coste-beneficio (ACB)

Es un tipo de evaluación económica completa en la que todos los resultados sanitarios (costes y beneficios) se miden en unidades monetarias. Las principales ventajas de este tipo de evaluación económica son:

1) **Medición de costes y resultados en las mismas unidades:** permitiendo por tanto comparar diferentes intervenciones sanitarias o no sanitarias que puedan tener valor para la sociedad.
2) **Regla de decisión más clara que ACE y ACU:** para ello se emplea el concepto VAN (valor actualizado neto). Viene representado por la siguiente fórmula:

$$VAN = \sum_{t=0}^{n} \frac{B_t - C_t}{(1+r)^t}$$

Donde:

Bt representa los beneficios incrementales (valor monetario de la ganancia incremental en salud) en el periodo t de un proyecto frente a sus alternativas, representa los costes incrementales en el periodo t y representa el factor de descuento en el periodo *t*, siendo *r* una tasa de descuento que debe reflejar el coste de oportunidad de los recursos presentes frente a los futuros.

Si el valor VAN de la inversión en el proyecto es positiva, es decir, si los beneficios, traducidos a valor monetarios, superan a los costes, ambos expresados en valores actualizados (a través de la tasa de descuento) y en términos incrementales, frente a otras posibles alternativas, entonces el proyecto merece la pena y debe llevarse a cabo. Si, por el contrario, los costes

exceden a los beneficios, el VAN será negativo y existirá una alternativa preferible a la inicialmente planteada.

3) **Facilita las comparaciones entre programas muy dispares.**

Sin embargo, este tipo de evaluaciones no es común en el ámbito sanitario. De hecho, apenas un 5% de las evaluaciones económicas de intervenciones sanitarias realizadas en España son de este tipo (Oliva et al., 2002). Ello es debido a que es muy difícil reducir a unidades monetarias todos los beneficios que puede reportar sobre la salud una intervención sanitaria.

Otras evaluaciones económicas

- **Estudios de coste de la enfermedad**

Es una evaluación económica parcial que proporciona información a las autoridades sanitarias del coste de manejo a diferentes niveles de una determinada patología o intervención sanitaria. Podríamos definir la utilidad de este tipo de evaluación económica como la consecución de un doble objetivo:

- Estimar el impacto financiero de una determinada patología o intervención sanitaria en un determinado contexto.
- Estimar la relevancia o peso relativo que tiene cada patología o intervención sanitaria en términos de costes.

Por ello los estudios de coste de la enfermedad deben ser innovadores, reflejar las consecuencias socioeconómicas de una determinada patología, estimar el coste real para la sociedad, identificar qué pacientes generan dichos costes, así como qué costes son los que presentan un mayor peso en el coste total, describir el manejo clínico actual de la enfermedad y ser capaces de explicar la variabilidad de los costes.

Por ello, este tipo de evaluaciones van a ser muy útiles con el objetivo de definir la magnitud de la enfermedad en términos económicos, así como para proporcionar un marco económico para los programas de evaluación. También se emplean como base para posteriores análisis coste-efectividad y/o coste-beneficio.

Sin embargo, es importante destacar que este tipo de evaluaciones económicas parciales no proporcionan ninguna fórmula directa para la asignación de recursos ni

comparan tecnologías sanitarias, por lo que no permiten establecer prioridades entre dichas alternativas.

- **Análisis de impacto presupuestario (AIP)**

Es un tipo de evaluación económica parcial que estudia la variación que provocará la introducción de una nueva intervención sanitaria sobre el presupuesto del financiador (Sullivan et al., 2014).

Nos permite evaluar si la introducción de una determinada alternativa en el protocolo de tratamiento de una patología resulta asumible en términos económicos por los financiadores.

La aplicación del AIP podría considerarse como un complemento a las evaluaciones económicas completas como ACE y ACU, ya que mientras estas últimas determinan si una estrategia es coste-efectiva, el AIP permite la priorización de la estrategia objeto de estudio en un determinado subgrupo de pacientes al evaluar la asequibilidad y factibilidad del financiador ante la introducción de nuevas intervenciones sanitarias.

La utilización de los AIP resulta de gran importancia para la toma de decisiones sobre el precio de los fármacos, para la elaboración de guías de práctica clínico-económicas, para la toma de decisiones sobre la financiación selectiva y para la inclusión de medicamentos en guías farmacoterapéuticas (Sullivan et al., 2014).

Perspectiva del análisis

La selección del público objetivo hacia el que va dirigido el estudio resulta de vital importancia desde un punto de vista metodológico para la correcta ejecución de la evaluación económica. Dicha elección es determinante ya que influirá de manera notable en el tipo de costes y resultados que determinarán el estudio (Figura 13).

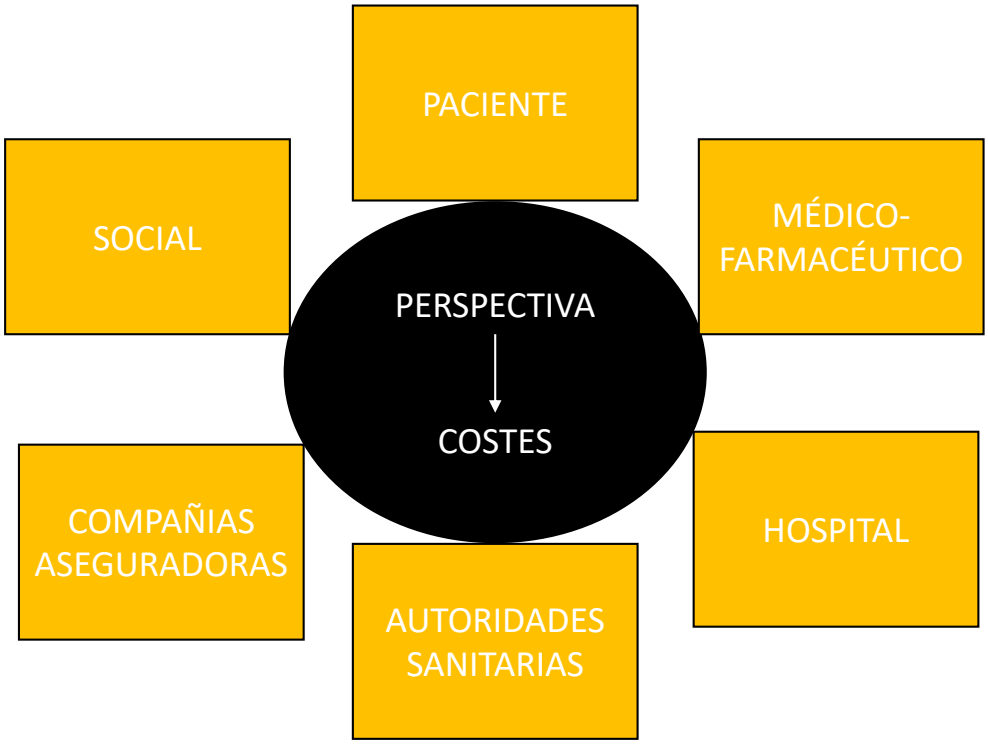

Figura 13. Perspectivas del análisis

Los diferentes tipos de perspectivas pueden ser desde la perspectiva de la institución concreta (hospital, por ejemplo) que será quien aplique la tecnología en estudio, la de las autoridades sanitarias financiadora, la de los pacientes y sus familias o la sociedad en su conjunto. Esta última, la perspectiva social, es la más amplia, ya que incluye todos los costes (sanitarios, abstención laboral, pérdida de productividad, etc.) y resultados en salud que permiten reflejar de una forma más precisa el impacto de la evaluación sanitaria sobre el conjunto de la sociedad. Es importante destacar que la perspectiva del paciente es distinta a la que puede tener el financiador (sistema sanitario público o compañías aseguradoras privadas), y todas ellas son distintas a la que podría tener el fabricante de dicha intervención sanitaria, en nuestro caso, la industria farmacéutica (Soto-Álvarez, 2012).

Si el objetivo de una evaluación económica es informar de la asignación de recursos en términos amplios, la perspectiva de elección debería ser la perspectiva social. La utilización de este tipo de perspectiva es clave en enfermedades incapacitantes, ya que desde el punto de vista de la sociedad podemos contabilizar de manera más

realista aspectos tales como la pérdida de productividad laboral y la necesidad de cuidadores externos a los propios sanitarios para el ámbito doméstico, que repercuten directamente en un incremento de los costes para la sociedad (López-Bastida et al., 2010; Soto-Álvarez, 2012).

Como norma general, la evaluación económica debería realizarse empleando un punto de vista lo más amplio posible, es decir, adoptando una perspectiva social. Ello supone la consideración de todos los costes y resultados en salud independientemente de quién sea el financiador o receptor de los mismos (López-Bastida et al., 2010; Ortega-Eslava A et al., 2016). Sin embargo, en muchas ocasiones no se emplea la perspectiva social, utilizándose otras perspectivas menos amplias como la del financiador. En estos casos, resultaría necesario justificar el motivo por el que los costes sociales no han sido incluidos, ya sea por revestir un peso poco relevante para los resultados o porque no se disponga de ellos (López-Bastida et al., 2010; Ortega-Eslava A et al., 2016).

Tipos de modelos farmacoeconómicos

Los modelos analíticos de decisión son la base metodológica sobre la cual se diseña la evaluación económica. Por ello, los modelos farmacoeconómicos se desarrollan en base a modelos analíticos de decisión que podríamos definir como como una aproximación sistemática a la evolución más probable de una enfermedad tras la administración de diferentes alternativas terapéuticas para su tratamiento, proyectando los resultados en salud que se van a obtener con cada una de las opciones administradas y los costes asociados en su consecución (Soto-Álvarez, 2012).

Todo modelo farmacoeconómico deberá representar de la manera más sencilla, realista y comprensible el desarrollo de la enfermedad, con el objetivo de obtener un modelo los más fiable, válido y preciso posible, que proporcione transparencia y comprensión a los financiadores/decisores u otros interesados en su utilización (Hay, 2004).

Los principales modelos para la realización de evaluaciones económicas son principalmente tres: los árboles de decisión, los modelos de Markov y los modelos de microsimulación.

Arboles de decisión

Uno de los modelos de decisión más simples son los árboles de decisión (Figura 14). El árbol de decisión tiene varios componentes que siempre están presentes y deben ser desarrollados cuidadosamente. Un modelo de decisión está formado por la propia estructura del modelo (el árbol de decisión) representado por nodos y ramas, las cuales representan a su vez tanto la decisión que se está tomando como los resultados que pueden producirse como consecuencia de cada decisión, las probabilidades de que se produzcan los distintos resultados y los valores de los resultados si se producen. Al igual que cualquier otro problema de investigación, el árbol de decisión debe comenzar con una formulación específica del problema, que en la figura es una elección entre la terapia A y la terapia B en una condición particular. En los modelos farmacoeconómicos, estos deben representar la elección real que se hace, y deben incluir los descriptores necesarios de la población en la que se toma la decisión para permitir al lector entender el contexto de la elección. El contexto va seguido de un nudo de decisión (representado en la figura como un cuadrado), y debe incluir como comparadores las opciones relevantes y reales que el decisor tiene a su disposición. En la figura, esta decisión concreta sólo tiene dos opciones representadas por las ramas del nodo de decisión etiquetadas como Elegir terapia A (Choose Therapy A) y Elegir terapia B (Choose Therapy B). Cada opción va seguida de una serie de nodos de acontecimiento o de azar (representados en la figura por círculos), que describen los posibles resultados que implica la toma de cada una de las opciones respectivas. Cada rama que nace de estos nodos lleva asociada una probabilidad específica (de p1 a p4 en la figura 14). Cada resultado se asocia también a uno o más valores (representados en la figura por los rectángulos), que describen los efectos clínicos y los costes de llegar a ese resultado concreto.

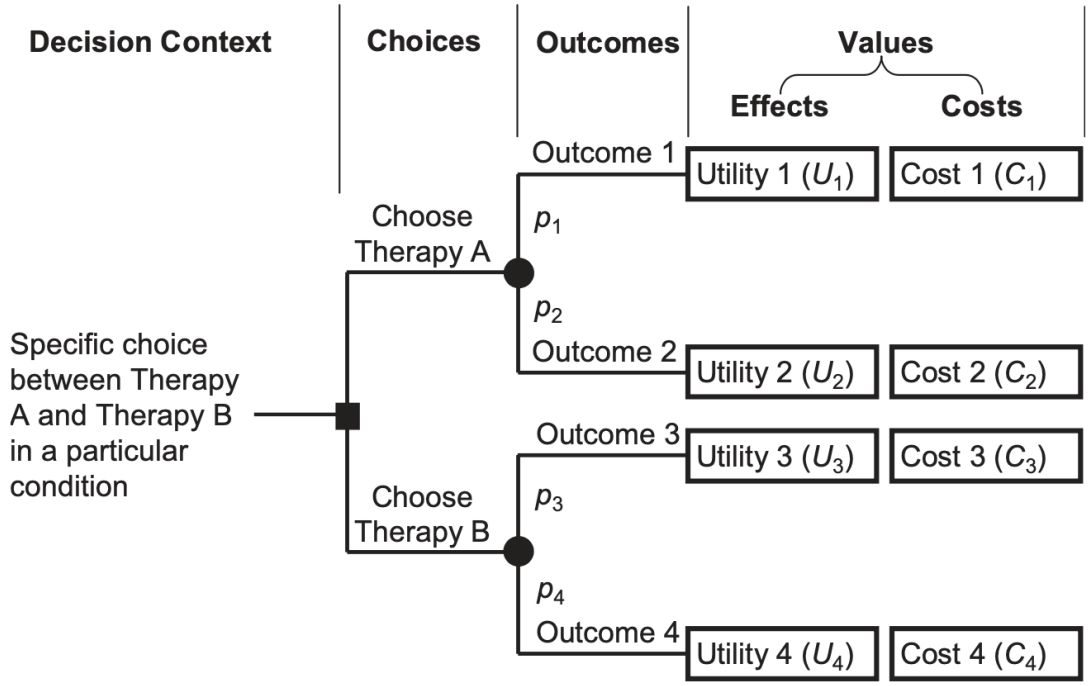

Figura 14. Estructura básica de un árbol de decisión (Arnold, 2010).

La aplicación de este proceso a los resultados en salud y a los costes asociados a cada una de las ramas permite estimar el valor esperado para cada alternativa estudiada.

Una de las principales limitaciones con este tipo de modelos es que resultan adecuados para evaluar enfermedades agudas (tales como bronquitis) en periodo de tiempo cortos. Sin embargo, en enfermedades crónicas y en aquellas enfermedades agudas con múltiples recaídas o con recidivas, se requieren modelos muy complejos y difíciles de analizar y manejar, que proporcionan poca utilidad para los decisores (Soto-Álvarez, 2012).

Modelos de Markov

Los modelos de Markov (Figura 15) se podrían definir como modelos estocásticos (incluyen la incertidumbre/azar como parte del cálculo) de una enfermedad, la cual se va a representar como una serie finita de estados de salud con una determinada probabilidad de transición entre ellos, asumiéndose que el paciente siempre se va a situar en uno de dichos estados de salud. Por ello, cada estado de salud es exhaustivo (deben estar presentes todos los estados posibles dentro de la enfermedad evaluada) y mutuamente excluyente (un paciente no puede estar en dos estados a la vez durante

el mismo ciclo) (Soto Álvarez, 2012). Los estados de Markov pueden ser de dos tipos diferentes:

a) **Estados absorbentes:** una vez alcanzado este estado, los pacientes no pueden seguir transitando. Habitualmente corresponde con el "estado muerte".
b) **Estado no absorbente:** cualquier estado a través del cual se puede transitar a otro diferente.

Los eventos que se van a producir como resultado de la evolución de la enfermedad serán reproducidos en el modelo como transiciones de unos estados de salud a otros, los cuales se van a desarrollar en periodos de tiempo fijos (ciclos de Markov) relacionados a unas probabilidades de transición de un estado de salud a otro. Estas transiciones entre estados de salud van a depender del estado en el que se encuentra el paciente y se obtienen habitualmente de la literatura, como ensayos clínicos o estudios observacionales.

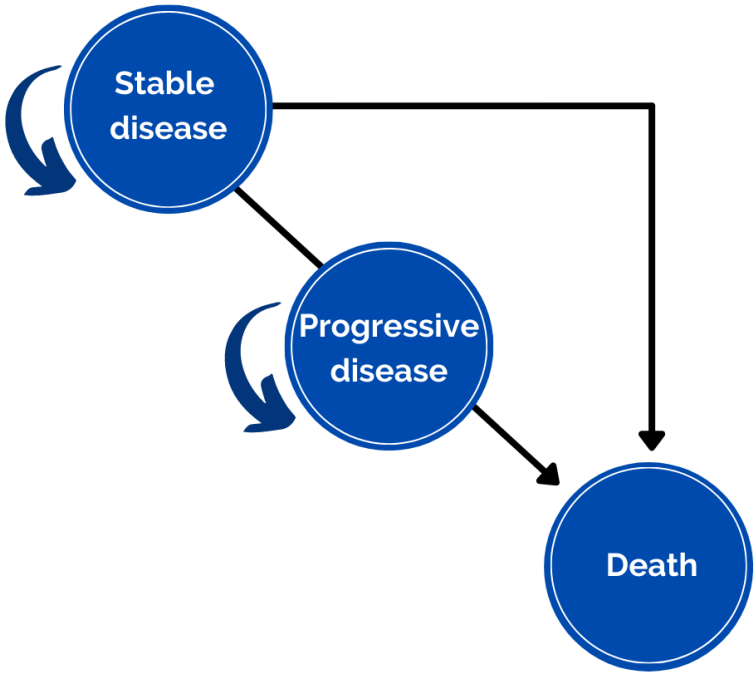

Figura 15. Modelo de Markov

Una de las principales ventajas de los modelos de Markov respecto a los árboles de decisión, es que permiten modelizar patologías crónicas de larga duración cuya evolución puede ser compleja y repetitiva, pero que puedan presentar una serie de etapas de evolución claras y precisas que permitan su modelado.

Es importante destacar el concepto de "asunción markoviana", el cual asume que el modelo carece de memoria y se debe de aceptar que todos los pacientes que se encuentren en un estado de salud tienen el mismo pronóstico, es decir, que la probabilidad de cambiar de un estado de salud a otro no depende de los estados por los que haya transitado previamente el paciente. Para intentar reducir esta "asunción markoviana" se podría expandir el número de estados de salud, permitiendo asociar una probabilidad distinta a cada estado. Sin embargo, esto complicaría en gran medida la realización del modelo y su posterior análisis (Rubio-Terres, 2000).

A cada paciente que va a transitar por los estados de salud definidos, se les van a imputar el empleo de una serie de recursos, así como los resultados en salud obtenidos en dichos estados. Tras cada ciclo, se obtendrá por tanto una serie de costes y resultados en salud, que deberán ser reflejados en el modelo con una serie de valores cuantitativos (Rodriguez-Barrios, 2004). El modelo terminará cuando los individuos hayan alcanzado el estado de salud absorbente, o cuando se hayan logrado el número de ciclos previamente establecidos (Rubio-Terres, 2000)

Modelos de microsimulación

Se trata de un modelo de transición entre diferentes estados de salud, entre los cuales van transitando uno a uno los pacientes de una determinada cohorte empezando por un primer estado de salud hasta alcanzar el estado absorbente. Este modelo se realiza a través de la técnica de simulación de Monte Carlo de primer orden, gracias al cual, para simular el paso de cada paciente de un estado de salud a otro, se utiliza un generador de números aleatorios en combinación con las probabilidades de transición, lo que permite determinar en qué estado de salud estará el paciente en cada nuevo ciclo del modelo.

Este modelo va a permitir superar la limitación de la "asunción markoviana", ya que permitirá incorporar la historia previa de cada paciente. Para que estos modelos puedan ser fiables y válidos, deberán incorporar un número de pacientes suficiente.

A pesar de ser el modelo más recomendado para aquellas patologías que presenten un número muy elevado de estados de salud, su utilización y elaboración minuciosa requiere mucho tiempo y han resultado ser muy complejos de realizar (Soto-Álvarez, 2012).

Evaluación de los resultados en salud

El punto de partida para la valoración del beneficio para la salud en las evaluaciones económicas es la medición de los efectos sobre la salud. Estos pueden ser mejoras en el principal resultado sanitario de interés (por ejemplo, la supervivencia) u otros efectos, como los efectos secundarios de la terapia, que podrían repercutir en la calidad de vida relacionada con la salud de forma positiva o negativa. Estos resultados en salud obtenidos tras la aplicación de cualquier opción terapéutica se van a poder expresar tanto en unidades clínicas tales como indicadores tumorales o complicaciones evitadas, así como en otro tipo de unidades derivadas de incrementar la calidad de vida y mejora en el estado de salud de los pacientes, realizando una explicación razonada de la forma en la se miden estos resultados (Ortega-Eslava et al., 2016).

Actualmente, a pesar de que todavía se siguen empleando variables clínicas subrogadas o intermedias para calcular los resultados en salud en los estudios farmacoeconómicos (ictus evitados, infartos de miocardio evitados, reducción de densidad mineral ósea en pacientes con osteoporosis, etc.), los expertos en evaluación económica están requiriendo la necesidad de emplear variables finales orientadas a valorar la reducción de la mortalidad tras el empleo de cualquier tratamiento o tecnología sanitaria. De esta manera, los diferentes decisores o financiadores sanitarios van a obtener una herramienta útil y estandarizada que permitirá determinar prioridades en la elección de un tratamiento para su inclusión en la cartera de servicios sanitarios.

En las evaluaciones económicas se recomienda, en la medida de lo posible, emplear variables que reflejen la disminución en mortalidad. El parámetro que más se utiliza para medir calidad y cantidad de vida en una única variable es el AVAC.

El AVAC se emplea para evaluar los efectos de una alternativa terapéutica en términos de expectativa de vida (años de vida ganados) y de calidad de vida, medida como utilidad (Soto-Álvarez, 2012).

La utilidad puede definirse como la proporción de tiempo vivida con una salud perfecta, y adopta un valor entre cero y 1, siendo cero el peor estado de salud posible, y 1 el mejor. Por ejemplo, un año de vida con un estado de salud perfecta equivaldría a

dos años de vida con un estado de salud que tuviera una utilidad de 0,5 (Torrance, 1987).

La utilidad o preferencia se refiere a la calidad de vida percibida o al deseo relativo de los diferentes sujetos entre dos o más estados de salud. Por ello, la utilidad define la preferencia por un estado de salud determinado, ya sea éste positivo o negativo, tras la incorporación de actitudes respecto al riesgo y la duración de la vida (Torrance, 1987).

Para el cálculo de la utilidad se emplean métodos directos (*rating scale*, escala visual analógica, equivalencia temporal o *time trade-off* y lotería estándar o *standard gamble*) e indirectos (cuestionarios como el EuroQol-5D (EQ-5D), el *Health Utilities Index III* (HUI-3) y el *Short Form 6-dimension Health Survey* (SF-6D)).

- **Métodos directos de medición de la utilidad:**
- ***Rating scale* y escala visual analógica:** el paciente selecciona su estado de salud, teniendo en cuenta sus preferencias, en una determinada escala representada por una línea en cuyos extremos se representa el mejor y el peor estado de salud posible (Torrance et al., 2002).
- ***Time trade off* o equivalencia temporal:** mediante una entrevista o cuestionario el paciente debe argumentar cual sería el período de tiempo en estado de salud perfecto el cual sería equivalente a un periodo de tiempo con un determinado estado de salud. El objetivo es que el paciente valore cual sería el mínimo tiempo posible en estado de buena salud que estaría dispuesto a cambiar durante un tiempo en otro estado de salud. Con este método se consigue evaluar la duración y calidad de vida, sin embargo, este método asume que el paciente tiene una percepción lineal del tiempo (valorando en mayor medida la supervivencia actual a la futura) (Soto-Álvarez, 2012).
- ***Standard gamble* o lotería estándar:** el paciente es preguntado por la probabilidad de asumir ciertos estados de salud mediante el empleo de un árbol de decisión en el que se discierne entre dos alternativas. Este método se asemeja a la realidad, ya que la mayoría de las decisiones médicas llevan asociadas cierto grado de incertidumbre y riesgo. Aun así, se trata de un método complejo y se requiere que los pacientes sean sinceros e intenten percibir el riesgo de manera objetiva (Green et al., 2012).

- **Métodos indirectos de medición de la utilidad:**

Para el cálculo de las utilidades por métodos indirectos se utilizan cuestionarios donde el paciente es preguntado por su estado de salud actual y, a continuación, mediante una serie de fórmulas y baremos que van a corregir el valor de utilidad acorde a lo valorado por una muestra de la población general, se calcula el valor de utilidad que corresponde al estado de salud del paciente. Los cuestionarios más habitualmente empleados son:

- **EQ-5D**
- **SF-36**
- **SF-6D**

El empleo de los cuestionarios EQ-5D y SF-36 permite de manera muy simple y rápida transformar los resultados obtenidos en utilidades, lo cual permite a su vez calcular de manera directa los valores AVACs.

En el caso del CPNM no existe un cuestionario validado que sea exclusivo para calcular el valor de utilidad en estos pacientes. Los organismos de evaluación de las autoridades sanitarias de distintos países, como el Instituto Nacional para la Excelencia Sanitaria y Asistencial (NICE) del Reino Unido, el Consorcio Escocés de Medicamentos (SMC), la Agencia Canadiense de Medicamentos y Tecnologías Sanitarias (CADTH), la Haute Autorité de Santé (HAS) francesa y el Comité Consultivo de Beneficios Farmacéuticos Australiano (PBAC) han manifestado una mayor consideración por métodos genéricos basados en las preferencias para el cálculo de los valores de utilidad (Paracha et al., 2018). De entre estos métodos genéricos, existe una mayor preferencia por el método EQ-5D, ya que éste reduce la variabilidad inducida cuando se utilizan diferentes instrumentos entre diferentes áreas de enfermedad.

Clasificación de costes y recursos

El principal objetivo de las evaluaciones económicas es relacionar los resultados en salud obtenidos mediante el empleo de una determinada tecnología sanitaria o fármaco para el tratamiento de una patología, con los costes que se derivan de su utilización. Por tanto, calcularemos la relación coste-efectividad existente y a continuación la compararemos con la de otra intervención sanitaria, con el objetivo de

determinar si es coste-efectiva y, en consecuencia, puede ser incluida en las diferentes guías farmacoterapéuticas de los sistemas sanitarios.

Para determinar adecuadamente que recursos o costes incluir en un determinado estudio farmacoeconómico, es muy importante identificar, cuantificar y valorar todos los recursos relevantes para el tratamiento de la enfermedad. Los costes calculados a partir de los recursos utilizados se clasifican como costes directos, indirectos e intangibles. En función de la perspectiva seleccionada para la elaboración de la evaluación económica se elegirán unos costes u otros, valorando también su disponibilidad y relevancia.

A continuación, detallamos los tipos de costes:

- **Costes directos:** son aquellos relacionados con la utilización de los servicios sanitarios por parte del paciente para el tratamiento de su enfermedad. Por tanto, no solo son los costes relacionados directamente con los servicios sanitarios empleados, sino también con los costes de los que se hace cargo la familia y el resto de la sociedad. Pueden subdividirse a su vez en:
  - **Costes directos sanitarios:** todos aquellos costes que estén relacionados con la asistencia sanitaria como costes de fármacos, hospitalización, pruebas diagnósticas, consultas externas, etc. Son los costes más importantes en CPNM y, por tanto, deben ser recogidos de manera minuciosa por los evaluadores e incluidos siempre en la evaluación económica.
  - **Costes directos no sanitarios:** todos aquellos costes asumidos/financiados por el paciente o sus familiares, y que por tanto no están incluidos en la financiación del sistema sanitario. Se incluyen el transporte requerido para los tratamientos o visitas médicas, los que se requieren para el cuidado del enfermo, contratación de terceras personas para el cuidado del paciente, etc.

El apartado más importante de los costes directos sanitarios es el coste de adquisición de los fármacos. Este coste en España está regulado por el Real Decreto-Ley 9/2011, de 19 de agosto (Boletín Oficial del Estado, 2011), el cual determina tanto la fijación de precios como la financiación de los nuevos medicamentos y productos sanitarios. Los precios de los fármacos hospitalarios, como los que se emplean en CPNM, se obtienen

a partir del precio de venta del laboratorio (PVL) y están sujetos a los descuentos oficiales regulados por el Real Decreto-Ley 8/2010 (Boletín Oficial del Estado, 2010). A su vez, a estos descuentos se les podrían añadir aquellos obtenidos por los diferentes gerentes de los servicios médicos tanto a nivel autonómico como del propio hospital o centro sanitario en cuestión. Todos los fármacos llevan aplicados un Impuesto del Valor Añadido (IVA) superreducido del 4%.

- **Costes indirectos:** son aquellos relacionados con la disminución de la productividad del paciente debido a la enfermedad. Se relacionan con la actividad laboral del paciente. Debemos diferenciar entre presentismo, menor productividad del paciente en el trabajo, y absentismo, días de trabajo perdidos debido a la pérdida de capacidad productiva. Estos costes, aunque medibles, no se suelen incluir en las evaluaciones económicas debido a la dificultad de su cálculo y transformación a unidades monetarias (Soto-Álvarez, 2012).
- **Costes intangibles:** son aquellos relacionados con la pérdida de bienestar por parte de pacientes y familiares, entre los que se destacan la ansiedad, el dolor, la incomodidad, etc. Son costes muy difíciles de medir y cuantificar, por lo que no suelen ser incluidas en las evaluaciones económicas (Soto-Álvarez, 2012).

Una vez hemos obtenido los costes unitarios de cada recurso, los costes finales se obtendrán multiplicando la cantidad de recuso consumido por el coste de este. Dichos costes unitarios se van a obtener de la literatura ya sea, a través de los Grupos Relacionados con el Diagnóstico (GRD), de otros artículos de evaluaciones económicas o bien, de las tarifas sanitarias que publican algunas autonomías en nuestro país. Sin embargo, muchos de estos costes pertenecen a años anteriores, por lo que sería necesario ajustarlos a la actualidad según el Índice de Precios al Consumidor (IPC).

Horizonte temporal y actualización de los costes

El horizonte temporal podría definirse como el periodo de tiempo durante el cual se valoran los efectos sobre la salud y los recursos consumidos. Este horizonte deberá ser lo suficientemente amplio para poder capturar todos los beneficios terapéuticos de las alternativas objeto de estudio. Es por ello, que será más reducido en patologías agudas y más amplio en las crónicas. En nuestros modelos de simulación, el horizonte temporal se divide en los conocidos como ciclos de Markov, los cuales deben ser

intervalos de tiempo iguales que deben recoger de forma precisa tanto los resultados en salud como los recursos consumidos y la evolución de la enfermedad.

En las diferentes evaluaciones económicas publicadas sobre CPNM no existe ningún criterio que determine un horizonte temporal concreto. Habitualmente se emplean horizontes temporales de entre 3 a 5 años, ya que suelen ser los que se emplean en los ensayos clínicos que sirven como base para obtener los resultados en salud (Holleman et al., 2020). La duración de cada ciclo varía en función del estudio. En nuestro caso, suele ser de 28 o 30 días, considerándose una duración adecuada para el ritmo de desarrollo del cáncer de pulmón y coincide con el número de comprimidos que lleva cada envase de fármaco TKI.

Sin embargo, la mayoría de los pacientes prefieren disfrutar de los beneficios terapéuticos lo antes posible y diferir o retrasar los costes lo más que sea posible. Por ello, en las evaluaciones económicas con una duración (horizonte temporal) superior a un año, es necesario aplicar un ajuste temporal conocido como tasa de descuento tanto a los resultados en salud como a los costes, que permita transformar éstos al momento presente en el que se realiza el estudio farmacoeconómico (Severens & Milne, 2004). A pesar de que no existe ninguna duda en la aplicación de las tasas de descuento en los costes, ha existido cierta disconformidad con la aplicación de estas en los resultados en salud (Bos et al., 2005). Sin embargo, actualmente sí que existe cierto consenso en la mayoría de las guías a favor de la aplicación de los ajustes temporales tanto a los resultados en salud como a los costes, ya que permite que se puedan realizar comparaciones de los resultados de diferentes evaluaciones económicas elaboradas con distintos horizontes temporales, puesto que de otra forma no podrían ser comparables entre sí (Zhao et al., 2018). Aunque habitualmente se emplean y recomiendan tasas de descuento que varían entre 3% al 5%, en España se suele recomendar un valor del 3% (López-Bastida et al., 2010). La tasa de descuento se calcula mediante la aplicación de la siguiente fórmula:

$$\text{Factor de descuento} = \frac{1}{(1 + Tasa\ de\ descuento)^{años}}$$

Manejo de la incertidumbre y análisis de sensibilidad

Los modelos farmacoeconómicos son representaciones de la realidad con las que se intenta simular todas las posibilidades que puedan suceder en un medio o largo plazo tras la aplicación de las intervenciones sanitarias objeto de estudio. Sin embargo, debido a la incertidumbre inherente a estos modelos, el empleo de análisis de sensibilidad resulta imprescindible para evaluar los cambios producidos en función de las variables principales. Por ello es importante definir las diferencias existentes entre *variabilidad, incertidumbre* y *heterogeneidad.* La *variabilidad* surge de las diferencias en el valor de una cantidad entre diferentes miembros de una población. Representa la variación natural que se va a producir entre los pacientes de una población en su respuesta ante un tratamiento, independientemente de que se hayan seleccionado dichos pacientes con unas características muy similares. Se define por medidas centrales (media, mediana), dispersión (ancha, estrecha) y la forma (simétrica o asimétrica). Además, resulta importante realizar un análisis por cada subgrupo (estratificación). La *incertidumbre* se podría definir como la falta de conocimiento del valor real de un parámetro para la población general, es decir, la imposibilidad de saber de manera segura e irrebatible la media esperada de costes y resultados en salud que un determinado tratamiento producirá en la población objeto de estudio. Para reducir dicha incertidumbre (nunca se podrá eliminar), se requiere una información adicional aportada gracias a la realización de los análisis de sensibilidad. La *heterogeneidad* se refiere a las diferencias existentes entre los pacientes que presentan diferentes características, por lo que deberían ser tratados de manera distinta.

Por lo que se refiere a las incertidumbres sobre los costes, beneficios y la relación entre ambos, se distinguen tres orígenes:

- **Incertidumbre metodológica:** se refiere a la incertidumbre sobre el método analítico empleado, es decir, se modificarán el valor de las variables consideradas del caso base mediante el análisis de sensibilidad determinístico.
- **Incertidumbre de los parámetros:** debido a que no se conocen o no pueden conocerse con certeza los verdaderos valores numéricos de los parámetros, se evalúa mediante el análisis de sensibilidad probabilístico.

- **Incertidumbre estructural o sobre el modelo:** se refiere a la incertidumbre derivada a la elección del modelo apropiado, ya que se trata de una simplificación de la enfermedad objeto de análisis.

Para manejar la incertidumbre, los métodos más empleados son los análisis de sensibilidad. Se distinguen dos tipos: análisis de sensibilidad determinístico (univariante o multivariante), y el análisis de sensibilidad probabilístico.

El **análisis de sensibilidad determinístico** permite identificar y medir los parámetros que resultan más influyentes en los resultados finales y sirve para valorar el grado de robustez del análisis. Una vez realizado este análisis se comprueba que ninguna de las variables estudiadas modifica en exceso los resultados del caso base, entonces se considera que el modelo es sólido y robusto (Claxton, 2012).

Si en este análisis se modifica un único parámetro, se denomina univariante, pero si se modifican dos o más parámetros entonces pasa a denominarse multivariante.

- **Análisis de sensibilidad univariante:** se trata de un tipo de análisis muy sencillo que permite calcular como afecta a los resultados finales la modificación de una única variable. Los parámetros modificados son independientes unos de otros y es fácilmente comprensible. La representación de los resultados se realiza mediante un "diagrama de Tornado", representado en la Figura 16.
- **Análisis de sensibilidad multivariante:** al modificar más de un parámetro, su realización resulta más complicada, así como la presentación de los resultados. Normalmente se representa como un "análisis de escenarios", cada uno de los cuales afecta a varios parámetros a un tiempo.

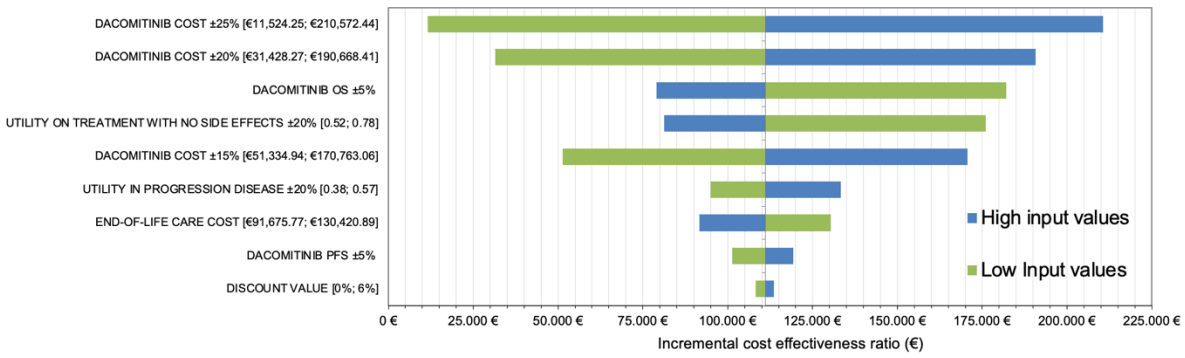

Figura 16. Diagrama de Tornado para análisis de sensibilidad univariante

Habitualmente, en las evaluaciones económicas resulta imprescindible la realización de **análisis de sensibilidad probabilísticos** que permitan completar los resultados obtenidos con el objetivo de que la estimación de los datos se aproxime en mayor medida a la realidad, así como valorar la incertidumbre global del modelo (Soto-Álvarez, 2012).

Los métodos probabilísticos consisten en representar cada uno de los parámetros del modelo mediante funciones de distribución probabilísticas en lugar de hacerlo mediante estimaciones puntuales, tal como se haría en un análisis determinístico. Se asignan rangos y distribución de probabilidades a las variables inciertas. De esta manera, además del posible rango de valores para cada variable incierta, se añade información sobre la probabilidad de que se presenten en realidad los distintos valores comprendidos en dicho rango.

Los análisis de sensibilidad probabilísticos se realizan a través de la simulación de Monte Carlo (Griffin et al., 2006). Se diferencian dos tipos de simulaciones de Monte Carlo:

- **Simulación de primer orden:** evalúa la variabilidad de la población estudiada a la cual pertenecen los pacientes del modelo.
- **Simulación de segundo orden:** cada una de las variables van a ser representadas mediante funciones de distribución probabilística. Se elegirá aquella distribución de probabilidad que sea compatible con el rango de los valores posibles de la variable, la naturaleza de la misma, la forma de los datos y el método de estimación empleado (Claxton et al., 2005). Las distribuciones habitualmente empleadas son: normal, beta, gamma, dirichlet, log-normal y Weibull.

En nuestro estudio, las distribuciones que hemos empleado han sido gamma para los costes, beta para los valores de utilidad y dirichlet para las probabilidades de transición.

Una vez obtenidos los valores del análisis probabilístico, éstos deben ser representados para su interpretación. Los métodos más habitualmente empleados son: **el plano coste-efectividad** (Figura 17) (ya explicado en el apartado *Análisis coste-efectividad*) y **la curva de aceptabilidad.**

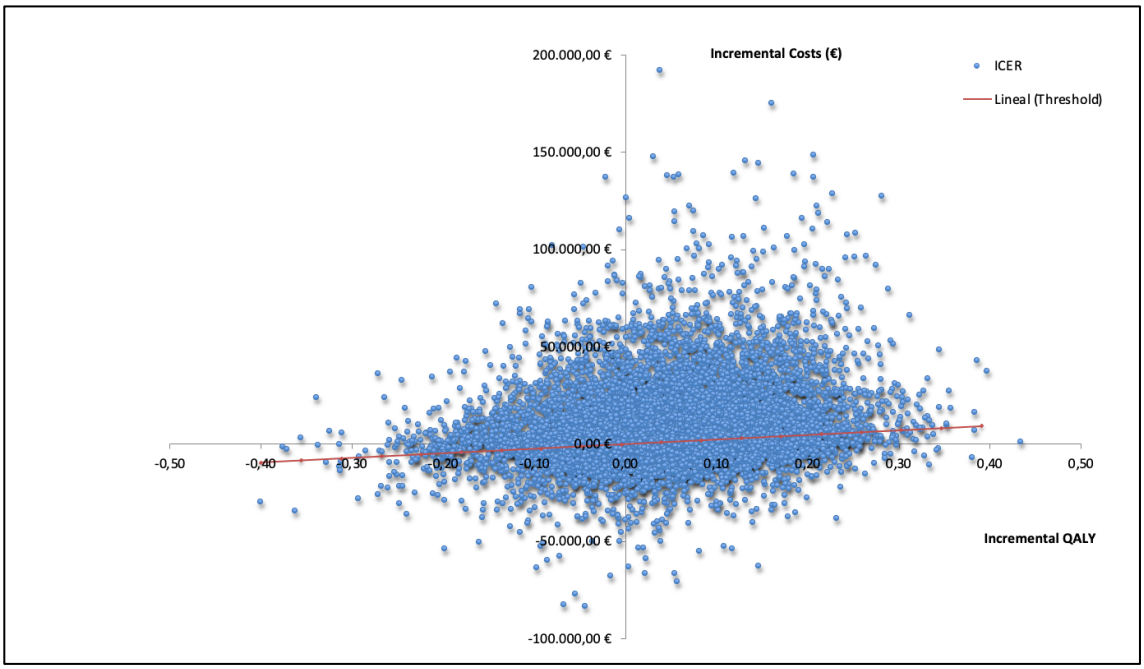

Figura 17. Representación de plano-coste-efectividad

La curva de aceptabilidad es una manera adicional de representar los resultados del plano coste-efectividad. Se trata de una adaptación gráfica del plano de coste-efectividad que permite relacionar el valor del RCEI obtenido en cada simulación con la probabilidad de ser coste-efectivo en función de los valores de diferentes umbrales. Mediante esta representación se consigue relacionar la incertidumbre del estudio con la toma de decisiones, todo ello en un único gráfico (Fenwick et al., 2004). Su representación se realiza mediante una gráfica en la que el eje de ordenadas refleja la probabilidad de coste-efectividad del fármaco, y en el de abscisas el umbral de coste-efectividad, frente a un comparador en función del umbral establecido (Figura 8).

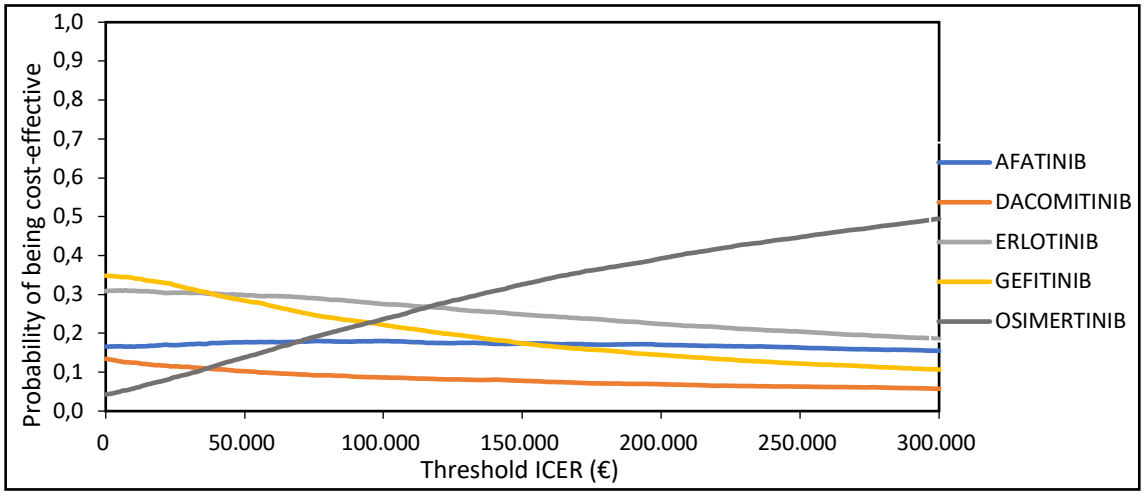

Figura 18. Curva de aceptabilidad

REVISIÓN SISTEMÁTICA Y METAANÁLISIS

Las **revisiones sistemáticas (RS)** empleadas en evaluaciones económicas son análisis científicos secundarios cuyo objetivo será sintetizar y analizar la evidencia económica respecto a un tema concreto de forma clara, estructurada y sistemática (Moher et al., 2009). Por tanto, cualquier revisión sistemática de evaluaciones económicas debería ser precisa, informativa, completa y rigurosa para ser considerada como válida para poder reducir el sesgo y ser reproducible (Soto-Álvarez, 2012).

El **meta-análisis** es un análisis estadístico de una amplia gama de análisis de resultados procedentes de una RS, a través del cual mediante métodos estadísticos, obtendremos un dato agregado del tamaño de efecto de las alternativas terapéuticas estudiadas frente a un comparador común a todas ellas, y donde el grado de heterogeneidad entre los estudios incluidos permita una comparación cualitativa (Moher et al., 2009; Soto-Álvarez, 2012).

Una revisión sistemática es el proceso de obtener estudios cuyos resultados pueden o no combinarse matemáticamente para llegar a una conclusión. Cuando los resultados de los estudios primarios se resumen, pero no se combinan con métodos estadísticos, el resultado se denomina **revisión sistemática cualitativa** o **revisión sistemática sin más.** Si los resultados se combinan con métodos estadísticos, se denomina revisión **sistemática cuantitativa o meta-análisis.** Si bien es una opción válida presentar una revisión sistemática sin meta-análisis, no es aceptable un meta-análisis que no derive de una revisión sistemática.

Para poder elaborar de manera adecuada una RS y meta-análisis, existen una serie de directrices ya consensuadas que únicamente estarán condicionadas por la calidad del método empleado y del contenido que presenten los estudios individuales incluidos. Estas directrices están basadas en el *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA), el cual es una actualización del QUality Of Reporting Of Meta-analysis (QUOROM), y que está integrada por una *cheklist* de 27 ítems y 4 diagramas de flujo de 4 fases (Liberati et al., 2009; Moher et al., 2009).

Una vez iniciada una RS, el primer punto a tratar es definir claramente los objetivos y el enfoque de esta, lo cual se consigue planteando preguntas claramente delimitadas y formuladas. Estas preguntas deben especificar:

- Tipo de personas (participantes).

- Patología o condiciones que se pretende estudiar.
- Población y ámbito de interés.
- Resultados concretos que se pretenden obtener.
- Tipo de estudios que se van a considerar (sólo ensayos clínicos o también estudios observacionales).

A continuación, se procederá a la selección de los estudios que formarán parte de la RS, todo ello a través de una estrategia de búsqueda que debe caracterizarse por ser completa, reproducible y exhaustiva. Por tanto, deberá de indicarse de manera clara y precisa las bases de datos que hayan sido consultadas (Medline, Embase, Excepta Medica, Cochrane library…) sin dejarse de incluir la llamada literatura "gris", la cual se refiere a referencias no indexadas, tesis doctorales, actas de congresos, documentos de sociedades científicas, etc. También deberán especificarse los componentes claves de la búsqueda (palabras clave), que generalmente incluyen la patología o tecnología sanitaria de interés, y los términos booleanos incluidos (Moher et al., 2009; Soto-Álvarez, 2012).

Resulta necesario que los estudios que se incluyan sean lo suficientemente adecuados para que tanto la RS como el posterior meta-análisis no presenten una baja calidad (Moher et al., 2009). Por ello, existen diferentes guías las cuales establecen mediante *cheklists* una serie de puntos que deben ser considerados para incluir el estudio en una RS en función del tipo de estudio que se evalúe. Las más destacables en función del tipo de estudio:

- Revisiones sistemáticas y meta-análisis: guía PRISMA (Liberati et al., 2009):
- Ensayos clínicos: guía Consort (Eldridge et al., 2016; Moher et al., 2012) y la Escala Jadad (Jadad et al., 1996).
- Estudios observacionales: guía STROBE (von Elm et al., 2007).
- Evaluaciones económicas: *cheklist* CHEERS (Husereau et al., 2013).

Una vez realizada la selección de los estudios, se procederá a la extracción de los datos de interés. Este proceso deberá realizarse mediante un formulario de recogida de datos, comprobando que cada estudio cumple los criterios de validez previamente consensuados. Se recomienda que la extracción de los datos la realicen dos personas.

Una vez ya ha sido elaborada la RS, se procederá a realizar el meta-análisis en red que servirá para realizar comparaciones y calcular los resultados. Encontramos dos tipos de aproximaciones a los meta-análisis en red:

- Aproximación **frecuentista** o tradicional: el parámetro desconocido es considerado fijo y se basa en la muestra aleatoria representativa de la población estudiada. Por tanto, se espera que el 95% de confianza para el parámetro objeto de estudio pueda contener el 95% de las veces el verdadero parámetro poblacional, mediante la realización de repetidos experimentos con distintas muestras de la misma población (Catalá-López et al., 2014).
- Aproximación **bayesiana:** utiliza el conocimiento previo para analizar los datos, de modo que si conoce la probabilidad de que un evento suceda, su valor variará cuando se disponga de dicha información externa, empleando dicho dato para calcular la inferencia (Catalá-López et al., 2014).

El **meta-análisis en red o *network* meta-análisis** permite evaluar los efectos relativos de las diferentes intervenciones que se comparan mediante múltiples comparaciones indirectas por pares, teniendo en cuenta toda la red de estudios implicados, tanto comparaciones directas como indirectas y mixtas, lo cual permite una evaluación más global de los efectos de las diferentes intervenciones utilizando una única medida (Catalá-López et al., 2014). Las comparaciones en un meta-análisis en red pueden ser de tres tipos:

- **Comparaciones directas:** son las menos frecuentes y se basan en comparar la tecnología sanitaria objeto de estudio con un tratamiento activo, considerado éste como *gold* estándar.
- **Comparaciones indirectas:** las más habituales, se basa en comparar dos intervenciones frente a un comparador común, generalmente placebo.
- **Comparaciones mixtas:** permiten combinar los resultados o efectos de los tratamientos procedentes de comparaciones directas e indirectas.

Hay que destacar que, a pesar de que los resultados de los ensayos clínicos *head-to-head* pueden ser determinantes, el hecho de combinarlos con los resultados de evaluaciones indirectas similares mejora la precisión de la estimación del resultado del tratamiento (Catalá-López et al., 2014; Dias et al., 2010).

Resulta de utilidad la representación del meta-análisis en red mediante un gráfico que permita entender y comprobar que tipo de comparaciones se han realizado entre los estudios incluidos (Catalá-López et al., 2014) (Figura 19).

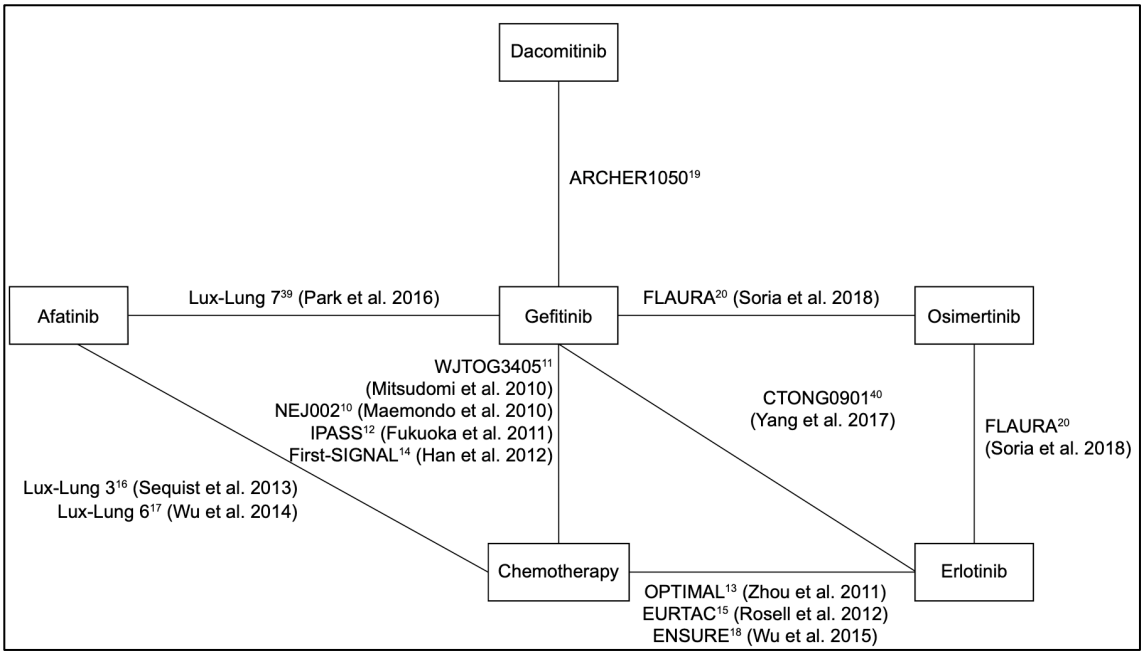

Figura 19. Representación de meta-análisis en red.

Los meta-análisis en red se realizan mediante una serie de software estadísticos. Los más habitualmente empleados son *R-Statistics, Stata* y *WinBUGS.*

Una vez ya se tenga planteado el meta-análisis, resulta imprescindible comprobar que se cumplan los siguientes criterios: consistencia, similitud y heterogeneidad.

- **Consistencia:** debe existir coherencia entre la evidencia procedente de las comparaciones directas e indirectas. En caso de que no lo fueran, se aconseja analizar las causas de la discrepancia (Catalá-López et al., 2014; Song et al., 2011). Para valorarlo se emplea el factor de inconsistencia.
- **Similitud:** se refiere a que los estudios analizados deben ser lo más parecidos posibles o, en su defecto, no deben existir grandes diferencias respecto a determinados factores modificadores del efecto como población, diseño, etc. El concepto *transitividad* se emplea indistintamente cuando nos referimos a *similitud*, sin embargo, también se refiere al supuesto que hay que adoptar cuando se establece una comparación indirecta a través de un comparador común (Catalá-López et al., 2014).

- **Heterogeneidad:** se refiere a la presencia de variabilidad no aleatoria, entre los efectos de los tratamientos que forman parte del meta-análisis (Catalá-López et al., 2014; Liberati et al., 2009). Resulta importante la valoración y cuantificación de la heterogeneidad, puesto que según su magnitud puede tener influencia en la validez de las conclusiones obtenidas.

- **¿Cómo se valora la heterogeneidad?**

La valoración y cuantificación de la heterogeneidad de los estudios evaluados en el meta-análisis, se realiza mediante diferentes métodos estadísticos:

- **Prueba Q de Cochran:** es la más empleada para valorar la existencia de heterogeneidad. Se basa en la prueba estadística de Chi-cuadrado basada en el cálculo de la suma de las desviaciones cuadráticas entre el resultado individual de cada estudio y el resultado global, ponderadas por el mismo peso con el que cada resultado interviene en el cálculo global (DerSimonian & Laird, 2015):

$$Q = \Sigma w_i (T_i - \overline{T})^2$$

  Sin embargo, si el número de estudios incluidos es pequeño, su capacidad para detectar heterogeneidad es baja, al poseer poca potencia de contraste. Tampoco sirve para comparar distintos meta-análisis en los que intervienen diferente número de estudios.

- **Índice de heterogeneidad I^2:** permite determinar como la posible heterogeneidad existente puede afectar a las conclusiones del meta-análisis. Este índice indica la proporción de la variación entre estudios respecto a la variación total, es decir, la proporción de la variación total que es atribuible a la heterogeneidad (Higgins & Thompson, 2002). Se calcula de la siguiente forma:

$$I^2 = \frac{\tau^2}{\tau^2 + \sigma^2}$$

  τ^2 = variablidad entre estudios

  σ^2= variabilidad interna en los estudios

Junto a este índice se suele acompañar un valor de intervalo de confianza, que determina una heterogeneidad baja, moderada o alta, si el valor I^2 es del 25%, 50% o 75%, respectivamente.

Los errores en la extracción de los datos de los diferentes estudios que componen el meta-análisis así como las diferencias entre los subgrupos de estos, suelen ser las causas más habituales que generan un valor de heterogeneidad alto (Gøtzsche et al., 2007).

La representación gráfica de las pruebas estadísticas existentes permite que de manera visual podamos comprobar la magnitud de la variabilidad entre estudios. Para ello, las representaciones más empleadas para cualquier tipo de estudio (observacional y experimental) será el gráfico de Galbraith (Galbraith, 1988)(Figura 10), mientras que emplearemos el gráfico de L'Abbé únicamente a meta-análisis de ensayos clínicos (L'Abbe et al., 1987)(Figura 20).

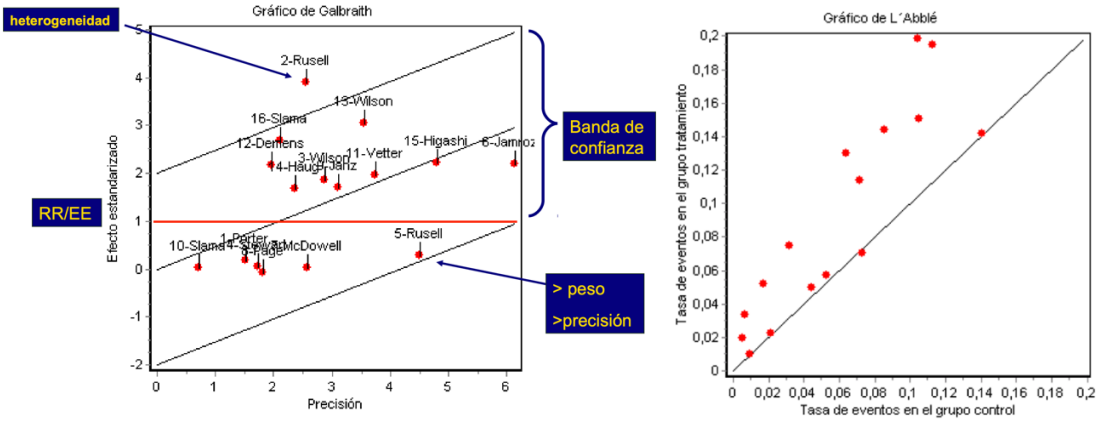

Figura 20. Gráfico de Galbraith y L'Abbé

- **¿Cómo se combinan y presentan los resultados de un meta-análisis?**

Una vez se han seleccionado los estudios que formarán parte del meta-análisis, la combinación y presentación de los resultados se podrá realizar mediante diferentes técnicas. La selección del método adecuado va a depender principalmente de dos factores: el tipo de medida de resultado/efecto empleado y de la valoración del grado de heterogeneidad de los resultados de los estudios. Para calcular el resultado de un

meta-análisis, éste se realiza mediante una media ponderada de los resultados de cada estudio, atribuyendo a cada estudio un peso en función de su precisión (inversa de la varianza), considerando para ello el tamaño muestral y la variabilidad. Por lo tanto, aquellos estudios que presenten una mayor variabilidad, como los estudios de pequeño tamaño muestral aportarán un menor peso al resultado del meta-análisis.

La combinación de los resultados se puede realizar mediante dos modelos, según si se incluye la variabilidad entre las intervenciones comparadas en un mismo estudio (modelo de efectos fijos), o se incluye además la variabilidad entre los distintos estudios incluidos en el meta-análisis (modelo de efectos aleatorios).

- **Modelo de efectos fijos:** parte del supuesto de que existe un único efecto en la población y no tiene en cuenta la variabilidad de los resultados entre los estudios. Por lo tanto, el tamaño de un estudio y su propia variabilidad (variabilidad dentro del estudio) son los únicos factores que determinan su peso en un meta-análisis.
- **Modelo de efectos aleatorios:** en cambio, tiene en cuenta la heterogeneidad potencial al considerar que los efectos de la exposición/intervención varían en la población y que los estudios incluidos en la revisión son sólo una muestra aleatoria de todos los efectos posibles. Esto tiene en cuenta no sólo la varianza intrínseca (variabilidad intra-estudio) sino también la variabilidad que puede existir entre los estudios (variabilidad entre-estudios).

No existe ningún consenso acerca de qué modelo emplear, puesto que ambos son válidos y ampliamente utilizados. No obstante, podemos encontrar diferencias que condicionan la decisión de llevar a cabo el meta-análisis con un modelo u otro. Por ello, se recomienda seleccionar el modelo con mejor equilibrio entre ajuste de los datos y parsimonia (sencillez) (Jansen et al., 2014).

Desde un enfoque Bayesiano, la elección del modelo más sencillo en función del ajuste de los datos debe basarse en el Deviance Information Criteria (DIC) (Ando, 2013). El cálculo de este parámetro se realiza como la suma de los parámetros efectivos del modelo (pD) y la media obtenida a posteriori de la deviación del modelo (Dbar). Dbar es un indicador que determina como de bien se ajusta el modelo a los datos y disminuye a media que aumenta el número de parámetros del modelo. Por lo que se refiere a pD, éste compensa dicho efecto, por lo que los modelos muy complejos se

ven penalizados. El parámetro DIC permite comparar y seleccionar modelos contrastando simultáneamente varias hipótesis específicas (Spiegelhalter et al., 2002).
Gracias a este método de aproximación bayesiana, podemos establecer un ranking de probabilidades en la que cada tratamiento puede ser seleccionado en comparación con los otros estudiados. Esto significa que la clasificación de probabilidades puede estimarse sobre la base de la localización, la prevalencia y las distribuciones superpuestas de los efectos relativos del tratamiento. No obstante, deben ser evaluados objetivamente para evitar posibles sesgos debidos a la exageración de pequeñas diferencias en los efectos relativos, sobre todo si se apoyan en información limitada (Spiegelhalter et al., 2002). Por lo tanto, hay que enfocarse en la magnitud de los efectos del tratamiento y su incertidumbre (Ando, 2013; Catalá-López et al., 2014).

- **Meta-análisis en red de datos de supervivencia con fracciones polinómicas.**

Cuando se realiza un meta-análisis en red utilizando la hazard ratio (enfoque Bayesiano), asumimos que los riesgos son proporcionales durante todo el periodo de tiempo. Esta hipótesis no sólo es a menudo inverosímil, sino que puede tener un enorme impacto en las decisiones basadas en el análisis de la eficacia de nuestro estudio de coste-efectividad. En los casos extremos, las curvas de supervivencia se cruzan y la razón de riesgos no es constante. Además, las curvas pueden no ser proporcionales, aunque no haya cruce.
En los ACE, las diferencias de supervivencia entre los fármacos objeto de estudio son muy significativas. La práctica habitual consiste en asumir una determinada función de supervivencia paramétrica para el fármaco de referencia (por ejemplo, Weibull) y utilizar la hazard ratio del meta-análisis (de red) para calcular la función de supervivencia correspondiente para el fármaco de interés. Debido a que la cola de la función de supervivencia tiene un gran impacto en la supervivencia esperada, las violaciones de la proporcionalidad en la hazard ratio, si se asume que es constante, pueden conducir a estimaciones muy sesgadas.
Como alternativa al meta-análisis en red de los datos de supervivencia, en el que el efecto del tratamiento está representado por un único parámetro, el empleo de este nuevo método permitirá que la hazard ratio presente un enfoque multivariante del efecto del tratamiento.

Por ello, mediante el método de las fracciones polinómicas se va a conseguir modelar la hazard ratio en función del tiempo. Este enfoque permite realizar meta-análisis en red de la supervivencia con modelos que se ajustan mejor a los datos. Además, se puede calcular la supervivencia esperada, lo que facilita el análisis de la relación coste-efectividad.

- **¿Cómo se representa gráficamente un meta-análisis?**

La presentación gráfica de los resultados del meta-análisis facilita una interpretación sencilla y rápida. Para ello se emplea los denominados diagramas de efectos o *forest plot* (Figura 21). Este gráfico es una especie de bosque, donde los árboles son los estudios primarios del meta-análisis, y donde cada uno de estos estudios está representado por un cuadrado cuya área suele ser proporcional a la contribución de cada estudio al resultado general. Asimismo, el cuadrado se encuentra dentro del segmento que representa los límites extremos del intervalo de confianza. Si estos intervalos no rebasan el valor nulo de la variable de resultado, entonces el estudio pasaría a ser considerado estadísticamente significativo. Hay que destacar que la medida resumen se representa habitualmente mediante un símbolo en forma de diamante, cuyo centro indica la estimación puntual y la anchura el rango del intervalo de confianza.

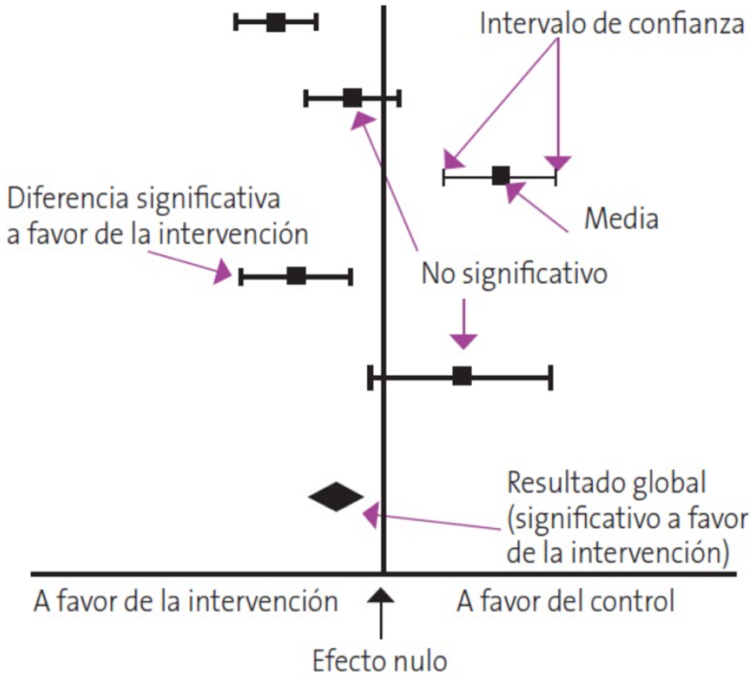

Figura 21. Gráfico de Forest Plot

JUSTIFICACIÓN

El Sistema Nacional de Salud español se enfrenta a uno de los retos más importantes de las últimas décadas: el aumento constante y progresivo del gasto sanitario. A este hecho cabría añadir la posibilidad de tratar muchas patologías que anteriormente resultaban mortales, generando un fenómeno de cronificación de la enfermedad, con los consiguientes costes económicos. Todo ello implica que las necesidades sanitarias de la población aumenten en un contexto donde los recursos económicos disponibles son cada vez más limitados.

En España, como en la mayor parte de los países desarrollados, el cáncer es una de las enfermedades con mayor impacto desde el punto de vista de la salud pública. Las muertes provocadas por cáncer son la segunda causa de muerte en España, únicamente superada por las enfermedades cardiovasculares. Miles de pacientes con cáncer de pulmón se someten cada año a diferentes procedimientos preventivos, diagnósticos y terapéuticos. Además, la financiación que se destina a los programas de diagnóstico precoz o a estrategias terapéuticas antineoplásicas es considerable, y se calcula que en los próximos años el incremento del gasto en oncología va a ser mayor en comparación con otras áreas de la medicina.

Hasta hace pocos años, los pacientes diagnosticados con CPNM avanzado y mutación EGFR recibían varios ciclos de quimioterapia complementaria, cuyo beneficio en su supervivencia era limitado. Sin embargo, la detección de esta mutación EGFR que representa un 15% de todos los casos de CPNM en nuestro país, ha permitido el desarrollo de tratamientos dirigidos muy eficaces, los llamados TKIs.

Actualmente se han desarrollado tres generaciones de TKIs para el tratamiento de CPNM que presentan mutaciones EGFR (primera generación: gefitinib y erlotinib; segunda generación: afatinib y dacomitinib, y tercera generación: osimertinib) cuya mejora en la supervivencia de los pacientes ha resultado muy significativa. Sin embargo, más de la mitad de los pacientes diagnosticados con CPNM EGFR-positivo desarrollaron resistencia al tratamiento con TKIs de primera y segunda generación, lo que se asocia a una mutación adquirida (T790M) en el gen EGFR. El desarrollo de los fármacos de tercera generación como osimertinib, permite el tratamiento de dicha mutación con resultados satisfactorios, pero con un coste más elevado.

Tal y como sucede con otros progresos en el ámbito sanitario, la inclusión de nuevas terapias conlleva un incremento tanto del consumo de recursos sanitarios como de los costes asociados. Por ello, en un contexto como el actual de recursos limitados y control del gasto sanitario, la cuantificación y el análisis de los costes y los resultados en salud no solo resulta deseable, sino imprescindible con el objetivo de ofrecer una atención sanitaria que sea costo-eficiente para el SNS y de calidad para los pacientes.

En la presente tesis, se ha realizado un estudio farmacoeconómico con el objetivo de evaluar el coste-utilidad de los tratamientos de primera línea como erlotinib, gefitinib, afatinib, dacomitinib y osimertinib, para pacientes diagnosticados con CPNM en estadio IIIB/IV que presenten mutaciones EGFR, en el contexto de España.

OBJETIVOS

Esta tesis doctoral se presenta mediante la modalidad de compendio de publicaciones, específicamente artículos científicos en revistas indexadas en el Journal Citation Reports (JCR). Los artículos que la conforman pretenden aportar información original y relevante para la selección del mejor tratamiento terapéutico que mejore la supervivencia y calidad de vida de los pacientes con CPNM avanzado con mutación EGFR.

Objetivo general

Evaluar la relación coste-utilidad de los tratamientos de primera línea, como erlotinib, gefitinib, afatinib, dacomitinib y osimertinib, en pacientes diagnosticados de CPNM en estadio IIIB/IV que presenten mutación EGFR.

Objetivos específicos

Para lograr el objetivo general descrito, es necesario llevar a cabo una serie de objetivos específicos que se describen con más detalle a continuación:

- Realizar un meta-análisis en red de los ensayos clínicos disponibles que permita obtener los datos de eficacia.
- Definir las principales fuentes de información para aportar los datos de calidad de vida y consumo de recursos que se precisan para la elaboración de los estudios de coste-utilidad.
- Implementar un modelo de Markov que permita describir la progresión del CPNM EGFR+ en pacientes que se encuentren en estadio IIIB/IV de la enfermedad, en un periodo de 15 años.
- Transformar variables intermedias como supervivencia libre de progresión (SLP) y supervivencia global (SG) en resultados en salud (AVAC), mediante el empleo de un modelo de Markov para el CPNM EGFR+, como base para la realización de los análisis coste-utilidad.
- Calcular el RCEI para cada uno de los tratamientos evaluados que permita estimar la eficiencia de los fármacos para el umbral de 24.000€/AVAC.
- Definir e identificar las variables que presenten un mayor impacto en el RCEI, y evaluar su influencia mediante la elaboración de un AS univariante.

- Evaluar la incertidumbre asociada a cada uno de los parámetros incluidos en el modelo y elaborar un AS probabilístico que posibilite la confección de un plano coste-utilidad y una curva de aceptabilidad para cada tratamiento evaluado.
- Establecer métodos de negociación para que las alternativas terapéuticas estudiadas puedan ser consideradas coste-efectivas.

MATERIAL Y MÉTODOS

REVISIÓN SISTEMÁTICA Y METAANÁLISIS

En los dos primeros artículos publicados y recogidos en esta tesis, no fue necesaria la elaboración de meta-análisis ni revisión sistemática, ya que únicamente se había publicado un ensayo clínico de cada uno de los fármacos objeto de estudio (dacomitinib y osimertinib), el cual era comparado con el standard-of-care disponible (primera generación de TKIs).

Sin embargo, el **Artículo III** requirió la elaboración de un meta-análisis en red, con el objetivo de valorar la eficacia y seguridad de todos los fármacos TKIs disponibles frente a CPNM en pacientes diagnosticados en estadio IIIB/IV con mutación en EGFR.

Los estudios incluidos fueron 13 ensayos clínicos aleatorizados que recogían datos de 3.539 pacientes con CPNM-EGFR+, procedentes de una revisión sistemática previamente publicada (Holleman et al., 2019a). No hubo restricción de tiempo, ni de idioma.

Las medidas de eficacia consideradas fueron SLP, SG, tasa de respuesta objetiva (TRO) y cuantificación de efectos adversos.

Por lo que se refiere a la evaluación de la seguridad y toxicidad de los fármacos, se tuvieron en cuenta los efectos adversos que afectaran a la calidad de vida y al coste de la enfermedad. Por ello, se consideraron los efectos adversos grado III-IV, es decir, aquellos cuya gravedad podría dar lugar a un ingreso hospitalario, poner en riesgo la vida del paciente o provocar una discapacidad significativa.

Tras la selección de los ensayos clínicos, se procedió a realizar un meta-análisis en red mediante aproximación estadística bayesiana empleando el método de Monte Carlo basado en cadenas de Markov (Markov Chain Monte Carlo, MCMC), y en la metodología propuesta por Dias (Dias et al., 2018). En primer lugar, utilizando el programa WebPlotDigitizer, digitalizamos los datos individualizados de los pacientes de las curvas Kaplan-Meier para la SLP y la SG, basados en los 13 ensayos clínicos previamente seleccionados. Los datos individuales de los pacientes (DIP) según el algoritmo propuesto por Guyot (Guyot et al., 2012). Se empleó un pseudo-DIP para estimar el número de pacientes con eventos en cada intervalo de tiempo. Para calcular la variación de la Hazard ratio de cada comparación a lo largo del tiempo, se utilizaron

las fracciones polinómicas. A partir de los resultados, se construyeron curvas de SG y SLP para cada uno de los fármacos. Este enfoque relaja la proporcionalidad de los riesgos y se ajusta mejor a los datos disponibles (Jansen, 2011).

Dos meta-análisis en red fueron realizados de manera independiente, uno para las curvas de SG y otro para las curvas de SLP, empleando el software estadístico R (versión 3.6.3) y el paquete J.A.G.S. (Depaoli et al., 2016). El muestreo posterior se llevó a cabo mediante el método de Montecarlo basado en cadenas de Markov en el que se realizaron cuatro cadenas de 15.000 muestras tras descartar un *burn-in* de 5.000 iteraciones. Se analizaron los datos utilizando tanto modelos de efectos fijos como de efectos aleatorios. Se asignaron distribuciones previas vagas a todos los parámetros estocásticos. Fracciones polinómicas de primer y segundo orden fueron evaluadas. Para ello se seleccionaron un conjunto de cinco valores (-2, -1, 0, 1, 2) para los exponentes p1 y p2. Basándose en el criterio DIC y en la inspección visual, se seleccionó el modelo que mejor se ajustaba para trazar las curvas de supervivencia agrupadas, prefiriéndose los valores DIC más bajos. Se seleccionaron modelos de efectos fijos, de primer grado y de exponente 0 tanto para la SG como para la SLP.

Modelo de Markov. Análisis Coste-utilidad.

Para la realización del análisis farmacoeconómico, se procedió a desarrollar un modelo de Markov en el que se modelizó una cohorte de pacientes con CPNM en estadio IIIB/IV y mutaciones en el EGFR.

El modelo presentó tres estados de salud mutuamente excluyentes a través de los cuales podían transitar los pacientes: enfermedad libre de progresión, enfermedad en progresión y muerte. Los pacientes ingresaban en el modelo una vez habían sido diagnosticados en estadio IIIB o IV de la enfermedad, y siempre y cuando, no hubiesen recibido previamente ningún tratamiento.

De acuerdo con los estados de salud que se muestran en la Figura 12, para cada ciclo de simulación de 28 días, se asumió que todos los pacientes ingresaban en el modelo en el estado enfermedad estable, y únicamente podían transitar de un estado de salud a otro, o permanecer en el mismo estado, una vez por cada ciclo. Los pacientes que se encontrasen en el estado enfermedad estable o en el estado enfermedad en progresión, podían transitar al estado muerte en cualquier ciclo. En el estado enfermedad estable, los pacientes recibían el tratamiento del TKI correspondiente, mientras que los pacientes del estado enfermedad en progresión recibían una segunda línea de tratamiento. Las probabilidades de transición se obtuvieron de la realización del meta-análisis en red explicado en el apartado anterior, y procedentes de los datos de SLP y SG de los 13 ensayos clínicos seleccionados.

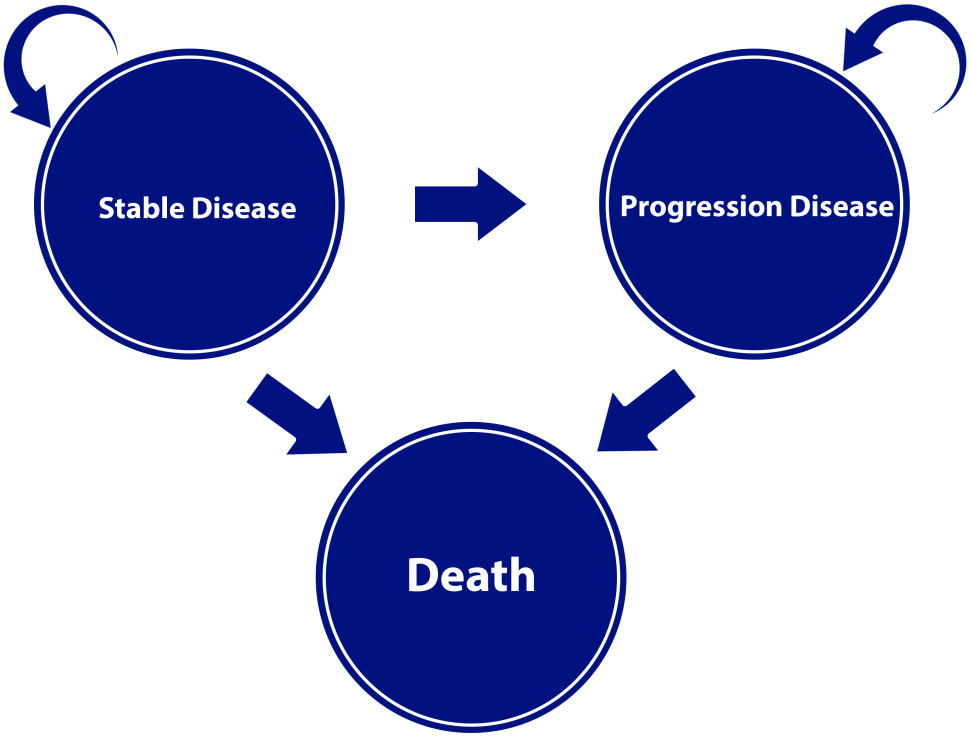

Figura 12. Modelo de Markov de CPNM

El modelo fue desarrollado bajo la perspectiva del Sistema Nacional de Salud español. El umbral para establecer si una alternativa resultaba coste-efectiva fue de 24.000 €/AVAC, según las recomendaciones en España (Vallejo-Torres et al., 2018). Un descuento del 3% fue empleado tanto para los costes como para los resultados en salud, de acuerdo con las directrices españolas (Bastida et al., 2010).

Se utilizó un horizonte temporal de 15 años, ya que refleja de forma exhaustiva los costes y los resultados en salud esperados de los pacientes durante toda la duración del estudio. Los resultados se presentaron como costes (€), AVACs y RCEIs.

Opciones de tratamiento

En cada uno de los tres artículos publicados, los pacientes incluidos habían sido recientemente diagnosticados en estadio avanzado de CPNM (estadio IIIB/IV) y presentaban mutación EGFR+. A continuación, se resumen las alternativas comparadas en cada artículo:

- En *Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Alós-Almiñana M, Cortijo J. Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-*

effectiveness analysis. J Comp Eff Res. 2019, se analizó la coste-utilidad, basándose en los datos de eficacia obtenidos del estudio FLAURA (Soria et al., 2018b), de osimertinib en comparación con la terapia estándar TKI-EGFR (erlotinib y gefitinib).

- En *Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Cortijo J. Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2021,* se analizó la coste-utilidad de dacomitinib frente a gefitinib, basándose en los datos de eficacia obtenidos del ensayo clínico ARCHER 1050 (Wu et al., 2017b).
- En *Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer. Expert Rev Pharmacoecon Outcomes Res. 2021,* se evaluó la coste-utilidad de los fármacos TKIs empleados como primera línea de tratamiento (erlotinib, gefitinib, afatinib, dacomitinib y osimertinib) frente a gefitinib, obteniéndose los datos de eficacia de un meta-análisis propio realizado y cuya explicación se resume en dicho artículo.

Estimación de los costes

Todos los costes obtenidos de fuentes anteriores al año de publicación de cada artículo fueron actualizados al año correspondiente basándose en los valores del IPC españoles. Los costes de los fármacos evaluados fueron calculados en base al PVL notificado por la Agencia Española del Medicamento, a los cuales se les restaba los descuentos correspondientes y, finalmente, se les añade el valor del 4% del IVA español. En los costes de adquisición de erlotinib y gefitinib puede observarse una diferencia substancial con respecto a los otros TKIs, debido a que se ha considerado los costes correspondientes de las presentaciones genéricas.

Los costes de manejo de la enfermedad se calcularon a partir de la opinión de un panel de expertos. Dicho coste por ciclo y paciente se estimó multiplicando el coste de los recursos sanitarios necesarios por el coste unitario de cada recurso consumido en el

horizonte temporal de 15 años. Los costes unitarios de cada recurso se obtuvieron del sistema de contabilidad analítica del Servicio Vasco de Salud – Osakidetza.

Los costes de manejo de los efectos adversos producidos por los fármacos TKIs fueron obtenidos de dos artículos publicados en España (Isla et al., 2017; Villa et al., 2015).

El coste de los últimos meses de vida *(end-of-life-care cost)* fue obtenido a partir de un artículo publicado en España (Nuño-Solinís et al., 2017).

Estimación de la calidad de vida

Con el objetivo de poder calcular los valores de AVAC, se precisaron valores de utilidad para los estados enfermedad estable y enfermedad en progresión. Sin embargo, en España no se había publicado ningún estudio que valorase dichos datos de utilidad. Por ello, se emplearon valores de utilidad procedentes de la literatura, que incluían población británica mediante el método *standard gamble* (Nafees et al., 2008).

Para evaluar el impacto de los efectos adversos en la calidad de vida de los pacientes, se calcularon las disutilidades. Para ello, empleando el método *time trade-off,* los valores de disutilidad asociados a los efectos adversos graves de grado 3/4 se obtuvieron de un estudio internacional llevado a cabo en diferentes países como Reino Unido, Francia y Australia (Nafees et al., 2017).

RESULTADOS

Artículo 1

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Alós-Almiñana M, Cortijo J. Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2019 Aug;8(11):853-863. doi: 10.2217/cer-2019-0029. Epub 2019 Sep 3. PMID: 31478399.

Artículo 2

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Cortijo J. Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2021 Mar;10(4):325-335. doi: 10.2217/cer-2020-0233. Epub 2021 Feb 26. PMID: 33635095.

Artículo 3

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer. Expert Rev Pharmacoecon Outcomes Res. 2022 Jun;22(4):637-646. doi: 10.1080/14737167.2022.1987220. Epub 2021 Oct 11. PMID: 34602008.

Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost–effectiveness analysis

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ABSTRACT

Background: osimertinib improves progression-free survival in first-line epidermal growth factor receptor mutation–positive (EGFR) in non-small-cell lung cancer.

Materials and methods: a Markov cohort model including costs, utilities and disutilities, was conducted to estimate quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER) when treating with osimertinib vs standard first-line Tyrosine Kinase Inhibitors (TKIs).

Results: osimertinib presented higher QALYs (0.61) compared to standard EGFR-TKIs (0.42). Osimertinib costs were €83,258.99, in comparison with €29,209.45 for the standard EGFR-TKIs. An ICER of €273,895.36/QALY was obtained for osimertinib.

Conclusions: osimertinib was more effective in terms of QALYs gained than comparators (erlotinib-gefitinib). However, to obtain a cost-effectiveness alternative, a discount greater than 60% in osimertinib acquisition cost is required.

Keywords: cost-effectiveness; EGFR-TKI; Markov; Non-small-cell lung cancer; osimertinib.

1. Introduction

Epidermal growth factor receptor (*EGFR)* mutations are the most usual oncogenic mutation in patients with Non-Small-Cell Lung Cancer (NSCLC) with adenocarcinoma. Detection of EGFR mutations are found in about 10 to 15% of Western patients and 30 to 35% of Asian patients [1]. In Spain, the mutation detection rate in advanced-NSCLC patients was found to be 11.6% in the REASON study (82.6% presenting in-frame deletions in exon 19 and 17.4% presenting L858R mutation in exon 21) [2]. The first-generation EGFR-tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are highly active against cancers with two EGFR common sensitizing mutations (in-frame deletions in exon 19 or L858R mutation in exon 21) [1].

Nevertheless, more than half of the patients with NSCLC with EGFR-activating mutations develop tumor resistance despite the initial beneficial response to first-generation TKIs (erlotinib and gefitinib), generally 9 to 14 months after treatment initiation target [3–8]. Disease progression while on therapy with first-generation EGFR-TKIs is associated with a T790M acquired mutation in the EGFR gene. Consequently, T790M resistance mutation reduces binding of first and second-generation EGFR-TKIs to the target receptor and forces a change of treatment [9–11]. Osimertinib is an oral, third generation, irreversible EGFR-TKI that is currently employed in NSCLC EGFR T790M resistance mutations, with successful results [11–14]. Additionally, FLAURA study has demonstrated the clinical benefit of osimertinib in EGFR-TKI-sensitizing mutations [15]. In FLAURA study, the median progression-free survival (PFS) in patients with untreated EGFR mutated NSCLC was demonstrated to be significantly longer with osimertinib than with standard first-line EGFR-TKIs (18.9 months vs. 10.2 months) with a similar safety profile and lower rates of serious adverse events [15]

To date, only two prior studies have been published evaluating the cost-effectiveness of osimertinib [16,17]. A decision analytic model analysis over a 10-year time horizon has been published evaluating the cost-effectiveness of osimertinib in first-line EGFR-positive NSCLC [17]. Another cost-effectiveness analysis containing a probabilistic Markov model has been published recently, comparing osimertinib vs. the first-generation employed EGFR-TKI in Canada [16]. Therefore, a complete Markov

pharmacoeconomic model analysis in a country with European healthcare system including a deterministic and a probabilistic model of osimertinib in first-line EGFR of osimertinib in first-line EGFR positive NSCLC adenocarcinoma could provide extremely valuable information for medical decision makers to facilitate the optimization of healthcare resources in Europe. The aim of this study is to evaluate the incremental cost-effectiveness ratio (ICER) of osimertinib vs. standard EGFR-TKIs (erlotinib and gefitinib), in order to determine which is the most efficient drug in first line.

2. Materials and methods

2.1. Cost-effectiveness analysis (CEA): Markov model

2.1.1. Design and perspective analysis

A Markov model was adopted to estimate the costs, the quality-adjusted life-years (QALYs) and ICER of two different treatment strategies (osimertinib vs. standard EGFR-TKIs) in two hypothetical cohorts of patients with EGFR-positive sensitizing mutations advanced NSCLC. The model was developed from the Spanish National Health System perspective. The threshold for determining whether a strategy is cost-effective was €24,000/QALY [18]. All the costs were estimated in euros (€) 2018, and a discount rate of 3% was used for costs and effects throughout the model. The Markov model was developed in Microsoft Excel 2011 (Microsoft Corp., Redmond, Washington), using a 15-year time horizon. The results were presented in terms of costs (€), QALYs gained and ICER.

2.1.2. Markov model structure

The model included three mutually exclusive health states: stable disease (SD), progressive disease (PD) and death. Each health state was associated with costs, health effects and the probability of moving to any other state. The structure and transitions allowed in the model are shown in *figure 1*. Initially, all patients were on SD and received one of the two treatment strategies described in *figure 1*. On each 28-day simulation cycle, the hypothetical cohort of patients could remain on SD, experience PD or death. Patients in SD continued treatment with the initial TKIs until progression occurred. When progression, patients were changed to a second-line regimen. After PD occurred, patients could remain in this state or die. PD was simulated until all patients died. Death of patients from any cause were included in this state.

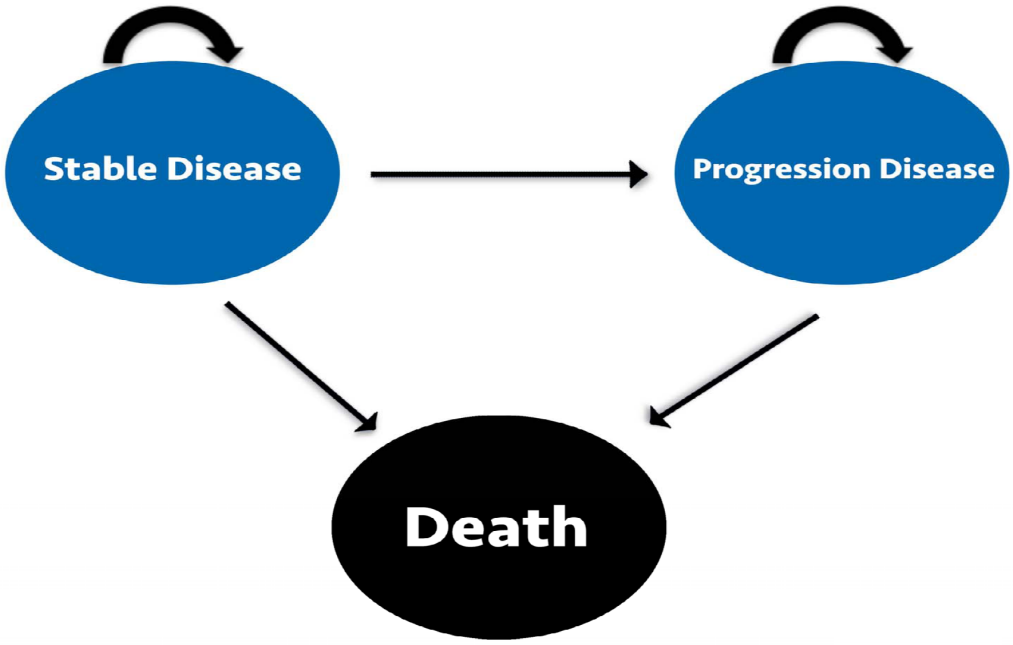


Figure 1. **Structure of Markov model.** Markov model health states.

2.1.3. Treatment alternatives

Each cohort was treated with osimertinib (at a dose of 80 mg once daily) or a standard oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily), according to FLAURA clinical trial [15]

2.1.4. Transitional Probability Data

Transition rates between different states were estimated based on progression of disease and survival values estimated from FLAURA clinical trial [15]. The method of Guyot et al. was employed to recreate the patient level data [19]. Due to the short follow-up of FLAURA trial, OS and PFS were not fully observed, therefore, results were extrapolated by using survival functions. In order to determine the most appropriate parametric survival curve, a goodness-of-fit analysis was conducted based on the best fit model among gamma, log-logistic, Weibull, lognormal, Gompertz, exponential, Royston-Parmar, generalized F and generalized gamma parametric distributions. These analyses were assessed using parametric plots, long-term projections and statistical tests (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) (*figure 2* and *supplementary table 1*). We used visual inspection of the Kaplan-Meier curves, goodness-of-fit statistics, and clinical plausibility to determine the parametric distribution with the best fit. The OS data is still immature (only complete in 25%) For

this reason, a single parametric model (gamma) has been selected for all the treatment arms.

Transition probabilities from SD and PD to death were obtained based on overall survival (OS) and PFS as shown in *supplementary figure 1* and *figure 2*. Finally, the difference between the OS and PFS curves was employed to calculate the probability of the patient remaining on PD state.

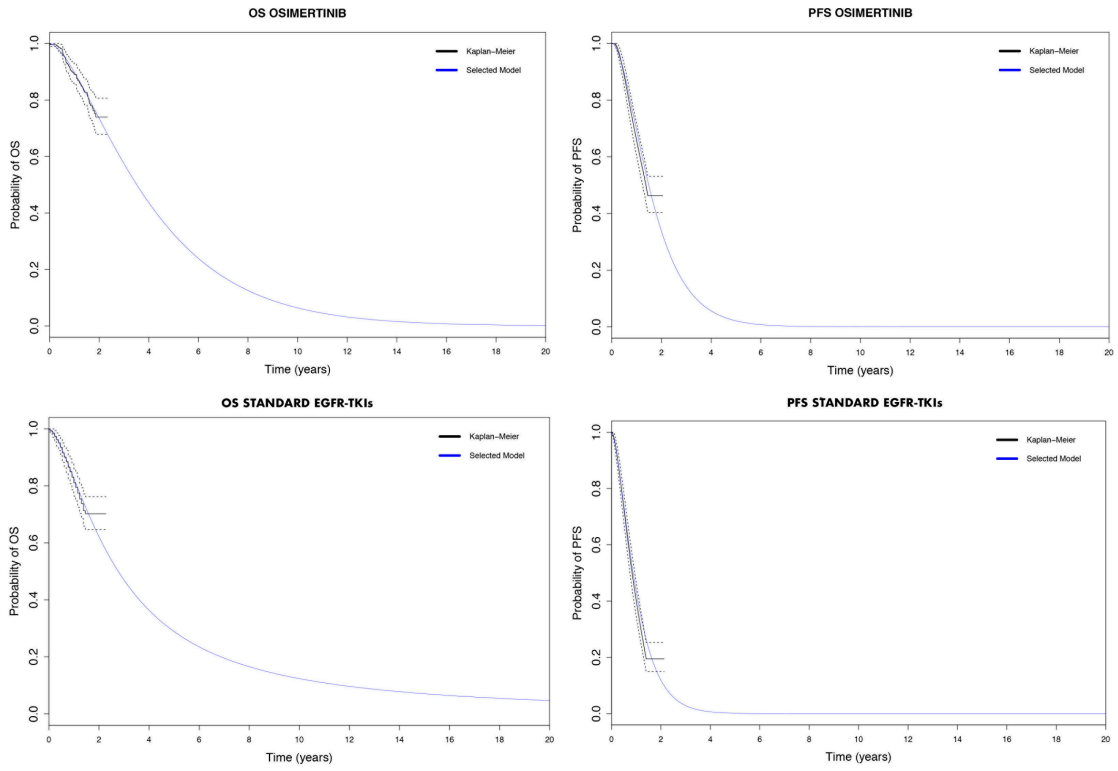


Figure 2. Overall survival and progression-free survival Kaplan–Meier plot and selected fitted curves. PFS: progression free survival; OS: overall survival. EGFR: epidermal growth factor receptor; TKIs: tyrosine-kinase inhibitors

2.1.5. Costs estimation

Only direct medical costs were calculated (drugs, disease management, adverse events (AE) and second-line treatment). The cost of erlotinib, gefitinib and osimertinib were calculated according to the officially notified listed prices (drug price - 7,5% official discount in Spain) * Value added tax (VAT)) *(table 1)* [20,21]. Disease management costs were estimated according to an expert panel's advice. Disease managment cost per patient and cycle was calculated multiplying the cost of healthcare resources employed by the unit cost of each resource consumed over a 15-year time horizon.

Table 1. **Model input parameters**

Management of NSCLC	**Cost per 28-day cycle and patient**	**References**
Erlotinib/Gefitinib	€1,836,48	[20][21]
Osimertinib	€5,447.36	
Second-line cost osimertinib	€9,294	[20][21]
Scheme (29% of total patients)		
EGFR-TKI scheme erlotinib/gefitinib (21%)		
Platinum-based chemotherapy schemes (36%)		
Non platinum-based chemotherapy schemes (35%)		
Others therapies (8%)		
Second-line cost standard EGFR-TKIs	€15,310	[20][21]
Scheme (47% of total patients)		
EGFR-TKI scheme treated with osimertinib (46%)		
Platinum-based chemotherapy schemes (13%)		
Non platinum-based chemotherapy schemes (12%)		
Others therapies (4%)		
Grade III-IV adverse events	**Median cost/cycle**	[23]
Diarrhea	€924.11	
Decreased appetite	€1,375.31	
Dry skin	€26.2	
Paronychia	€341.41	
Stomatitis grade 3	€2,332.14	
Stomatitis grade 4	€5,325.7	

Pruritus	€341.41	
Fatigue	€106.78	
Anemia	€992.22	
Vomiting	€681.51	
Rash	€341.41	
Alanine aminotransferase elevation grade 3	€559.91	
Alanine aminotransferase elevation grade 4	€1,799.09	
Aspartate aminotransferase elevation	€559.91	
Utilities scenario	**Value**	[24]
On treatment with no side effects	0.84	
Diarrhea	0.32	
Vomiting	0.25	
Rash	0.15	
Stomatitis	0.25	
Dry skin	0.15	
Decreased appetite	0.41	
Paronychia	0.15	
Anemia	0.41	
Fatigue	0.41	
Disease progression	0.17	

The second-line therapy regimens were obtained from table S3 of supplementary FLAURA study [15] as is shown in table 1. In osimertinib second-line arm, 21% of the patients were re-challenged with standard EGFR-TKI (erlotinib-gefitinib), 36% with platinum-based chemotherapy, 35% with non platinum-based chemotherapy and 8% with other therapies (PD-1/PD-L1, anti-VEGF and others targeted therapies). In standard-EGFR TKIs second-line arm, 46% of the patients were treated with

osimertinib, 13% with platinum-based chemotherapy, 12% with non platinum-based chemotherapy and 4% with others therap(PD-1/PD-L1, anti-VEGF and others targeted therapies). To calculate second-line costs, patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m^2. As PFS second-line treatment curves were not available in FLAURA clinical trial, we employed AURA3 clinical trial PFS2 curves to calculate second-line treatment duration[14]. We estimated the Area Under the Curve (AUC) in the PFS AURA3 trial curve comparing osimertinib vs. platinum-pemetrexed in NSCLC patients who had disease progression after first-line EGFR-TKI therapy to obtain second-line treatment duration. We employed Guyot et al. method to simulate the best survival curve [19]. In order to obtain the best adjusting method, this survival curve was fitted with a Weibull distribution.

Unit costs were obtained from an official database published in Spain [22]. Side effects management costs in Spain (*table 1*) were obtained from an internal database [23]. Adverse effect (grade III-IV events) frequencies associated with osimertinib and gefitinib-erlotinib treatments were obtained from FLAURA study [15]. Model costs are presented in Euros (€) 2018 (*table 1*).

2.1.6. Utilities estimation

Health state utility inputs and disutility values for the base case were obtained from recent data published from UK [24]. Different utilities values were applied considering the different health states (SD and PD) and are summarized in *table 1*. A health utility of zero was applied to the health state of death.

2.1.7. Disutilities estimation

Only disutility values associated with grade III-IV were addressed. To calculate the disutility values associated with grade III-IV in SD, disutilities parameters of each AE extracted from Nafees et al. was multiplied by the relative frequency of the corresponding event obtained from FLAURA trial to calculate a weighted average disutility value for each event profile. Disutility values calculated for each grade III-IV AE were subtracted from utility values while patients remained in SD.

2.1.8. Univariate Sensitivity Analysis

A deterministic univariate sensitivity analysis (DUSA) was performed to address the uncertainty of the ICER estimated value. In DUSA a single parameter in the model

(drug costs, utilities or discounts) was modified to examine the effect on the ICER result. Drug costs were modified in three different ranges (±20%, ±40% and ±60%). Utilities values were varied in a range of ±15%. The 2008 utility value (0.473) in progression disease employed in previous article of quality of life [25], was used in order to determine if the ICER value is modificated**.** Discount values in the DUSA model were varied in a percentage of 0% and 6%.

2.1.9. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the uncertainty of the estimated results in the DUSA. The analysis was performed using 10,000 Monte Carlo simulations. Different parameters (AEs values, management, second-line treatment costs, acquisition costs, utilities and transition probabilities) of the model were varied to determine the robustness of the model. In addition, the PSA was employed to obtain acceptability curves, showing the probability of each alternative being cost-effective across a range of possible values of willingness to pay for an additional QALY [26].

According to the characteristics of each variable, different types of probability distributions were employed to variate the model parameters [27]. Gamma distributions were applied for costs, beta for utilities and Dirichlet distributions for transition probabilities.

3. Results

Under base-case assumptions, the total QALYs were 0.61 and 0.42, for osimertinib and standard EGFR-TKIs, respectively. Osimertinib provided a 0.20 increase in QALYs compared with the standard EGFR-TKIs. For osimertinib arm, the mean costs of the intervention were €83,258.99 discounted over the 15-years horizon, in comparison with the €29,209.45 for the standard EGFR-TKIs. These costs and QALY values yielded an incremental ICER of €273,895.36/QALY for osimertinib compared to standard EGFR-TKIs. The results of the baseline scenario analysis are shown in *table 2*. Additionally, the net gain in life-years (LYG) in osimertinib group compared to standard EGFR-TKI group was 0.25 (1.05 life-years vs. 0.80 life-years for osimertinib and standard EGFR-TKIs, respectively).

Table 2. **Cost-effectiveness results.**

Variable	Strategy	
	Standard EGFR-TKIs	**Osimertinib**
Total Cost/pt	€29,209.45	€83,258.99
Treatment cost/pt	€19,214.00	€74,651.43
Disease management/pt	€2,307.05	€2,638.15
Adverse events costs/pt	€35.30	€55.01
2L cost /pt	€7,653.10	€5,914.40
QALY gained /pt	0.42	0.61
ICER (€/QALY) **Osimertinib vs Erlotinib-Gefitinib**	€273,895.36/QALY	
EGFR: epidermal growth factor receptor; TKI: tyrosine-kinase inhibitor; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; 2L: second-line pt: patient.		

The DUSA showed significant changes in the ICER after modifying osimertinib costs, utilities and discount values as is shown in Tornado diagram (*figure 3*) and supplementary *table 2*. Hence, the results of the DUSA showed that discounts greater than 60% in drug acquisition cost produced an ICER value below the threshold of 24,000€ per QALY gained fixed in Spain.

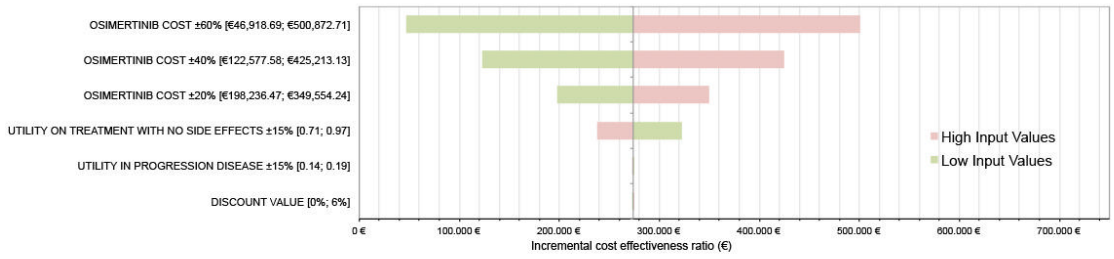


Figure 3.**Tornado diagram (deterministic sensitivity analysis)**

Furthermore, the PSA results were consistent with the base-case analyses. According to the cost-effectiveness plane shown in *figure 4*, standard EGFR-TKIs were more

effective and less costly in 62.28% of the iterations in the simulation. Only in 37.72% of the iterations, osimertinib was more effective and less costly than standard EGFR-TKIs.

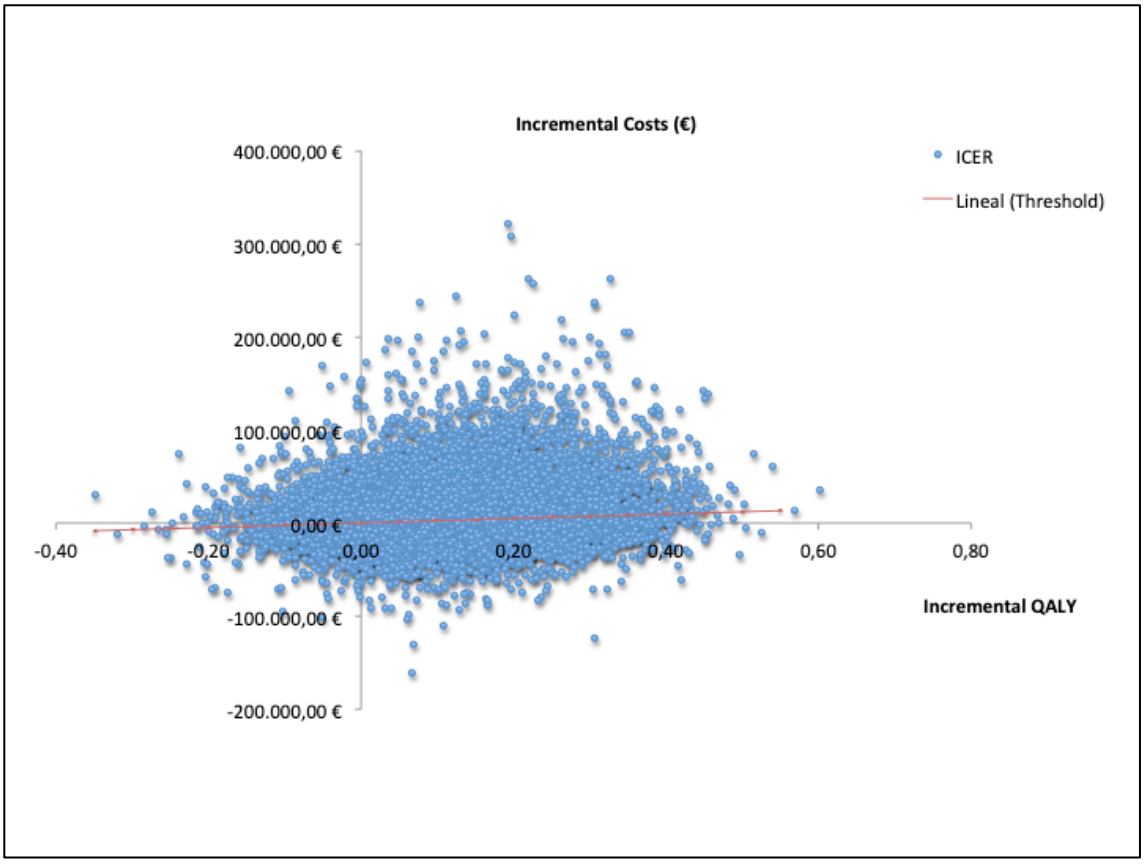


Figure 4. **Scatter plot of Monte Carlo probabilistic sensitivity analysis for osimertinib vs. first-line EGFR-TKIs (erlotinib-gefitinib).**

Finally, the likelihood of osimertinib being considered cost-effective was determined for a range of acceptability ratios, as shown in the acceptability curve. At the base-case scenario, there is a 42.94% probability of osimertinib being cost-effective at a threshold of €24.000/QALY (*figure 5*).

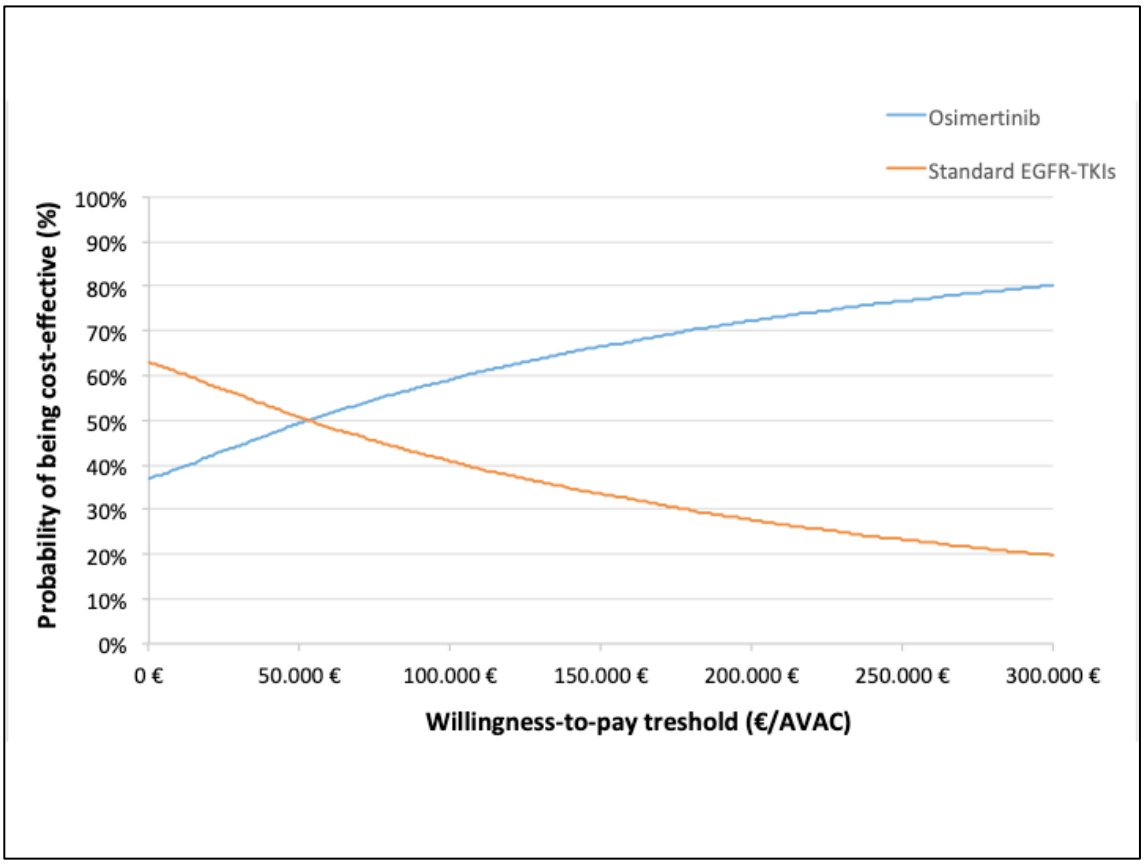


Figure 5. **Cost-effectiveness acceptability curve osimertinib vs. first-line EGFR-TKIs (erlotinib-gefitinib).** Graph plot willingness to pay (WTP) scenario (x-axis) vs. the likelihood in percentage that the treatment would be considered cost-effective (y-axis). ICER: incremental cost-effectiveness ratio.

4. Discussion

Recently, osimertinib has demonstrated a clinically meaningful benefit in patients with EGFR T790M mutation who have developed acquired resistance to TKIs [12–14]. Additionally, FLAURA study has demonstrated the clinical benefit of osimertinib in EGFR-TKI-sensitizing mutations. Therefore, we developed a complete cost-effectiveness analysis to compare osimertinib vs. standard first-line EGFR-TKIs (erlotinib-gefitinib) in patients with previously untreated, EGFR mutation–positive advanced NSCLC, based on FLAURA study [15]. We demonstrated that osimertinib is considered more effective in comparison with standard TKIs in sensitizing EGFR mutations, in terms of QALYs gained (0.20). However, our study showed that osimertinib was not cost-effective compared to EGFR-TKIs because the ICER (€273,895.36/QALY) was higher than the commonly accepted threshold in Spain of €24,000/ QALY [18]. In addition, in our study, we established that discounts greater

than 60% are crucial in the osimertinib acquisition costs to be considered a cost-effective alternative.

To date, only four different studies have compared the cost-effectiveness of osimertinib [16,17,28,29]. However, two of these studies are not comparable because they only compare osimertinib vs. pemetrexed-platinum based chemotherapy in patients with demonstrated T790M mutation [28,29]. In the study published by Bin Wu et al. [29] they estimated that osimertinib was not cost-effectiveness in the USA due to the high acquisition cost of osimertinib drug as we demonstrated. In addition, we can conclude that ICER value obtained (scenario 3 patients without metastasis) in USA by Bin Wu et al. [29] is really approximate to ours with $222,030/QALY. In the recently published article by Aguiar Jr et al. [17], the authors performed an innovative decision analytic-model over a 10-year time horizon to evaluate the cost-effectiveness of osimertinib from data collected from FLAURA study. The authors compared two different strategies: the first one comparing osimertinib in second-line in patients who harbor T790 mutation vs. chemotherapy or immunotherapy in patients without this mutation; the second strategy they addressed in the aim of the study was similar to our purpose and consisted of the comparison of osimertinib in first-line continued by a standard second-line therapy at disease progression. The results obtained in the USA by Aguiar Jr. et al. are really in concordance with ours in Spain, obtaining an approximate ICER of $230.000/QALY, a QALY value for osimertinib of 2.12 and a 0.594 incremental number of QALY gained compared to the standard EGFR-TKIs (gefitinib-erlotinib-afatinib) in first-line. However, in the study recently published by Aguiar Jr. et al., the authors only performed a DUSA over a 10-year time horizon. Generally, to reinforce the results obtained in the DUSA a PSA is frequently performed [30]. Therefore, in our study, the deterministic results obtained are complemented with a PSA to demonstrate the robustness of the ICER values obtained and to indicate accurately the osimertinib cost-effectiveness thresholds. Additionally, to improve the quality of the analysis, we changed the lifetime horizon in our study from the classical 10-year to a 15-year lifetime horizon analysis. Nonetheless, Aguiar et al. conclude that high cost of the drug makes osimertinib a not so cost-effective alternative, unlike the superior values of PFS or OS obtained.

To our knowledge, this is the first complete economic study in Europe to provide a direct comparison of osimertinib against the first-line standard of care (gefitinib-erlotinib) for the patients with EGFR mutated NSCLC. To reinforce our obtained results, another recently published Markov analysis by Ezeize et al. in Canada showed a similar non cost-effectiveness analysis with an incremental gain of 0.79 QALYs and an incremental ICER of 223.133$/QALY [16]. Therefore, our findings show that the choice of treatment in this study should be essentially determined by the drug acquisition cost. Considering the efficacy and the quality of life, osimertinib should be the treatment of choice. Osimertinib is expected to provide an incremental 0.20 QALYs gained in the study. However the acquisition cost was higher compared with the cost of standard EGFR-TKI, resulting in a difference of €55,437.43 per patient.

In addition, the acceptability curve of WTP obtained in our study shows a range of threshold values, as an aid for context-dependent decision making. We demonstrated that with standard WTP thresholds, osimertinib may be considered not cost-effective in Spain due to the high price of drug acquisition. Currently, the defined cost-effectiveness threshold in the Spanish setting is €24,000/QALY [18]

Nowadays, the establishment of different innovative purchasing algorithms such as pay-for-performance (P4P) are increasingly implemented in developed healthcare systems. These algorithms have demonstrated promoting improvements in healthcare quality and to reduce the acquisition costs of different innovative therapies [31,32]. To facilitate physician prescribing decision, different institutions such as European Society for Medical Oncology (ESMO) [33] or American Society of Clinical Oncology (ASCO) [34] have recently created pharmacoeconomic tools. Therefore, these results may be useful for health administrators and policy-makers in negotiations of prices with drug manufacturers, as also by the drug manufacturers themselves to consider reducing prices of this drug to encourage adoption of new generation of TKIs regimens.

There are some limitations in our study. Firstly, common to all Markov models, there is the implicit uncertainty from combination of data from numerous sources and assumptions. Secondly, the result of the model could be impacted by the assumptions around curve extrapolation. Nonetheless, the algorithm used for extrapolation, Guyot et al. [19], provides excellent accuracy for the calculation of survival probabilities. Thirdly, we only contemplate the payers' perspective of Spanish National Health

System and not indirect costs (absenteeism, changes of individual productivity, unpaid assistance from a family member). In addition, the utility values considered in the model were extracted from a validated study published in the population of UK [24] but not from our own country, Spain, since these data were not available. The utility values of 0.17 assigned to disease progression could be lower than the utility values obtained in 2008 by Nafees et al. (0.473) [25]. This difference is due to the change of methodology employed to calculate these utilities values. In Nafees et al. study 2008 [25] authors employed a standard gamble method, while in 2017 study a time-trade-off method was employed by the authors[24]. Different authors as Stiggelbout et al. [35] conclude that these two methods are not equal estimating utility values, therefore producing the time-trade-off method lower utilities values. In order to determine the influence of utility values in definitive ICER results in our model, we included the 2008 utility value employed in Nafees et al. study (0.473) [25] in the deterministic univariate sensitivity analysis (DUSA), to determine if the ICER value is modificated by different utility values and we concluded that there was no difference (€273,895.36 vs. €264,691.25) Fourth, individual data from erlotinib and gefitinib patients cannot be extracted from supplementary data of FLAURA study, therefore a combined arm is evaluated in this study. Fifth, when disease progression while on therapy with first-generation EGFR-TKI, a second generation TKI, afatinib, is normally prescribed [36]. However, we did not include an afatinib arm in the economic analysis, because in the FLAURA study a direct comparison between afatinib and osimertinib is not evaluated.

5. Conclusions

From Spanish National Health System perspective, treatment with osimertinib was more effective in terms of QALYs gained than treatment with standard EGFR-TKIs erlotinib-gefitinib. However, osimertinib has been proved not to be a cost-effective alternative in first line therapy for advanced EGFR-mutated NSCLC patients, compared with erlotinib-gefitinib due to the high acquisition costs of the drug. Additionally, our study could also be applied to other TKIs treatments with similar efficacy rates that become available in the future.

Key issues

- In FLAURA study, the median progression-free survival (PFS) in patients with untreated EGFR mutated NSCLC was demonstrated to be significantly longer with osimertinib than with standard first-line EGFR-TKIs (18.9 months vs. 10.2 months).
- Osimertinib presented higher QALYs (0.61) compared to standard EGFR-TKIs (0.42).
- Osimertinib total costs of the intervention were €83,258.99, in comparison with the €29,209.45 for the standard EGFR-TKIs.
- An ICER of €273,895.36/QALY was obtained for osimertinib compared to standard EGFR-TKIs.
- From Spanish National Health System perspective, osimertinib has been proved not to be a cost-effective alternative in first line therapy for advanced EGFR-mutated NSCLC patients, compared with erlotinib-gefitinib due to the high acquisition costs of the drug.
- A discounts greater of 60% discount in osimertinib acquisition cost could produce an ICER value below the established threshold of €24,000 per QALY gained in Spain to result a cost-effectiveness alternative.

Author contributions

All the authors interpreted data, read and approved the final manuscript.

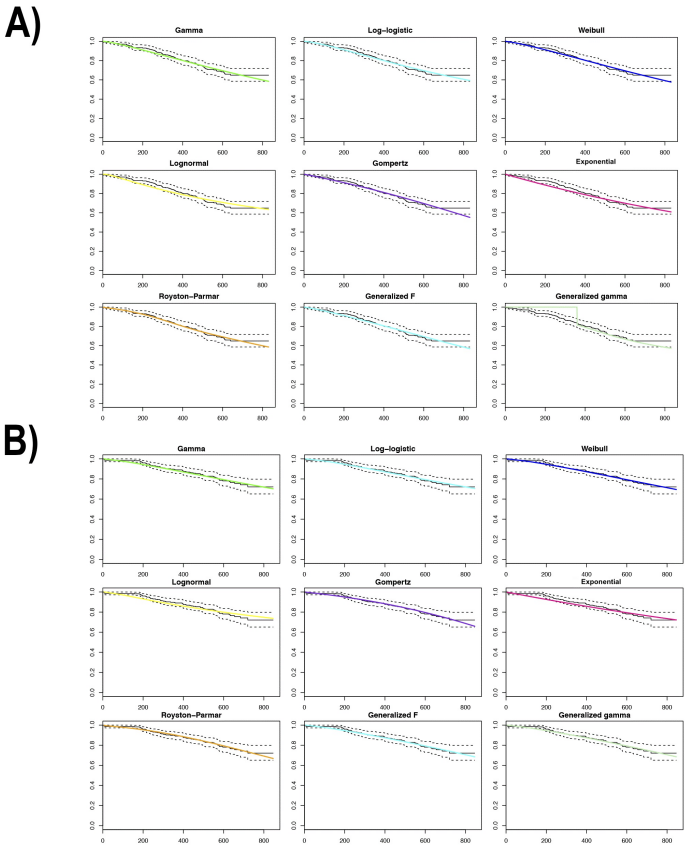
Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization

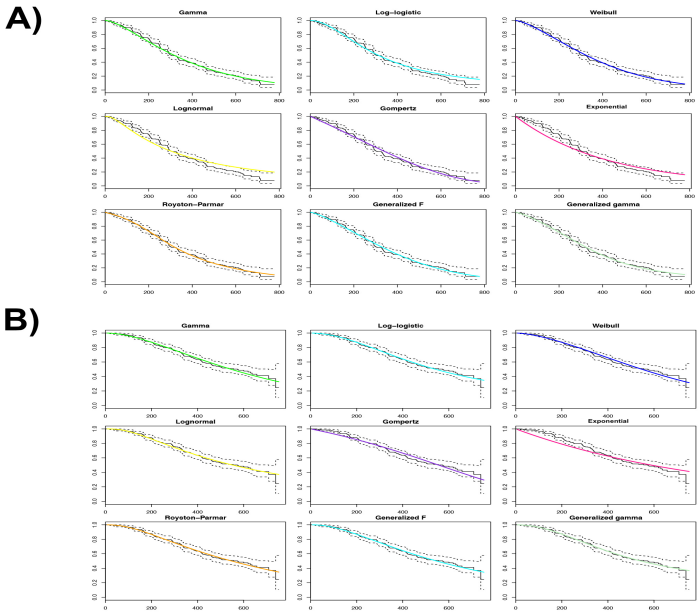
or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Supplementary Material



Supplementary-1. *Figure 1*. Fitted Kaplan-Meier curves with different extrapolated models. A) Estimated overall survival first-line EGFR-TKI (erlotinib-gefitinib). B) Estimated overall survival first-line osimertinib.



Supplementary-2. *Figure 2.* Fitted Kaplan-Meier curves with different extrapolated models. A) Progression free survival first-line EGFR-TKI (erlotinib-gefitinib). B) Progression free survival first-line osimertinib.

S3- Table 1. **Goodness-of-fit statistics for modeling PFS and OS for osimertinib and standard-EGFR TKIs (erlotinib and gefitinib) fom FLAURA study.** OS: overall survival; PFS: progression free survival; AIC: Akaike information criterion; BIC: Bayesian information criterion; EGFR: epidermal growth factor receptor; TKIs: tyrosine-kinase inhibitors

	OS OSIMERTINIB		PFS OSIMERTINIB	
	AIC	BIC	AIC	BIC
Gamma	**1046.34**	**1053.61**	**2060.58**	**2067.84**
Lognormal	1058.49	1065.75	2061.65	2068.92
Weibull	1045.63	1052.89	2062.91	2070.17
Gompertz	1042.96	1050.22	2075.29	2082.56
Generalized Gamma	1046.79	1057.68	2061.66	2072.55
Exponential	1047.74	1051.37	2093.26	2096.89
Log-logistic	1046.72	1053.98	2059.38	2066.65
Generalized F	1048.79	1063.31	2062.84	2077.37
Royston-Parmar spline model	1041.87	1052.76	2061.38	2072.27
	OS STANDARD-EGFR TKIs		PFS STANDARD-EGFR TKIs	
	AIC	BIC	AIC	BIC
Gamma	**1398.35**	**1405.60**	**2879.91**	**2887.16**
Lognormal	1414.38	1421.63	2944.17	2951.42
Weibull	1397.77	1405.02	2875.91	2883.16
Gompertz	1397.44	1404.69	2880.32	2887.57
Generalized Gamma	1399.77	1410.64	2877.26	2888.13
Exponential	1400.29	1403.91	2907.04	2910.66
Log-logistic	1398.72	1405.97	2888.14	2895.39
Generalized F	1510.56	1510.56	2878.00	2892.50
Royston-Parmar spline model	1395.43	1409.93	2869.94	2884.44

S4- Table 2. **Deterministic univariate sensitivity analysis. (DUSA)**

Parameter	Value		ICER (€/QALY)
	BC	***SA***	
Osimertinib Cost + 20 %			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€349,554.24
Osimertinib	€5,447.36	€6,536.83	
Osimertinib Cost - 20%			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€198,236.47
Osimertinib	€5,447.36	€4,357.89	
Osimertinib Cost + 40%			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€425,213.13
Osimertinib	€5,447.36	€7,626.30	
Osimertinib Cost - 40%			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€122,577.58
Osimertinib	€5,447.36	€3,268.42	
Osimertinib Cost + 60%			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€500,872.71
Osimertinib	€5,447.36	€8,715.78	
Osimertinib Cost - 60%			
Standard EGFR-TKIs	€1,836.48	€1,836.48	€46,918.69
Osimertinib	€5,447.36	€2,178.95	
Utility on treatment with no side effects + 15%			
Standard EGFR-TKIs	SD: 0.840 PD: 0.166	SD: 0.966 PD: 0.166	€238,263.64
Osimertinib	SD: 0.840 PD: 0.166	SD: 0.966 PD: 0.166	
Utility on treatment with no side effects - 15%			
Standard EGFR-TKIs	SD: 0.840	SD: 0.714	

	PD: 0.166	PD: 0.166	€322,058.36
Osimertinib	SD: 0.840 PD: 0.166	SD: 0.714 PD: 0.166	
Utility in progression disease + 15%			
Standard EGFR-TKIs	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.191	€273,390.32
Osimertinib	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.191	
Utility in progression disease - 15%			
Standard EGFR-TKIs	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.141	€274,402.26
Osimertinib	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.141	
Discount value 6%			
Standard EGFR-TKIs	3%	6%	€273,119.78
Osimertinib	3%	6%	
Discount value 0%			
Standard EGFR-TKIs	3%	0%	€274,710.57
Osimertinib	3%	0%	
Utility in progression disease 0.473			
Standard EGFR-TKIs	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.473	€268,012.36
Osimertinib	SD: 0.840 PD: 0.166	SD: 0.840 PD: 0.473	

ICER: Incremental cost-effectiveness ratio; BC: base case; DUSA: deterministic univariate sensitivity analysis; SD: stable disease; PD: progression disease; EGFR: epidermal growth factor receptor; TKIs: tyrosine-kinase inhibitors.

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Artículo 1

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Alós-Almiñana M, Cortijo J. Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2019 Aug;8(11):853-863. doi: 10.2217/cer-2019-0029. Epub 2019 Sep 3. PMID: 31478399.

Artículo 2

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Cortijo J. Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res. 2021 Mar;10(4):325-335. doi: 10.2217/cer-2020-0233. Epub 2021 Feb 26. PMID: 33635095.

Artículo 3

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer. Expert Rev Pharmacoecon Outcomes Res. 2022 Jun;22(4):637-646. doi: 10.1080/14737167.2022.1987220. Epub 2021 Oct 11. PMID: 34602008.

Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis

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ABSTRACT

Aim: to assess the cost-effectiveness of first-line treatment with dacomitinib compared to gefitinib in patients newly diagnosed with advanced NSCLC EGFR-positive in the context of Spain.

Materials & methods: A partitioned survival model was developed including costs, utilities, and disutilities to estimate quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio when treating with dacomitinib vs gefitinib.

Results: Dacomitinib presented higher QALYs (0.51) compared with gefitinib (0.45). Dacomitinib costs were €33,061 in comparison with €26,692 for gefitinib arm. An incremental cost-effectiveness ratio of €111,048 was obtained for dacomitinib.

Conclusions: Dacomitinib was more effective in terms of QALYs gained than gefitinib. However, to obtain a cost-effectiveness alternative, a discount greater than 25% in dacomitinib acquisition cost is required.

Lay abstract

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors represent the standard of care in patients with EGFR mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC). The introduction of new oncology therapies can result in financial pressure for healthcare payers. Therefore, the development of a cost-effectiveness study for assessing the gains in health relative to the costs of different health interventions is required. In this study, we compare dacomitinib to gefitinib as first-line treatment from Spanish National Health System perspective, by estimating how much it costs to gain a unit of a health outcome, like a life year gained or quality-adjusted life-year. Dacomitinib has been proved not to be a cost-effective alternative because despite being more effective in terms of life year gained or quality-adjusted life-year than gefitinib, it was also much more expensive due to the high acquisition cost of dacomitinib.

Keywords: cost-effectiveness; EGFR-mutated; EGFR-TKI; dacomitinib; non-small cell lung cancer; partitioned survival model; economic evaluation.

1. Introduction

Lung cancer is the most common cancer and the most frequent cause of cancer death worldwide [1]. In terms of histology, non-small cell lung cancer (NSCLC), being diagnosed in 80-85% of cases, is the most widespread type of lung cancer. [2]. Epidermal growth factor receptor (EGFR) mutations are reported to be associated in approximately 14–19% of Western patients and 40–48% of Asian patients with NSCLC with adenocarcinoma [3], [4]. In Spain, the REASON study revealed that the mutation detection rate in advanced NSCLC patients was found to be 11.6% (17.4% presenting L858R mutation in exon 21 and 82.6% presenting in-frame deletions in exon 19) [5].

EGFR tyrosine kinase inhibitors (TKIs) are the standard treatment for patients with NSCLC harboring an EGFR mutation [6]. To date, three first-line TKIs are normally used in clinical practice: erlotinib, gefitinib, and afatinib. These TKIs have demonstrated significantly improved progression-free survival (PFS) as the first-line treatment compared to platinum-based therapy [7]–[14]

Recently, based on the ARCHER 1050 study [15], the Food and Drug Administration (FDA) approved dacomitinib, a second-generation EGFR-TKI, for the first-line treatment of patients with metastatic NSCLC with EGFR mutation-positive [16]. This study showed that dacomitinib was superior to gefitinib in terms of progression-free survival (PFS) and overall survival (OS). A seven-month improvement in OS was shown in the dacomitinib arm compared to gefitinib [17]. Nonetheless, second-generation EGFR TKIs are frequently associated with EGFR-mediated toxicities due to the relatively potent EGFR inhibition. Therefore, in the ARCHER 1050 study, a dose reduction was performed on the dacomitinib arm. Additionally, in another study, tolerability-guided dose modifications enabled patients to continue with dacomitinib and benefit from PFS and OS improvement [18].

Although dacomitinib caused more side effects than gefitinib, these were considered manageable. Therefore, on April 2019, the European Medicines Agency (EMA) decided that the benefits of dacomitinib are greater than its risks, and it was authorized for use in the European Union. Consequently, dacomitinib could be considered one of the standard first-line options for patients with advanced EGFR-mutated NSCLC. Additionaly, a new network meta-analysis comparing OS have demonstrated that

treatment with dacomitinib could be considered a first-line treatment option in comparison to other standard EGFR TKIs as afatinib (hazard ratio [HR] 0.87; 95% credible interval [CrI]: 0.61–1.24), erlotinib (HR: 0.79; 95% CrI: 0.44–1.42), gefitinib (HR: 0.75; 95% CrI: 0.59–0.95) and osimertinib (HR: 0.94; 95% CrI: 0.68–1.29) [19]

To our knowledge, no prior incremental cost-effectiveness analysis (ICER) has been performed comparing dacomitinib vs gefitinib in Spain. This study aims to evaluate the cost-effectiveness of first-line treatment with dacomitinib compared to gefitinib in patients newly diagnosed with advanced NSCLC EGFR-positive in the context of Spain. Our study could help clinicians and policymakers in the decision-making process to promote the sustainability of the Spanish National Health System.

2. MATERIAL AND METHODS

2.1. Cost-Effectiveness Analysis (CEA): partitioned survival model

2.1.1. Design and Perspective Analysis

A partitioned survival model model was constructed using clinical data from the ARCHER 1050 randomized study [15]. The quality-adjusted life-years (QALYs), the costs, and ICER of two different treatment strategies (dacomitinib vs. gefitinib) were estimated in two hypothetical cohorts of patients with newly diagnosed advanced NSCLC and one EGFR mutation (exon 19 or Leu858Arg). We modelled the health states of patients with similar criteria to those enrolled in the ARCHER 1050 study: patients in IIIB/IV stage, with new or recurrent diagnosis, and histological or cytopathological confirmation. The presence of at least one documented EGFR mutation (exon 19 deletion or the Leu858Arg mutation, with or without the Thr790Met mutation) was required. The model was developed from the perspective of the Spanish National Health System. The threshold for determining the cost-effectiveness of a strategy was €24,000/QALY [20]. All the costs were estimated in euros (€) 2019, and a discount rate of 3% was used for costs and effects throughout the model. The partitioned survival model was developed in Microsoft Excel 2011 (Microsoft Corp., Redmond, Washington) using a 15-year time horizon, which was selected because it was sufficient to collect all the costs and benefits generated in the model. The results were presented in terms of costs (€), QALYs gained and ICER.

2.1.2. Partitioned survival model Structure

The model included three mutually exclusive health states: stable disease, progressive disease and death. As shown in *figure 1*, all patients were initially on stable disease and received one of the two treatment strategies (dacomitinib or gefitinib). On each 28-day simulation cycle, the model redistributes the hypothetical cohort of patients among the three health states according to the transition probabilities. On progressive disease, the patients received a second-line regimen, and after the occurrence of progressive disease, they could remain in this state or die. Progressive disease was simulated until all the patients died. A half-cycle correction was applied.

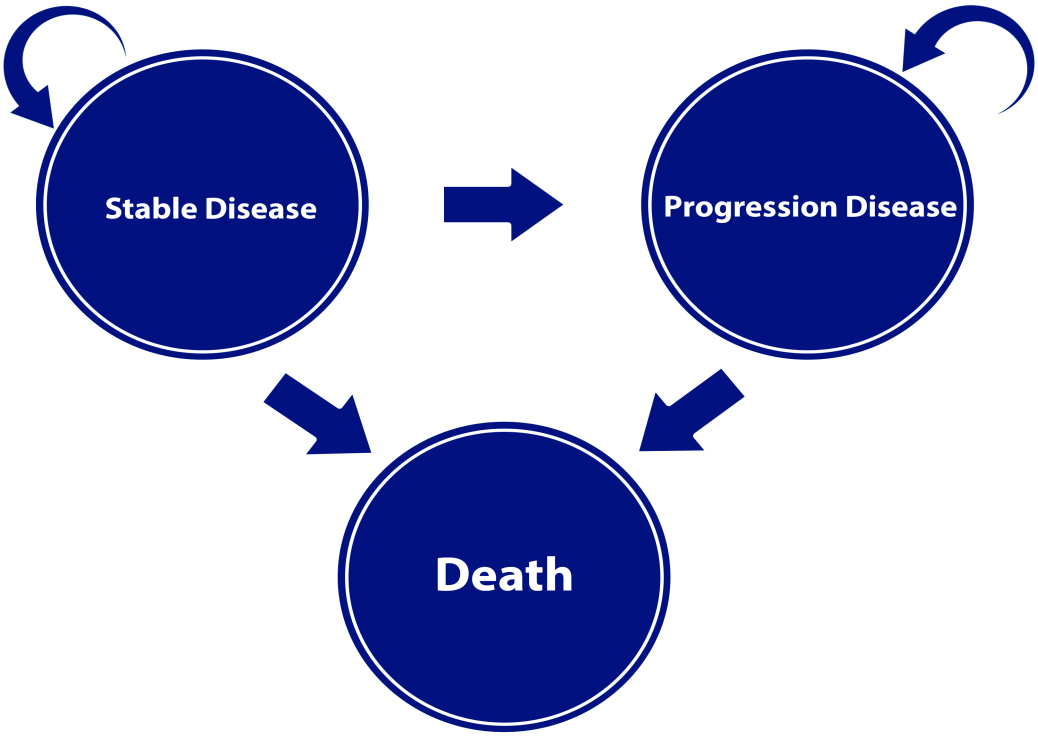


Figure 1. **Structure of partitioned survival model.** Partitioned survival model health states.

2.1.3. Treatment Alternatives

The model cycle length was 28 days (4 weeks), consistent with the labeled dose frequency of the two treatments. Patients in the dacomitinib group were treated with oral dacomitinib 45 mg once daily in 28-day cycles. Of the patients in this group, 66% experienced a dose reduction, 38% received the lowest dose of 30 mg/day and 28% received the lowest dose of 15 mg/day, according to the ARCHER 1050 trial [15]. The

patients in the gefitinib group received gefitinib 250 mg orally once daily in 28-day cycles.

2.1.4. Transitional Probability Data

The clinical effectiveness data of PFS and OS were obtained from the ARCHER 1050 trial [15], [17], via the techniques outlined in Guyot et al.[21]. WebPlotDigitizer was used to recreate Kaplan-Meier graphs to project outcomes to the end of the 15-year time horizon using Flexurv, an R package for the fully parametric modelling of survival data [22][23] (R version 3.3.3). The following parametric distributions were considered to determine the most appropriate parametric survival curve as recommended by the NICE Decision Support Unit (DSU) [24]: gamma, log-logistic, Weibull, lognormal, Gompertz, exponential, generalized F and generalized gamma. The distributions were selected based on statistical tests (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)), visual inspection of fit to Kaplan-Meier plots, goodness-of-fit statistics, and clinical plausibility. (*figure 2* and *supplementary table 2*).

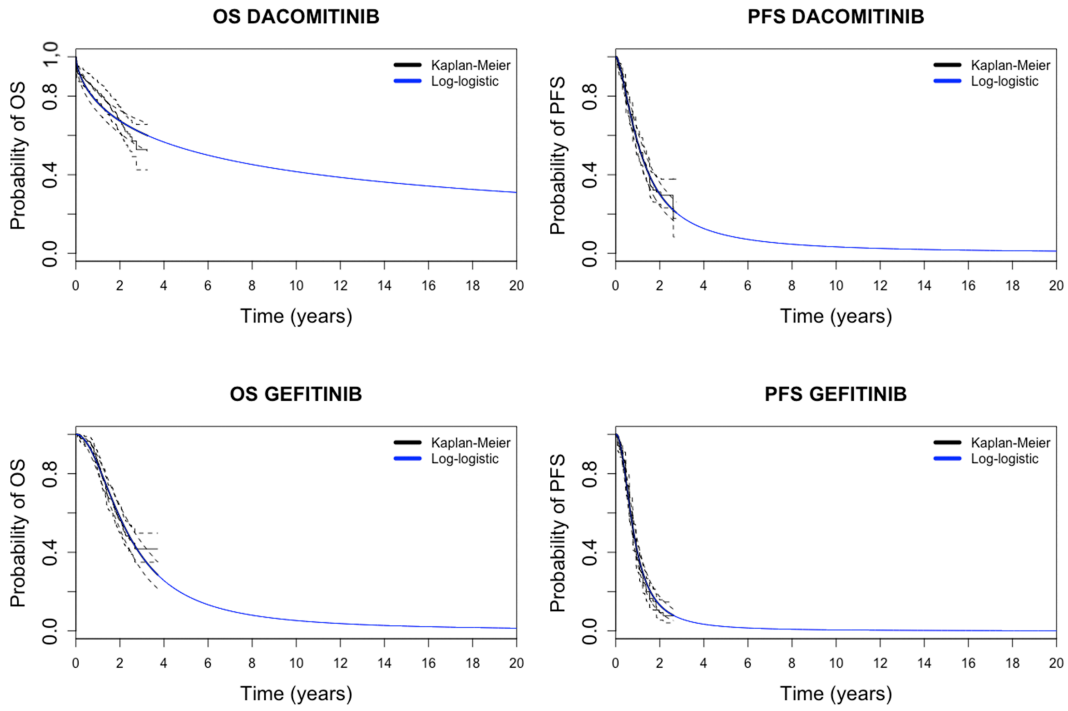


Figure 2. Overall survival and progression-free survival Kaplan–Meier plot and selected fitted curves. PFS: progression-free survival; OS: overall survival.

For PFS and OS, a log-logistic distribution was selected. This distribution has the best visual and statistical fit; the hazards consistent with the observed hazards in the ARCHER 1050 trial [15], do not yield implausible projections with the survival curves for the two arms crossing (*supplementary annex, figure S1, figure S2, figure S3 and figure S4)*. For each TKI, the probability that patients remain in stable disease at each time is determined by the values of the PFS curve at that time. In addition, the probability of patients to achieve the death state is determined as 1 minus the OS curve at that time. From this, the probability of patients in progressive disease follows, as the three states together should always add up to 100%.

2.1.5. Cost Estimation

Table 1 outlines the calculated costs. Direct medical costs include treatment costs, disease management costs, end-of-life care costs, adverse events costs, and second-line treatment costs. The cost of gefitinib and dacomitinib were calculated according to the officially notified listed prices (drug price - 7,5% official discount in Spain) * Value added tax (VAT)) [25], [26]. The cost of dacomitinib can be considered part of the problem because up to the date of publication of this article an official Spanish price for this drug has not been published, and it has been obtained from National Institute for Health and Care Excellence (NICE) guidance [27]

Disease management costs were estimated according to an expert panel's advice. Disease management cost per patient and cycle was calculated by multiplying the cost of healthcare resources employed by the unit cost of each resource consumed over a 15-year time horizon. The unit costs were obtained from an official database published in Spain [28]

End-of-life care costs were applied to each patient entering the death state and were obtained from an article published in Spain [29]

The costs of side-effects management from the perspective of the Spanish National Health System (*table 1*) were obtained from published articles [30] [31]. Adverse effect (grade 3/4 events) frequencies associated with dacomitinib and gefitinib treatments and reported in at least 3% of patients were obtained from the ARCHER 1050 study [15].

The second-line therapy regimens were obtained from table S1 of supplementary ARCHER 1050 study [15] as is shown in *table 1*. In dacomitinib second-line arm, 23.8%

of the patients were treated with pemetrexed, 13.7% with carboplatin, 13.2% with cisplatin and 7.9% with osimertinib. In gefitinib second-line arm, 25.9% of the patients were treated with pemetrexed, 13.8% with carboplatin, 17.9% with cisplatin and 12.9% with osimertinib. The patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m2.

All cost inputs from prior years were inflated to 2019 Spanish values using the Consumer Price Index. The model costs are presented in Euros (€) 2019 (*table 1*).

Table 1. **Model input parameters**

Management of NSCLC	**Cost per 28-day cycle and patient**	**Distribution**	**References**
Gefitinib	€2,045	Gamma	[25][26][27]
Dacomitinib	€3,023	Gamma	
Second-line cost gefitinib	€1,233	Triangular	[15][25][26]
Scheme (43.8% of total patients)			
Permetrexed (25.9%)			
Carboplatin (13.8%)			
Cisplatin (17.9%)			
Osimertinib (12.9%)			
Median number of post-progression systemic treatments per patients in gefitinib arm	1 (1-6)		[15]
Second-line cost dacomitinib	€1,854	Triangular	[15][25][26][27]
Scheme (59% of total patients)			
Permetrexed (23.8%)			
Carboplatin (13.7%)			

Cisplatin (13.2%)			
Osimertinib (7.9%)			
Median number of post-progression systemic treatments per patients in dacomitinib arm	2 (1-5)		[15]
End-of-life care cost	€12,909	Gamma	[29]
Grade III-IV adverse events (frequency >3%)	**Median cost/cycle**		[30] [31]
Diarrhea	€1,552	Gamma	
Dermatitis acneiform	€2.11	Gamma	
Stomatitis	€1,352	Gamma	
Rash	€2.11	Gamma	
Maculopapular rash	€2.11	Gamma	
Postular rash	€2.11	Gamma	
Alanine aminotransferase elevation	€68	Gamma	
Aspartate aminotransferase elevation	€68	Gamma	
Utilities scenario	**Value**		[31][32]
On treatment with no side effects	0.65	Beta	
Diarrhea	0.32	Beta	
Dermatitis acneiform	0.15	Beta	
Stomatitis	0.25	Beta	
Rash	0.15	Beta	
Maculopapular rash	0.15	Beta	
Postular rash	0.15	Beta	

Alanine aminotransferase elevation	0	Beta	
Aspartate aminotransferase elevation	0	Beta	
Disease progression	0.47	Beta	

2.1.6. Utilities Estimation

The ARCHER 1050 study has not reported health state utilities. Thus, utility inputs and disutility values for the base case were estimated from the recent data published in the literature [31], [32]. In order to estimate QALYs, utility and disutility values were applied considering the different health states (stable disease and progressive disease) and are summarized in *table 1.* A health utility of zero was applied to the health state of death.

2.1.7. Disutilities Estimation

The disutility values associated with grade 3/4 adverse events while the patients remained in stable disease were adopted from a recently published international study that evaluated the disutilities and complications for advanced NSCLC in different countries like the United Kingdom, France, Australia and Republic of China by employing a time trade-off technique [33].To calculate the disutility values associated with grade 3/4 in stable disease, the disutility parameters of each adverse event extracted from Nafees et al. were multiplied by the relative frequency of the corresponding event obtained from the ARCHER 1050 trial to calculate a weighted average disutility value for each event profile as is shown in *supplementary table 1*. The disutility values calculated for each grade 3/4 adverse event were subtracted from the utility values while the patients remained in stable disease.

2.1.8. Univariate Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was performed to explore the impact of the essential variables on the ICER estimated value. Thus, a single parameter in the model (drug costs, utilities or discounts) was varied to test the effect on the ICER result. The utilities values were varied in a range of ±20%. The drug acquisition costs were modified in three different ranges (±15%, ±20%, and ±25%). The end-of-life care costs

were varied in two different ranges (±10% and ±20%), and the discounts values in the DSA were modified in a percentage of 0% and 6%. The transition probability values of PFS and OS were varied in a range of ±5. The results of the DSA were presented in a tornado diagram.

2.1.9. Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the influence of parameter uncertainties using 10,000 Monte Carlo simulations. Different parameters (side effects management costs, disease management costs, second-line treatment costs, acquisition costs, end-of-life care costs, utilities, and transition probabilities) of the model were varied to determine the robustness of the model. The results of the PSA was employed to obtain the cost-effectiveness acceptability curves (CEAC), showing the probability of each alternative being cost-effective across a range of possible values of willingness to pay for an additional QALY [34]

The different types of probability distributions were applied to variate the model parameters according to the characteristics of each variable [35]. Gamma distributions were employed for costs, beta for utilities and Dirichlet distributions for transition probabilities. The number of post-progression systemic treatments per patient were assumed to follow a triangular distribution.

3. RESULTS

The base-case cost-effectiveness results for dacomitinib and gefitinib are reported in *table 2*. The total QALYs were 0.51 and 0.45 for dacomitinib and gefitinib, respectively. The incremental number of QALYs gained with dacomitinib compared with gefitinib was 0.06. The number of incremental life-years gained (LYG) in the base case was 0.06 (0.86 life-years vs. 0.80 life-years for dacomitinib and gefitinib, respectively). The mean costs for dacomitinib arm were €33,061 discounted over the 15-years horizon and €26,692 for the gefitinib arm, resulting in an additional cost of €6,369. These costs and QALY values yielded an incremental ICER of €111,048 for dacomitinib compared to gefitinib.

Table 2. **Cost-effectiveness results.**

Variable	**Strategy**	
	Gefitinib	**Dacomitinib**
Total Cost/pt	€26,692	€33,061
Treatment cost/pt	€11,120	€22,833
Disease management/pt	€2,219	€1,869
Adverse events costs/pt	€63	€87
End-of-life care cost	€12,785	€7,229
2L cost /pt	€505	€1,043
QALY gained /pt	0.45	0.51
ICER (€/QALY) **Dacomitinib vs Gefitinib**	€111,048/QALY	

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; 2L: second-line pt: patient.

The results from the DSA showed significant changes in the ICER after modifying dacomitinib acquisition costs, end-of-life care costs, utilities and discount values as shown in the Tornado diagram (*figure 3*) and *supplementary table 3*. The model outcome was sensitive to the drug acquisition cost of dacomitinib, showing that discounts greater than 25% produced an ICER value below the threshold of 24,000€ per QALY gained fixed in Spain.

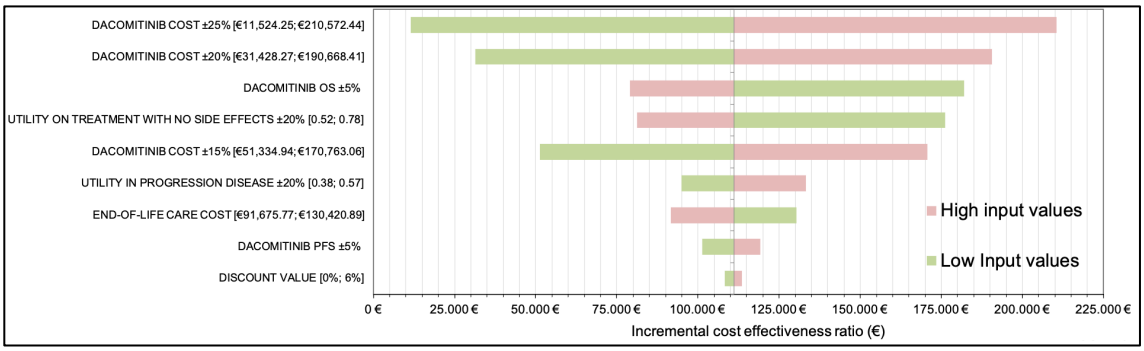


Figure 3. **Tornado diagram (deterministic sensitivity analysis).**

As shown in *figure 4,* the PSA results were consistent with the base-case analyses. Dacomitinib was non-cost effective in 46.63% of the simulations, dominated in 17.84%, cost effective in 16.11% and dominant in 19.42%.

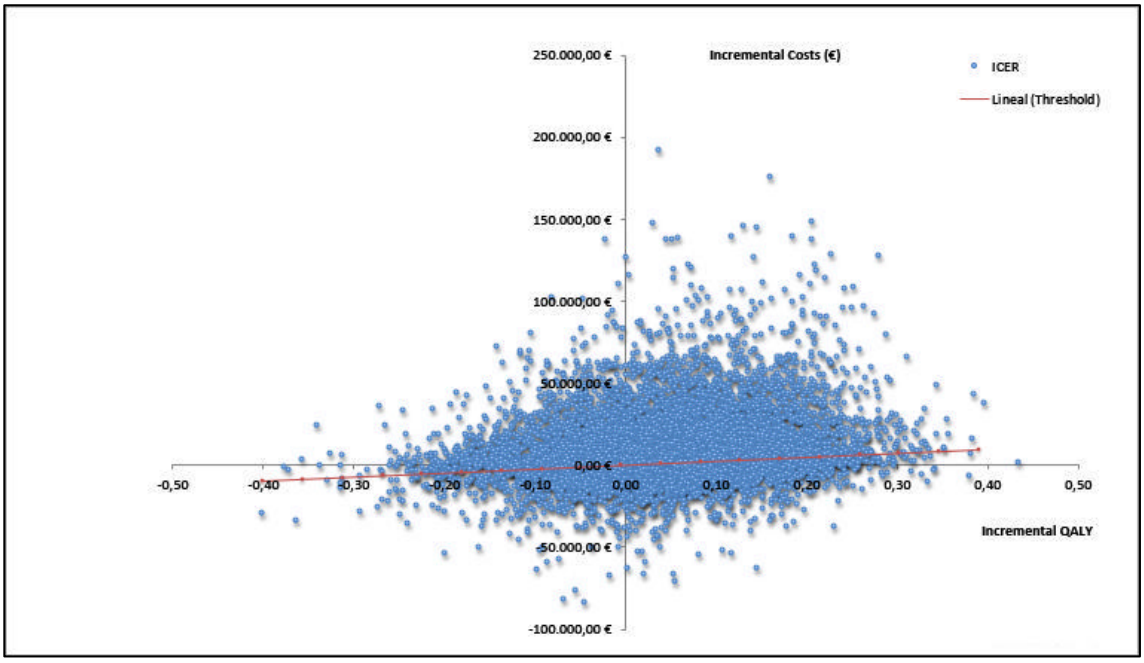


Figure 4. **Scatter plot of Monte Carlo probabilistic sensitivity analysis for dacomitinib vs. gefitinib.**

Finally, the results plotted in a cost-effectiveness plane (*figure 4*) were used to construct the CEA curve, which shows the probability that dacomitinib becomes cost-effective for different willingness to pay (WTP) thresholds. Therefore, in the base-case scenario, there is a 35.53% probability of dacomitinib being cost-effective and dominant at a threshold of €24.000/QALY (*figure 5*).

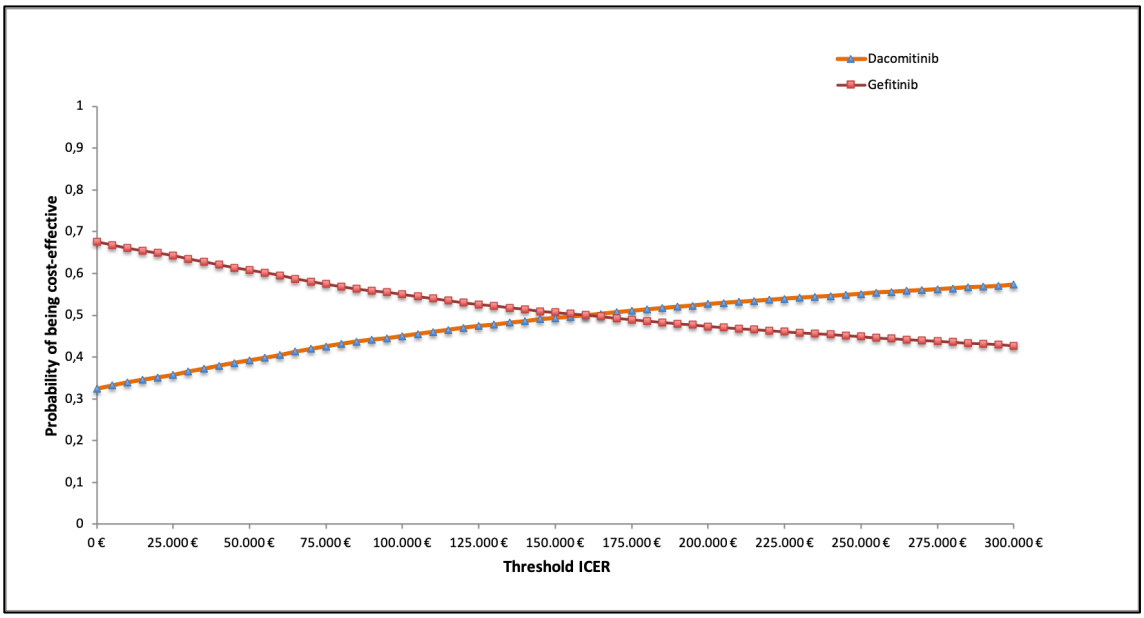


Figure 5. **Cost-effectiveness acceptability curve dacomitinib vs. gefitinib.** Graph plot willingness to pay (WTP) scenario (x-axis) vs. the likelihood in percentage that the treatment would be considered cost-effective (y-axis). ICER: incremental cost-effectiveness ratio.

3. Discussion

Recently, the European Commission has approved dacomitinib for the frontline treatment of adult patients with locally advanced or metastatic NSCLC [36]. Dacomitinib has demonstrated superiority over gefitinib in both PFS and OS in phase III head-to-head comparison study [15], [17]. Additionally, a recent network meta-analysis demonstrated treatment with dacomitinib versus gefitinib (HR: 0.75; 95% CrI: 0.59–0.95), afatinib (HR: 0.87; 95% CrI: 0.61–1.24), erlotinib (HR: 0.79; 95% CrI: 0.44–1.42) and osimertinib (HR: 0.94; 95% CrI: 0.68–1.29) trended directionally toward improved OS, in patients with advanced or metastatic EGFR+ NSCLC [19]. However, the published meta-analysis is not showing a significant difference, confidence intervals are very wide due to the low number of studies included.

The lack of comparative long-term efficacy data can pose challenges for health technology appraisals. Therefore, we developed a complete cost-effectiveness analysis to compare dacomitinib versus gefitinib in patients with newly diagnosed advanced NSCLC and one EGFR mutation based on the ARCHER 1050 study [15]. Over a 15-year time horizon, we demonstrated that dacomitinib is considered slightly more effective in comparison with gefitinib in terms of QALYs gained (0.06). Nonetheless, our study

showed that dacomitinib was not cost-effective compared with EGFR-TKIs because the ICER (€111,048/QALY) was higher than the commonly accepted threshold in Spain of €24,000/QALY [20]. Thus, the base case results indicate that discounts greater than 25% are crucial for the dacomitinib acquisition costs to be considered cost-effective.

At the time of the investigation, this is the first cost-effectiveness analysis to contribute a direct comparison of dacomitinib against the first-generation EGFR-TKI (gefitinib) for patients with newly diagnosed advanced NSCLC EGFR-mutated.

NICE has recommended dacomitinib for locally advanced or metastatic EGFR mutation-positive in adults. The evidence review group of NICE (ERG) constructed a fixed-effects network meta-analysis using data from the ARCHER 1050 for dacomitinib and from LUX-Lung 7 for afatinib [37], [38]. The results of this study showed that PFS and OS might be better for dacomitinib than afatinib, although there was no significant difference between the two treatments (progression-free survival HR 0.80, 95% CI 0.57 to 1.12; overall survival HR 0.88, 95% CI 0.61 to 1.29).

In our study, the small difference in the incremental QALY values (0.06) is mainly attributable to the differences in efficacy between the two drugs. The decrease in utility values due to adverse reactions does not have a relevant impact on the model. This fact can be seen in the DSA, where the drug is not able to be cost-effective, despite the decrease of 20% in the utility value of dacomitinib in stable disease.

In our study, dose modifications are needed to reduce the incidence and severity of treatment-related adverse events [18]. However, adjustment to dose reduction is not expected to have a large impact on the cost-effectiveness results since the price of the different doses of dacomitinib are uniformly based on NICE guidance [27].

In addition, a cost-effectiveness acceptability curve (CEAC) was constructed based on the results plotted in a cost-effectiveness plane to obtain the probability that dacomitinib is cost-effective compared to gefitinib for a different WTP threshold. We demonstrated that, with the defined cost-effectiveness threshold in Spain of €24,000/QALY [20], dacomitinib may be considered not cost-effective due to the high price of drug acquisition.

Lung cancer morbidity and mortality have a significant economic impact on the healthcare system and society. The poor long-term prognosis and high healthcare cost highlight the need to balance patient access to best treatment with healthcare

sustainability and societal burden, particularly in the advanced NSCLC setting [39]. Economic evaluations, like the present cost-effectiveness analysis, are widely used to inform policymakers and health administrators about which treatment innovations should be reimbursed or promoted and to consider reducing prices in the drug acquisition cost.

Our study has some limitations. First, we employed a partitioned survival model, a theoretical model which, by definition, constitutes a simplified simulation of reality. Second, the utility values in the analysis model were extracted from a verified study published in the population of UK [32] but not from Spain because, to date, these data are not available. Third, until the publication of this article, the acquisition cost of dacomitinib has not yet been approved in Spain. Therefore, the value obtained by NICE was selected [27] . Fourth, patients with brain metastases were excluded from participation in the ARCHER 1050 study because the brain penetration of dacomitinib was not known at the time of the study and this could affect the final QALY values [40].

4. Conclusion

This study showed that, from Spanish National Health System perspective, treatment with dacomitinib was more effective in terms of QALYs gained than treatment with gefitinib. However, dacomitinib has been proved not to be a cost-effective alternative in first-line therapy for advanced EGFR-mutated NSCLC patients in Spain because the ICER (€111,048/QALY) appears to be too high given the Spanish threshold. The price of dacomitinib should be reduced by 25% to become a cost-effective alternative.

Key issues

- In ARCHER 1050 study, the median progression-free survival (PFS) in patients with newly diagnosed advanced non-small cell lung cancer (NSCLC) and one epidermal growth factor receptor (EGFR) mutation (exon 19 deletion or Leu858Arg) was demonstrated to be significantly longer with dacomitinib than with gefitinib (14.7 months vs. 9.2 months).
- Dacomitinib presented higher quality-adjusted life years (QALYs) (0.51) compared to gefitinib (0.45).
- Dacomitinib total costs of the intervention were €33,061, in comparison with the €26,691.88 for gefitinib arm.

- An ICER of €111,048/QALY was obtained for dacomitinib compared to gefitinib.
- Dose modifications are needed to reduce the incidence and severity of treatment-related adverse events
- From Spanish National Health System perspective, dacomitinib has been proved not to be a cost-effective alternative in first line therapy for advanced EGFR-mutated NSCLC patients, compared with gefitinib due to the high acquisition costs of the drug.
- A discount greater of 25% in dacomitinib acquisition cost could produce an incremental cost-effectiveness ratio value below the established threshold of €24,000 per QALY gained in Spain to result a cost-effectiveness alternative.

Author contributions

All the authors interpreted data, read, and approved the final manuscript.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization

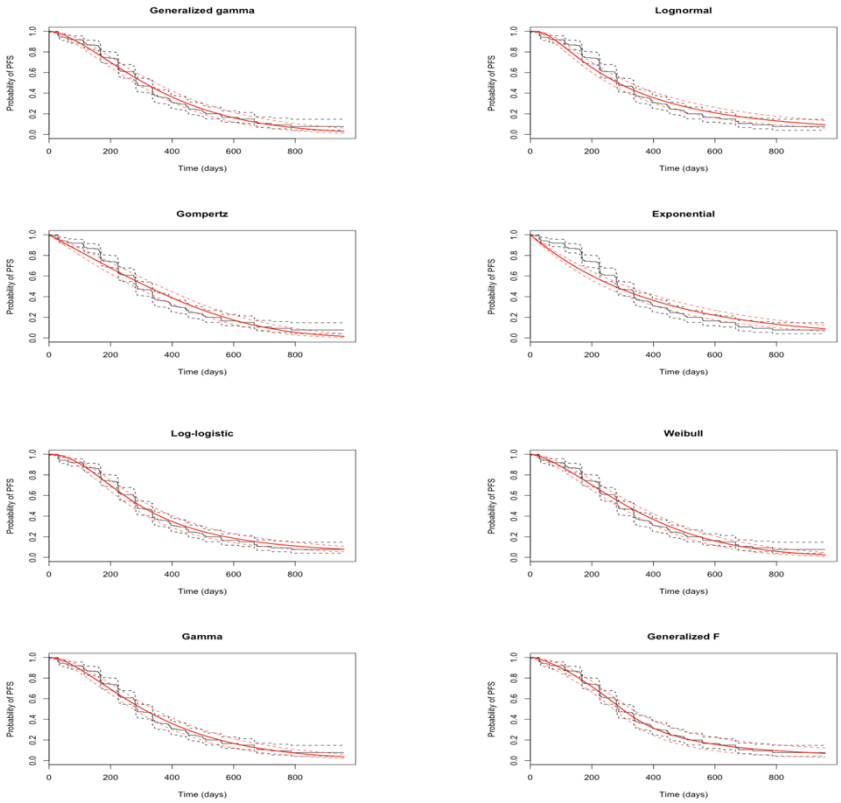
or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

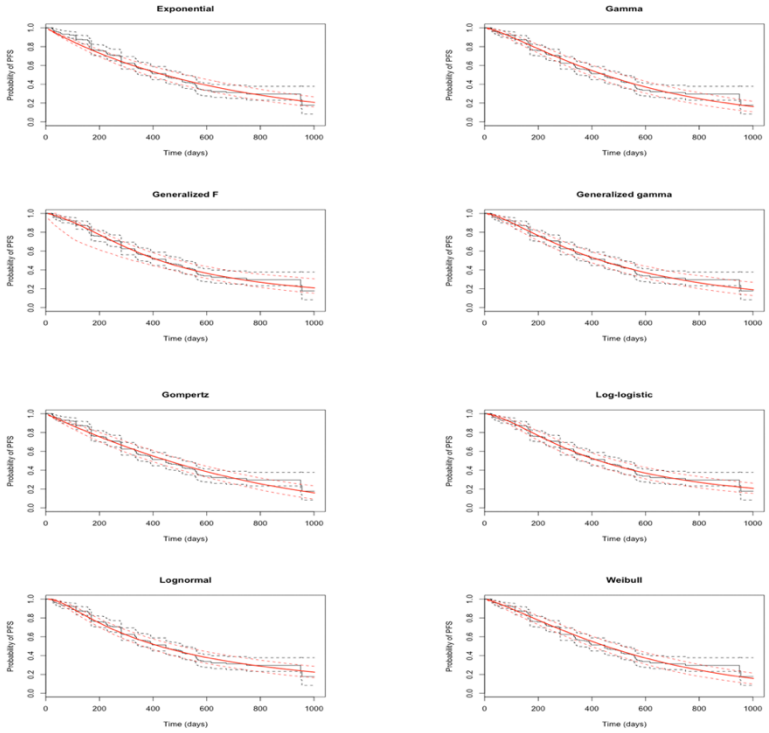
Ethical conduct of research

Our study used mathematical modeling and was not an active clinical trial; therefore, no approval was required from the Institutional Research Ethics Board.

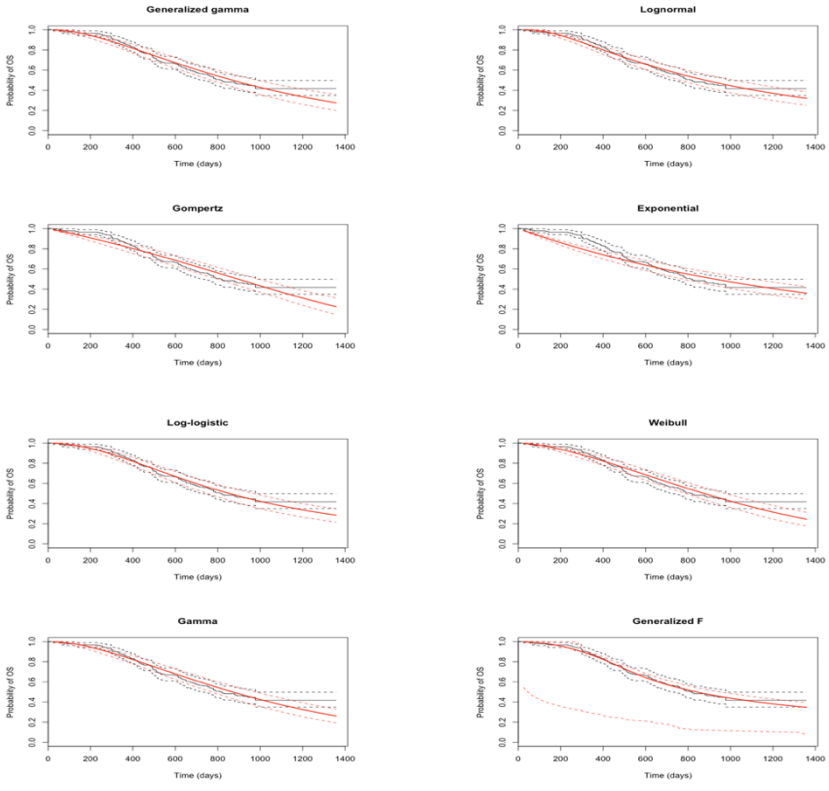
Supplementary Material



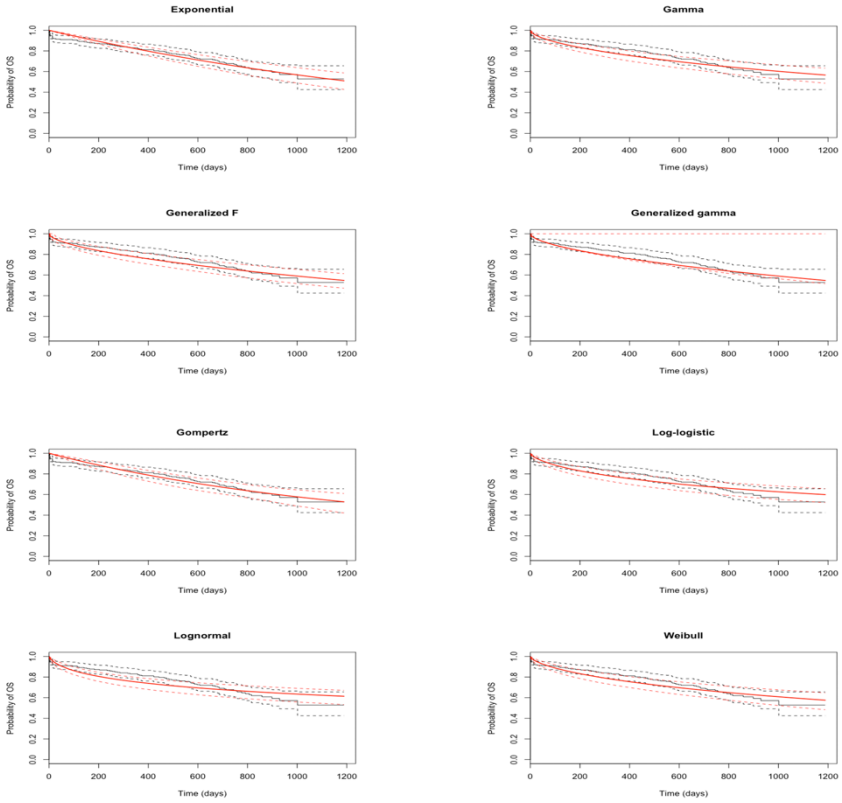
Supplementary-1. ***Figure 1.*** **Fitted Kaplan-Meier curves with different extrapolated models.** Progression-free survival gefitinib.



Supplementary-2. *Figure 2*. Fitted Kaplan-Meier curves with different extrapolated models. Progression-free survival dacomitinib.



Supplementary-3. *Figure 3*. Fitted Kaplan-Meier curves with different extrapolated models. Overall survival gefitinib.



Supplementary-4. *Figure 4*. Fitted Kaplan-Meier curves with different extrapolated models. Overall survival dacomitinib.

Supplementary-5. *Table 1.* Utility and disutility weights.

Adverse event	Dacomitinib				Gefitinib			
	Original values (frequencies) from ARCHER 1050 study	Adjusted frequency	Disutility	Weighted average disutility values	Original values (frequencies) from ARCHER 1050 study	Adjusted frequency	Disutility	Weighted average disutility values
Diarrhoea	0.08 (8%)	0.0052	0.32	0.0017	0.01 (1%)	0.001	0.32	0.00032
Dermatitis acneiform	0.14 (14%)	0.0094	0.15	0.0014	0	0	0	0
Stomatitis	0.04 (4%)	0.0026	0.25	0.00064	0.01 (1%)	0.001	0.25	0.00025
Rash	0.04 (4%)	0.0026	0.15	0.00038	0	0	0	0
Maculopapular rash	0.04 (4%)	0.0026	0.15	0.00038	0.01 (1%)	0.001	0.15	0.00015
Pustular rash	0.04 (4%)	0.0026	0.15	0.00038	0	0	0	0

S6- Table 2. **Goodness-of-fit statistics for modeling PFS and OS for dacomitinib and gefitinib from ARCHER 1050 study.** OS: overall survival; PFS: progression free survival; AIC: Akaike information criterion; BIC: Bayesian information criterion.

	OS DACOMITINIB		PFS DACOMITINIB	
	AIC	BIC	AIC	BIC
Gamma	1283.08	1289.93	2007.94	2014.79
Lognormal	1298.75	1305.60	2009.07	2015.92
Weibull	1285.84	1292.69	2009.30	2016.15
Gompertz	1309.15	1315.00	2014.62	2021.47
Generalized Gamma	1282.76	1293.03	2008.38	2018.66
Exponential	1307.51	1310.94	2015.08	2018.51
Log-logistic	**1291.05**	**1297.90**	**2006.22**	**2013.07**
Generalized F	1248.73	1298.43	2009.94	2023.94
	OS GEFITINIB		PFS GEFITINIB	
	AIC	BIC	AIC	BIC
Gamma	1874.57	1881.40	2424.09	2430.93
Lognormal	1878.20	1885.04	2450.00	2457.83
Weibull	1876.96	1883.79	2423.96	2430.79
Gompertz	1889.99	1896.82	2439.01	2445.84
Generalized Gamma	1876.13	1886.38	2425.42	2435.67
Exponential	1903.05	1906.46	2459.07	2462.49
Log-logistic	**1871.20**	**1878.03**	**2426.84**	**2433.67**
Generalized F	1869.52	1883.19	2417.45	2431.11

S7- Table 3. **Deterministic sensitivity analysis. (DSA)**

Parameter	**Value**		**ICER (€/QALY)**
	BC	***SA***	
Dacomitinib Cost + 15 %			
Gefitinib	€2,045.38	€2,045.38	€170,763.06
Dacomitinib	€3,022.93	€3,476.37	
Dacomitinib Cost - 15%			
Gefitinib	€2,045.38	€2,045.38	€51,334.94
Dacomitinib	€3,022.93	€2,569.50	
Dacomitinib Cost + 20%			
Gefitinib	€2,045.38	€2,045.38	€190,668.41
Dacomitinib	€3,022.93	€3,627.52	
Dacomitinib Cost - 20%			

Gefitinib	€2,045.38	€2,045.38	€31,428.27
Dacomitinib	€3,022.93	€2,418.34	
Dacomitinib Cost + 25%			
Gefitinib	€2,045.38	€2,045.38	€210,572.44
Dacomitinib	€3,022.93	€3,778.66	
Dacomitinib Cost - 25%			
Gefitinib	€2,045.38	€2,045.38	€11,524.25
Dacomitinib	€3,022.93	€2,267.20	
Utility on treatment with no side effects + 20%			
Gefitinib	SD: 0.653 PD: 0.473	SD: 0.783 PD: 0.473	€81,189.96
Dacomitinib	SD: 0.653 PD: 0.473	SD: 0.783 PD: 0.473	
Utility on treatment with no side effects - 20%			
Gefitinib	SD: 0.653 PD: 0.473	SD: 0.522 PD: 0.473	€176,115.37
Dacomitinib	SD: 0.653 PD: 0.473	SD: 0.522 PD: 0.473	
Utility in progression disease + 20%			
Gefitinib	SD: 0.653 PD: 0.473	SD: 0.653 PD: 0.567	€133,256.36
Dacomitinib	SD: 0.653 PD: 0.473	SD: 0.653 PD: 0.567	
Utility in progression disease - 20%			
Gefitinib	SD: 0.653 PD: 0.473	SD: 0.653 PD: 0.378	€94,893.62
Dacomitinib	SD: 0.653 PD: 0.473	SD: 0.653 PD: 0.378	
Discount value 6%			

Gefitinib	3%	6%	€113,631.89
Dacomitinib	3%	6%	
Discount value 0%			
Gefitinib	3%	0%	€108,337.95
Dacomitinib	3%	0%	
End-of-life care cost + 20%			
Gefitinib	€12,909.24	€15,491.09	€91,675.77
Dacomitinib	€12,909.24	€15,491.09	
End-of-life care cost - 20%			
Gefitinib	€12,909.24	€10,327.39	€130,420.89
Dacomitinib	€12,909.24	€10,327.39	

ICER: Incremental cost-effectiveness ratio; BC: base case; SA: sensitivity analysis; SD: stable disease; PD: progression disease; QALY: quality-adjusted life-year.

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Artículo 1

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Artículo 2

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Artículo 3

Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Trigo-Vicente C, Cortijo J. Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer. Expert Rev Pharmacoecon Outcomes Res. 2022 Jun;22(4):637-646. doi: 10.1080/14737167.2022.1987220. Epub 2021 Oct 11. PMID: 34602008.

Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer

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ABSTRACT

Aim: to evaluate the cost-effectiveness of first-line treatments such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib, for patients diagnosed with stage IIIB/IV NSCLC harbouring EGFR mutations, with Spain as a context.

Materials & methods: a partitioned survival model was developed comprising three mutually exclusive health states with a fifteen-year time horizon and the perspective of the Spanish National Health System. The primary endpoints were total costs,, life years (LY), quality-adjusted life years (QALY), and incremental cost-effectiveness ratios (ICER). Two Bayesian NMAs were performed independently, by using the polynomial fraction method to fit Kaplan-Meier curves for overall survival and progression-free survival. The willingness-to-pay (WTP) threshold was set to 24,000€/QALY. Sensitivity analyses were conducted including univariate and probabilistic sensitivity analyses (PSA).

Results: the ICER was calculated for the four first-line treatemnts by comparing them with gefitinib and the ratios obtained were: €166,416/QALY for osimertinib, €183,682/QALY for dacomitinib, €167,554/QALY for afatinib, €36,196/QALY for erlotinib. It was seen that patients who received osimertinib presented higher QALYs (0.49), followed by dacomitinib (0.33), afatinib (0.32), erlotinib (0.31), and gefitinib (0.28). Total discounted costs per patients was studied and it revealed that patients who were administered Gefitinib treatment received the highest discount of €44,566, followed by erlotinib (€45,638), afatinib (€51,542), dacomitinib (€53,438), and osimertinib (€77,637).

Conclusions: the results of the present analysis suggest that gefitinib would be the most cost-effective treatment. In terms of QALYs gained, Osimertinib was more effective than all other TKIs. Nevertheless, with a Spanish threshold of €24,000/QALY, the reduction in the acquisition cost of osimertinib will have to be greater than 70%, to obtain a cost-effectiveness alternative.

1. INTRODUCTION

Lung cancer is one of the most commonly diagnosed types of cancer and the leading cause of cancer-related mortality worldwide [1]. From 2008 to 2013, lung cancer was the fourth most commonly diagnosed cancer, after colorectal, prostate and breast cancers, among the sexes with a five-year survival rate of 12.7% in men and 17.6% in women [2].

Lung cancer is further divided into small-cell and non-small-cell lung cancer (NSCLC). NSCLC is the most widespread type of lung cancer that has been diagnosed in approximately 85% of all lung cancer cases [3]. The presence of somatic mutations in the gene encoding the epidermal growth factor receptor (EGFR) could be associated in approximately 14–19% of Western patients and 40–48% of Asian patients suffering from NSCLC with adenocarcinoma [4,5]. In Spain, EGFR mutations were detected in 11.6% of NSCLC patients, out of which 17.4% presented L858R mutation in exon 21 and 82.6% presented in-frame deletions in exon 19, which is discussed later [6].

Until a few years ago, four to six cycles of platinum-based doublet chemotherapy had been selected as standard first-line treatment for patients with advanced NSCLC [7]. However, it provides limited benefits with regard to survival, with nearly one-year median overall survival (OS) [8–10].

In recent years, patients with NSCLC and activating somatic EGFR mutations have shown better clinical outcomes in both progression-free survival (PFS) and OS, when treated with EGFR tyrosine kinase inhibitors (TKI) than with chemotherapy [11,12]. Actually, three generations of EGFR TKIs have been developed (first generation: gefitinib and erlotinib; second generation: afatinib and dacomitinib, and third generation: osimertinib) [13]. However, more than half of the patients diagnosed with NSCLC EGFR-positive developed resistance to treatment with first-generation and second-generation EGFR TKIs, which is associated with an acquired mutation, T790M, in the EGFR gene [14–16]. Consequently, the T790M mutation forces a change in a third-generation drug such as osimertinib, which is currently employed with successful results [17–21].

However, since there are no direct comparative randomized controlled trials (RCTs) for all EGFR TKI, different network meta-analyses (NMA) have been published [22–30]. In

our study, we have selected the NMA published by Holleman et al. [24] to obtain efficacy data.

The management of morbidity and mortality in lung cancer have a significant economic impact on the healthcare system and society. In Spain, the mean cost per patient in NSCLC ranged between €13,218 and €16,120 [31].

To the best of our knowledge, no prior cost-effectiveness analysis (ICER) has been developed to compare the three generations of EGFR TKIs (erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib). Hence, this study aims to evaluate the cost-effectiveness of first-line treatments such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib, for patients diagnosed with stage IIIB/IV NSCLC harbouring EGFR mutations, in the context of Spain. Our study could provide extremely valuable information for clinicians and medical decision makers in order to promote the sustainability of the Spanish National Health System.

2. Material & methods

2.1 Model structure and settings

The cost-utility analysis was performed using a partitioned survival model. It was constructed to select which of the five main TKIs used as first-line treatment is the most cost-effective, for patients diagnosed with stage IIIB/IV NSCLC harbouring EGFR mutations. To assess cost effectiveness, the incremental cost per quality-adjusted life-year (QALY) gained, the incremental cost per life-year (LY) gained, and the incremental costs were set as the main outcome measures. The model was developed from the perspective of the Spanish National Health System. The threshold for establishing the cost-effectiveness of an alternative was €24,000/QALY, as recommended in Spain [32]. Health outcomes and costs were discounted at a rate of 3%, in line with the Spanish guidelines [33]. All the costs were estimated in euros (€) 2021. The partitioned survival model was created in Microsoft Excel 2021 (Microsoft Corp., WA, USA). A 15-year time horizon was employed as it comprehensively captures the expected costs and health outcomes of patients over their remaining lifetime from the initiation of first-line treatment. The results were presented in terms of costs (€), QALYs gained, and ICER.

The three mutually exclusive health states chosen to conduct the study on were progression-free disease (PFS), progressive disease (PD), and death. The OS was split into alive with PFS and alive with PD. The proportion of alive with PFS was calculated

by the area under the PFS curve. The proportion of alive with PD was estimated by the difference between the OS and PFS curves.

According to the transition probabilities, shown in *figure 1*, for each 28-day simulation cycle, it was assumed that all patients entered the model with a stable disease and they could only transition from one health state to another or stay in the same state during a cycle. Patients in both stable and progressive disease states could transition to the death state in any cycle. In progressive disease state, the patients received a second-line regimen. Progressive disease state was simulated until all the patients died, after which a half-cycle correction was applied.

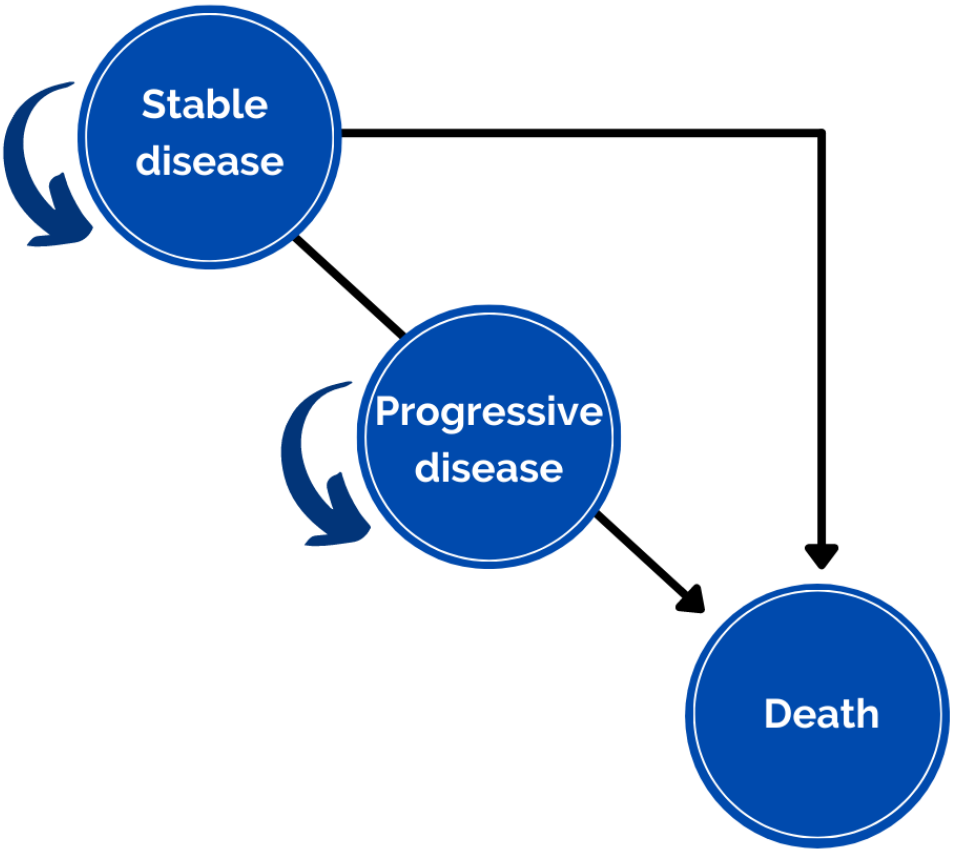


Figure 1. **Structure of the partitioned survival model.** Partitioned survival model health states.

2.2 Target population

The target population from the NMA, by Holleman [24]**,** was simulated in this model and we have added the final OS results for osimertinib [34]. In this NMA, gefitinib was studied in eight RCTs (NEJ002, WJTOG3405, IPASS, First-SIGNAL, Lux-Lung 7, CTONG0901, ARCHER1050, and FLAURA) [21,34–41]. Erlotinib was studied in four RCTs

(OPTIMAL, EURTAC, ENSURE, and CTONG0901) [40,42–45]. Afatinib was studied in three RCTs (Lux-Lung 3, Lux-Lung 6, and Lux-Lung 7) [39,46–48]**.** Dacomitinib was studied in one RCT (ARCHER 1050) [41,49] and osimertinib in one RCT (FLAURA) [21,34] **.**

2.3 Comparators

The comparator used in this analysis was gefitinib. Platinum-based chemotherapy was excluded as standard first-line therapy in our study because TKIs have shown a better tolerance to and a longer prolongation of PFS, as demonstrated in several studies [35,36,42,43,46,47,50]**.**

2.4 Effectiveness estimates

Erlotinib, gefitinib, afatinib, dacomitinib and osimertinib efficacy (PFS and OS) were estimated through a NMA based on 13 RCTs [24]. A Bayesian NMA was carried out using Markov chain Monte Carlo (MCMC) methods, based on the methodology proposed by Dias et al. [51]. Firstly, using WebPlotDigitizer, we digitized individual patient data from the Kaplan-Meier curves for PFS and OS based on the 13 RCTs [52]. The individual patient data (IPD) was reconstructed according to an algorithm proposed by Guyot [53]. A pseudo-IPD was used to estimate the number of patients with events in each time interval. With fractional polynomials, we modelled the hazard over-time from each study arm to achieve an overall set of estimated parameters for each treatment. This approach relaxes the proportionality of risks and fits better with the available data [54].

Two NMAs were conducted independently, one each for OS and PFS. The Bayesian NMAs were performed using R statistical software (version 3.6.3) and the rjags package [55]. Posterior sampling was conducted using Markov chain Monte Carlo method, where four chains of 15,000 samples were held after discarding a burn-in of 5,000 iterations. Models of both fixed-effect and random-effect were fitted to the data. Vague prior distributions were assigned to all stochastic parameters. First-order and second-order fractional polynomials were evaluated. A set of five values (-2. -1, 0, 1, 2) was selected for the exponents p1 and p2. Based on the deviance information criterion (DIC) (*table 1*) and the visual inspection, the best-fitting model was selected to plot the pooled survival curves with lower DIC values being preferred. Fixed-effects,

first-degree, and 0-exponent models were selected for both overall survival and progression-free survival (*supplementary annex, figure S1 and figure S2).*

Table 1. **Goodness-of-fit statistics for modeling PFS and OS.** OS: overall survival; PFS: progression free survival; DIC: deviance information criterion; NC: non convergence

Order	Exponents	Random effects	DIC SLP	DIC OS
1	2	FALSE	5490.3	14745.9
1	1	FALSE	4547.2	5122.4
1	0	FALSE	4025.4	4885.3
1	-1	FALSE	3851.2	NC
1	-2	FALSE	NC	NC
1	2	TRUE	5787.4	NC
1	1	TRUE	4489.8	5124.4
1	0	TRUE	3961.1	4885
1	-1	TRUE	3799.7	NC
1	-2	TRUE	NC	NC
2	2, 2	FALSE	16092.1	48760.9
2	1, 2	FALSE	6396.8	20477.9
2	0, 2	FALSE	5299.4	15400.3
2	-1, 2	FALSE	4640.1	13574.7
2	-2, 2	FALSE	4656.5	13970.4
2	2, 1	FALSE	6576.5	20114.4
2	1, 1	FALSE	3955.5	5805.5
2	0, 1	FALSE	3824.8	4872
2	-1, 1	FALSE	3855.2	4882.8
2	-2, 1	FALSE	NC	4924.5
2	2, 0	FALSE	5218.4	14775.5
2	1, 0	FALSE	3830.1	4872.1
2	0, 0	FALSE	3848.2	4852.9
2	-1, 0	FALSE	NC	NC
2	-2, 0	FALSE	NC	NC
2	2, -1	FALSE	4678.8	14029.6
2	1, -1	FALSE	3869.2	4894
2	0, -1	FALSE	3867.1	NC
2	-1, -1	FALSE	NC	NC
2	-2, -1	FALSE	NC	NC
2	2, -2	FALSE	4765.1	14654.8
2	1, -2	FALSE	NC	NC
2	0, -2	FALSE	NC	NC
2	-1, -2	FALSE	NC	NC
2	-2, -2	FALSE	NC	NC
2	2, 2	TRUE	11755.5	NC
2	1, 2	TRUE	6509.9	16284.4
2	0, 2	TRUE	5679.1	17959.5
2	-1, 2	TRUE	5006.6	NC
2	-2, 2	TRUE	4950.4	NC
2	2, 1	TRUE	6742.8	17223.1
2	1, 1	TRUE	3915.3	5918.7

2	0, 1	TRUE	3780	4889.4
2	-1, 1	TRUE	3804.3	4889.5
2	-2, 1	TRUE	NC	4912.1
2	2, 0	TRUE	5537.2	17568.3
2	1, 0	TRUE	3777.4	4876.1
2	0, 0	TRUE	3799.8	4849.4
2	-1, 0	TRUE	3815.3	NC
2	-2, 0	TRUE	NC	NC
2	2, -1	TRUE	4889.3	NC
2	1, -1	TRUE	3806.2	4906.2
2	0, -1	TRUE	3807.1	NC
2	-1, -1	TRUE	NC	NC
2	-2, -1	TRUE	NC	NC
2	2, -2	TRUE	4877	NC
2	1, -2	TRUE	NC	4930.4
2	0, -2	TRUE	NC	NC
2	-1, -2	TRUE	NC	NC
2	-2, -2	TRUE	NC	NC

2.5 Cost estimations

All results were expressed in euros (€). All costs from prior years were inflated to 2021 for Spanish values using the consumer price index (CPI). *Table 2* outlines the calculated costs. Direct costs include treatment costs, disease management costs, end-of-life care costs, adverse events costs and second-line treatment costs. The costs of the five TKIs were calculated according to the officially notified listed prices ([drug price - 7.5% official discount in Spain] + 4% Value added tax [VAT]) [56,57]. When compared to other EGFR-TKIs, there is a substantial difference seen in the costs of gefitinib and erlotinib because we have considered the generic drug values of these drugs.

Table 2. **Model input parameters.**

Management of NSCLC	Cost per 28-day cycle and patient	Distribution	References
Erlotinib	€494	Gamma	[56][57]
Gefitinib	€292	Gamma	
Dacomitinib	€2,424	Gamma	
Afatinib	€1,714	Gamma	

Osimertinib	€5,447	Gamma	
Second-line cost osimertinib	€11,880	Weibull	[21][56][57]
Scheme (29% of total patients)			
EGFR-TKI scheme erlotinib/gefitinib (21%)			
Platinum-based chemotherapy schemes (36%)			
Non platinum-based chemotherapy schemes (35%)			
Others therapies (8%)			
Second-line cost erlotinib, gefitinib, afatinib and dacomitinib	€15,310	Weibull	[21][56][57]
Scheme (47% of total patients)			
EGFR-TKI scheme treated with osimertinib (46%)			
Platinum-based chemotherapy schemes (13%)			
Non platinum-based chemotherapy schemes (12%)			
Others therapies (4%)			
End-of-life care cost	€12,947	Gamma	[61]
Grade III-IV adverse events (frequency >3%)	**Median cost/cycle**		[59][60]
Diarrhea	€1,556	Gamma	

Dermatitis acneiform	€2.11	Gamma	
Stomatitis	€1,352	Gamma	
Rash	€2.11	Gamma	
Maculopapular rash	€2.11	Gamma	
Postular rash	€2.11	Gamma	
Alanine aminotransferase elevation	€68	Gamma	
Aspartate aminotransferase elevation	€68	Gamma	
Fatigue	€176	Gamma	
Neutropenia	€1,910	Gamma	
Decreased appetite	€10.31	Gamma	
Paronychia	€2.11	Gamma	
Weight decreased	€10.31	Gamma	
Dyspnoea	€176	Gamma	
Asthenia	€176	Gamma	
Utilities scenario	**Value**		[62][63]
On treatment with no side effects	0.65	Beta	
Diarrhea	0.32	Beta	
Dermatitis acneiform	0.15	Beta	
Stomatitis	0.25	Beta	
Rash	0.15	Beta	
Maculopapular rash	0.15	Beta	
Postular rash	0.15	Beta	
Alanine	0	Beta	

aminotransferase elevation			
Aspartate aminotransferase elevation	0	Beta	
Fatigue	0.41	Beta	
Neutropenia	0.46	Beta	
Decreased appetite	0.41	Beta	
Paronychia	0.03	Beta	
Weight decreased	0.41	Beta	
Dyspnoea	0.41	Beta	
Asthenia	0.41	Beta	
Disease progression	0.47	Beta	

Disease management costs were calculated based on an expert panel's advice. This cost per patient cycle was estimated by multiplying the cost of healthcare resources incurred with the unit cost of each resource consumed over a 15-year time horizon. The unit costs of each resource were extracted from an official database published in Spain [58].

The costs endured in managing side effects were obtained from published articles [59,60]. Costs of severe adverse events (grade 3/4) included the total costs of the treatment for an adverse event per patient and were multiplied by the probability of each adverse event obtained in the NMA [24].

The second-line therapy regimens were obtained from supplementary table 3 of FLAURA study [21]. In the osimertinib second-line arm, 21% of the patients were re-challenged with standard EGFR–TKI (erlotinib–gefitinib), followed by 36% with platinum-based chemotherapy, 35% with non-platinum-based chemotherapy, and 8% with other therapies (PD-1/PD-L1, anti-VEGF and others targeted therapies). For the four other TKI second-line arms (erlotinib, gefitinib, dacomitinib and afatinib), 46% of the patients were treated with another EGFR–TKI including osimertinib, 13% with

platinum-based chemotherapy, 12% with non-platinum-based chemotherapy and 4% with others therapies (PD1/PD-L1, anti-VEGF and others targeted therapies). To calculate second-line costs, patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m2. Since the second-line treatment curves corresponding to PFS were not available in the FLAURA clinical trial, we employed the PSF2 curves available in the AURA3 clinical trial to calculate the duration for second-line treatment [20]. For this, we estimated the area under the curve (AUC) in the PFS2 AURA3 trial curve by comparing osimertinib with platinum/pemetrexed-based chemotherapy in NSCLC for patients who experienced a progression in the disease after receiving first-line EGFR–TKI therapy. We employed the method proposed by Guyot et al to simulate the best survival curve [53], which was then fitted with a Weibull distribution to obtain the best adjusting method.

End-of-life care costs were applied to each patient entering the death state and were obtained from an article published in Spain [61].

2.6 Utility estimates

To estimate QALYs, values of utilities for stable disease and progressive disease were estimated from data published in literature [62]. A health utility of zero was applied to the health state of death. By employing a time trade-off technique, the disutility values associated with grade 3/4 adverse events were obtained from an international study for advanced NSCLC conducted in different countries such as the UK, France, and Australia [63].

2.7 Univariate sensitivity analyses

Deterministic sensitivity analyses (DSA) was conducted to estimate the impact of the essential variables on the ICER value. Hence, different parameters in the model, such as drug costs, utilities, and discount rates, were varied to test their influence on the ICER result. The results of the DSA were presented in a tornado diagram.

2.8 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to quantify the impact of combined uncertainty of all model-input parameters using 10,000 Monte Carlo simulations and the results were plotted on a cost-effectiveness plane. Different parameters of the model, such as disease management costs, side effects management costs, second-line treatment costs, drug costs, end-of-life care costs, and

utilities, were varied to determine the robustness of the model. The cost-effectiveness acceptability curve was calculated after the PSA results were obtained, showing the probability of each TKI drug being cost-effective across a range of possible values of willingness-to-pay (WTP) for an additional QALY [64]. Depending on the characteristics of each variable, different types of probability distributions were applied, namely gamma distributions for costs, beta for utilities, and Dirichlet for transition probabilities.

3. Results

3.1 Base-case analysis

Effectiveness and costs were outlined according to each treatment and were summarized in table 3. Highest QALY per patient was observed in patients who received osimertinib (0.49), followed by patients who received dacomitinib (0.33), afatinib (0.32), erlotinib (0.31), and gefitinib (0.28). Furthermore, afatinib was associated with the lowest total costs (€22,859) and osimertinib with the highest total costs (€56,881). It was seen that in Spain, no treatment strategy was cost-effective with a WTP threshold of €24.000/QALY. When compared to gefitinib, the most cost-effective therapy was erlotinib with an ICER of €36,196 per QALY gained, followed by osimertinib with an ICER of €166,416/QALY.

Table 3. **Cost-effectiveness results.**

	Treatment cost / pt	Disease management cost / pt	Adverse events cost / pt	End-of-life care cost / pt	2L cost / pt	**Total Cost / pt**	**LYG / pt**	**QALY / pt**	**ICER (€/QALY)**
Gefitinib	22,859	1,114	16	12,922	7,655	44,566	0.48	0.28	-
Erlotinib	23,994	1,071	6	12,912	7,655	45,638	0.52	0.31	36,196
Afatinib	29,672	1261	49	12,905	7,655	51,542	0.45	0.32	167,554
Dacomitinib	31,850	975	36	12,922	7,655	53,438	0.47	0.33	183,682
Osimertinib	56,881	2008	6	12,807	5,935	77,637	0.64	0.49	166,416

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; 2L: second-line; pt: patient.

3.2 Deterministic sensitivity analysis

The results of the DSA for each drug are represented in the four tornado diagrams in *figure 2*. The DSA showed significant changes in the ICER, after modifying acquisition costs and OS values in each drug. However, only when the acquisition cost is reduced by 40% for erlotinib and 70% for osimertinib, do we obtain an ICER value below the threshold of 24,000€ per QALY gained, which is fixed in Spain. For all other parameter variations, when acquisition cost is reduced by 40% the ICER of each drug comparison exceeded the WTP per QALY for Spain.

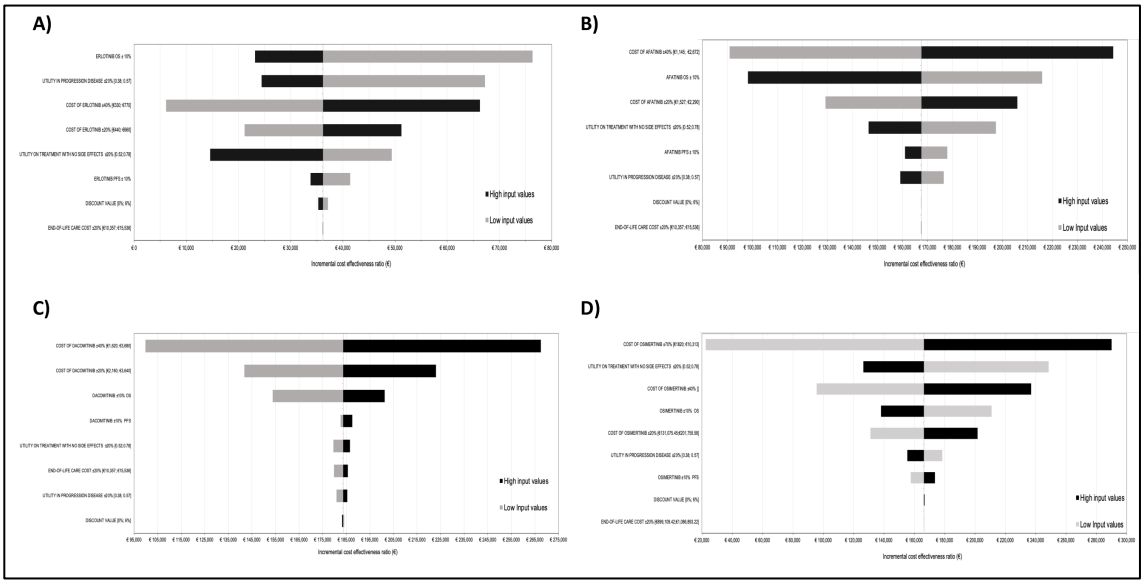


Figure 2. **Tornado diagram representing one-way sensitivity analyses with changing baseline parameters. Comparisons represented: (A) erlotinib vs. gefitinib, (B) afatinib vs. gefitinib, (C) dacomitinib vs. gefitinib and (D) osimertinib vs. gefitinib.**

Figure 3 shows the four scatter plots of Monte Carlo probabilistic sensitivity analysis. For erlotinib versus gefitinib, about 25.70% of the PSA iterations were dominant, 23.54% of the PSA iterations were cost-effective, 19.91% were dominated, and 30.85% were non-cost-effective.

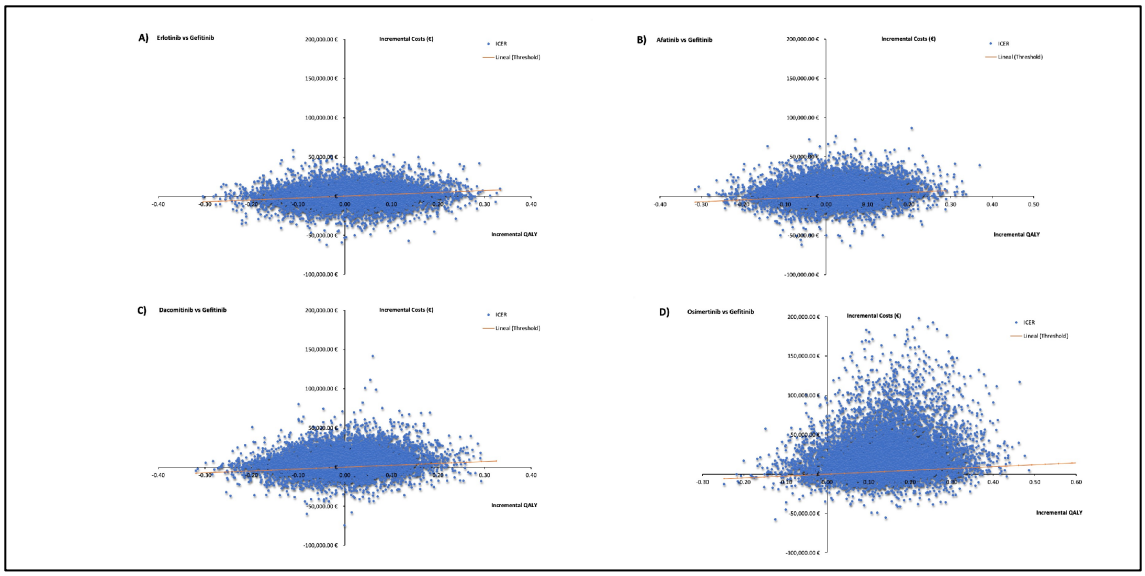


Figure 3. **Scatter plot of Monte Carlo probabilistic sensitivity analysis for (A) erlotinib vs. gefitinib , (B) afatinib vs. gefitinib, (C) dacomitinib vs. gefitinib, and (D) osimertinib vs. gefitinib.**

Cost-effectiveness acceptability curve (CEAC) is shown in *figure 4* for varying values of WTP. It showed that with a Spanish threshold of €24,000/QALY, gefitinib had the highest probability of being cost-effective (32.56%). Meanwhile, erlotinib, afatinib, dacomitinib, and osimertinib had a probability of 30.43%, 16.96%, 11.49%, and 8.56%, respectively. Finally, at a threshold of €300,000/QALY, osimertinib demonstrated a 50% probability of being cost-effective.

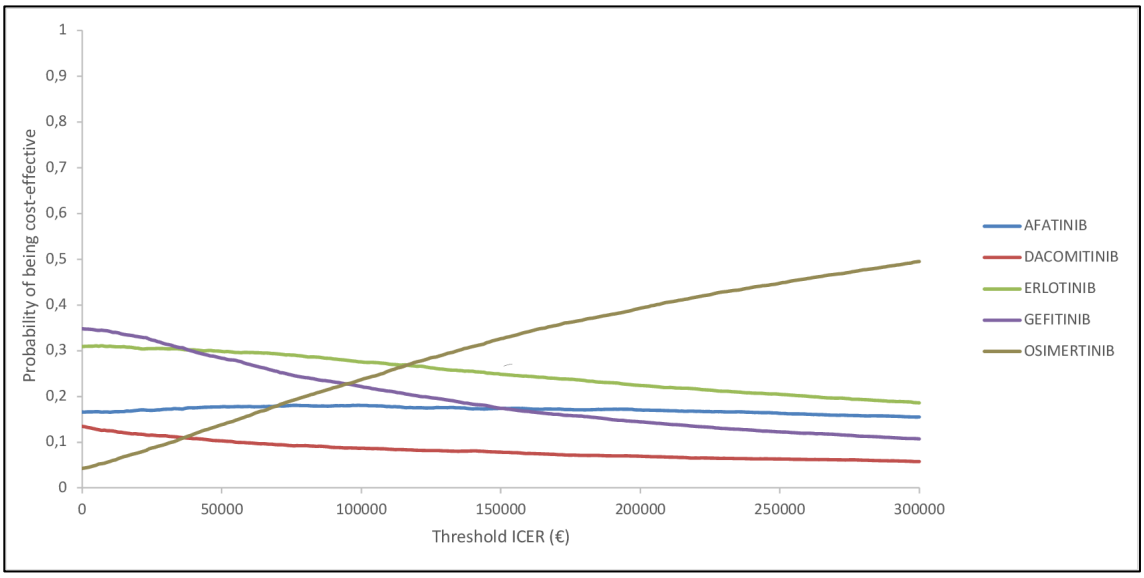


Figure 4. **Cost-effectiveness acceptability curve demonstrating the probability at different WTP levels for erlotinib vs. gefitinib (A), afatinib vs. gefitinib (B), dacomitinib vs. gefitinib (C), and osimertinib vs. gefitinib (D).** Graph plot WTP scenario (x-axis) vs. Likelihood in percentage that the treatment would be considered cost-effective (y-axis). ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

4. DISCUSSION

In a context of limited resources, the economic evaluations of the impact of different treatments for NSCLC EGFR+ could become an essential tool for clinicians and policymakers to select the best cost-effectiveness treatment for patients and sustainability of the Spanish National Health System. At the time of this study, this is the first cost-effectiveness analysis that compared first-line gefitinib, erlotinib, afatinib, dacomitinib and osimertinib in patients with stage IIIB/IV NSCLC EGFR-mutated in the context of Spain. Our study demonstrated that over a 15-year time horizon, osimertinib was slightly more effective in terms of QALYs gained than gefitinib (0.20), followed by dacomitinib (0.05), afatinib (0.04), and erlotinib (0.03). Nevertheless, the results showed that with the current WTP threshold in Spain (€24,000/QALY), none of the TKIs were cost-effective when compared to standard first-generation EGFR-TKI, gefitinib, for patients diagnosed with advanced NSCLC EGFR-positive. Although the ICER threshold selected can be considered quite rigorous, this value is similar to that used in other studies conducted in the same setting [65–68]. According to the study conducted by Cameron et al. describing the "official thresholds" for seventeen countries, €24,000 per QALY threshold appears to be much lower than the "official thresholds" used in other countries such as Portugal (€31,890), Sweden (€50,173), or

The Netherlands (€80,000) [69]. However, it is difficult to compare these thresholds across countries because they have been calculated using different methodologies and techniques.

The findings from our study confirm the results of other cost-effectiveness studies, such as Holleman et al. [70], where osimertinib was shown to be the most effective, followed by afatinib, erlotinib, and gefitinib in The Netherlands. However, afatinib was found to be cost-effective (ICER €22,514/QALY) and gefitinib dominant, when compared to gefitinib respectively. A major difference with respect to our study is that Holleman et al. included only four TKIs and excluded dacomitinib. In line with our results, several economic evaluations published in other countries have shown that osimertinib would not be cost-effective as a first-line treatment when compared to first-generation and second-generation EGFR TKIs [71–76]. In two different studies that were conducted, dacomitinib was observed to be cost-effective in China and dominant compared to gefitinib in Portugal [77,78]. However, in our recent study published in Spain, dacomitinib was found not to be cost-effective when compared to gefitinib [79]. For afatinib, our results differ from other economic evaluations published in France, China, and Canada, which showed afatinib to be cost-effective when compared to gefitinib as first-line treatment in patients with EGFRm NSCLC [80–82].

Our one-way sensitivity analysis showed that all variables that could have a significant impact on the results were included. The two most influential parameters impacting the results were OS values and first-line drug treatment costs, which were modified by increasing or decreasing them using the upper or lower boundaries. Hence, only significant changes in those variables would potentially modify the results of the ICER.

Based on the results obtained in the cost-effectiveness plans for each of the EGFR-TKIs, we constructed a cost-effectiveness acceptability curve to determine the probability of cost-effectiveness of each drug for different WTP thresholds. It was deduced from the curve that, with the established cost-effectiveness threshold in Spain (€24,000/QALY) [32], none of the EGFR-TKIs evaluated in this study could be considered cost-effective due to the high acquisition cost of the drugs.

An important strength of our study is that we have selected an NMA that compiles the most important and relevant clinical trials for each of the EGFR TKIs [24], in addition to

this, we have updated the mature OS results of osimertinib from the FLAURA study [34]. Furthermore, a novel aspect of our current study was the use of the polynomial fraction methodology using which we obtained the survival values of OS and PFS for each TKI, which could be fitted closely to our data. Hence, assuming constant ratio of hazards implies a constant difference in effectiveness through time; fractional polynomial method can be selected as a better approach over traditional NMA, to assess relative efficacy of TKIs [83].

This study has several limitations. First, due to the lack of head-to-head clinical trials comparing these five first-line TKIs, an NMA in this study was selected for an indirect comparison, although moderate heterogeneity in patient characteristics which was assumed. Second, some key clinical inputs, such as utility values, were extracted from a verified study published in the population of the UK [62] because when the study was conducted, these values were not available in Spain. However, the sensitivity analyses demonstrated only slight impacts on this value. Third, the comparator chosen for our study has been gefitinib, because it is the alternative with lesser efficacy. Fourth, for second-line treatment we selected the scheme followed in the FLAURA trial, because till date, no valid scheme has been established in our country by the Spanish National Health System. Fifth, in our study, we have not evaluated the penetration of EGFR-TKIs into the central nervous system (CNS). Owing to the high incidence of EGFR mutation positivity among patients with brain metastases, ranging between 44 and 63% as opposed to the usually reported 10% incidence of EGFR mutation in all patients diagnosed with NSCLC [84], this could be considered an important limitation. Osimertinib demonstrated better CNS efficacy and activity against both parenchymal brain metastases and leptomeningeal disease, and a greater reduction in the risk of CNS progression, as compared to first-generation EGFR-TKIs [21,85,86]. To make further observations, a comprehensive study of this subgroup of patients would be required.

The potential effectiveness of osimertinib, the first third-generation EGFR-TKI, to improve survival was a decisive determinant of clinical and economic results of our study. In Europe, the European Society for Medical Oncology (ESMO) guidelines recommended first-line treatment with monotherapy of other treatments such as erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib (ESMO 2018). However, in the

updated version published on 15th September 2020, the ESMO Guidelines Committee recommended osimertinib as the preferred option for NSCLC patients with sensitising EGFR mutations instead of first-generation and second-generation EGFR-TKIs [87,88]. However, our findings demonstrated that in the context of Spain, osimertinib could not be considered as a cost-effective option compared to first-generation and second-generation TKIs. Therefore, for osimertinib to be cost-effective in Spain, the acquisition costs of osimertinib will have to be reduced.

5. CONCLUSION

This study showed that, from the perspective of the Spanish National Health System, none of the treatments proved to be cost-effective for a Spanish threshold of €24,000/QALY. The most effective drug was osimertinib, when compared to gefitinib. However, the ICER obtained for osimertinib versus gefitinib (€166,415/QALY) appears to be too high, for the given Spanish threshold. The price of osimertinib should be reduced by 70%, for it to become a cost-effective alternative.

Author contributions

All the authors interpreted data, read and approved the final manuscript.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization

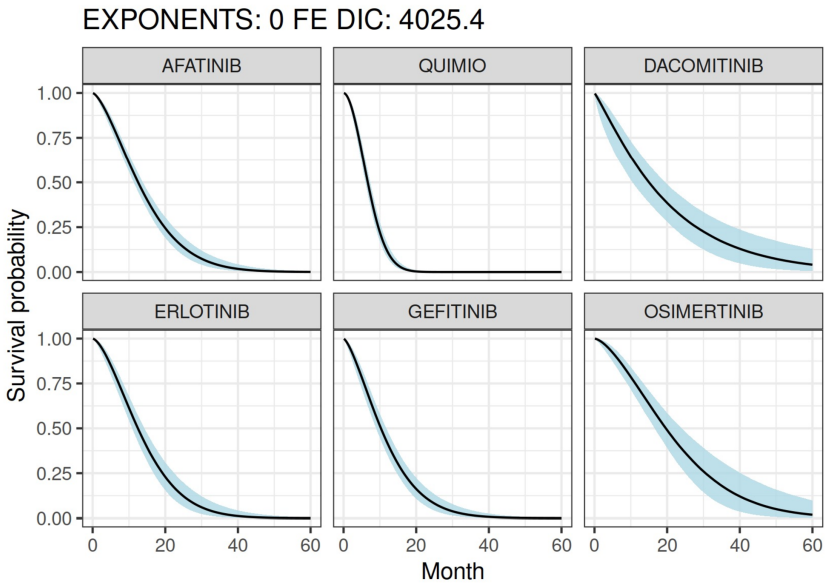
or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

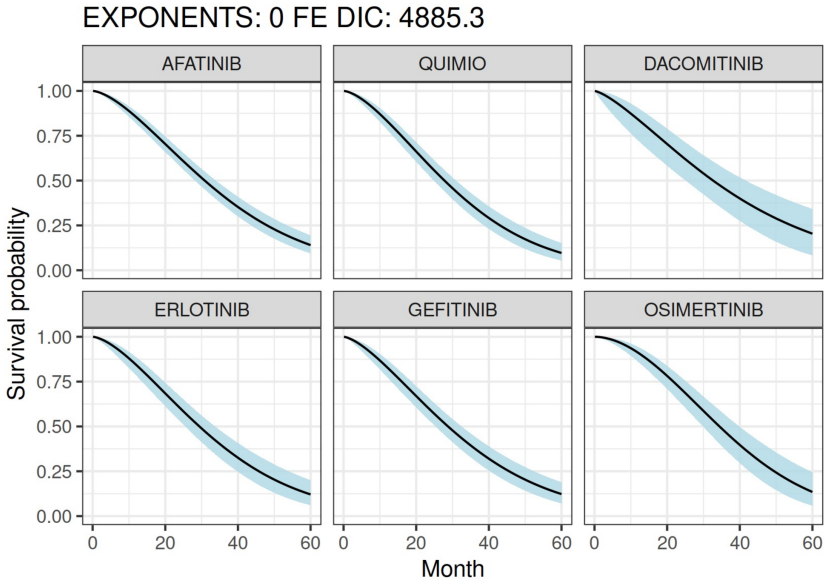
Ethical conduct of research

Our study used mathematical modeling and was not an active clinical trial; therefore, no approval was required from the Institutional Research Ethics Board.

Supplementary Material



Supplementary-1. *Figure 1.* Survival over time for each of the interventions as obtained with fixed-effects, first-degree and 0-exponent. Progression-free survival. FE: fixed effects; DIC: deviance information criterion.



Supplementary-2. *Figure 2.* Survival over time for each of the interventions as obtained with fixed-effects, first-degree and 0-exponent. Overall survival. FE: fixed effects; DIC: deviance information criterion.

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DISCUSIÓN

La elaboración de esta tesis doctoral se ha realizado en base a tres artículos científicos cuyo objetivo fue estimar la razón coste-efectividad de los fármacos disponibles en primera línea de tratamiento para CPNM EGFR+ estadio IIIb/IV en el contexto del Sistema Nacional de Salud. Por un lado, las publicaciones buscaban revisar la evidencia y evaluar la eficacia comparativa de las alternativas terapéuticas disponibles para el tratamiento CPNM en estadios avanzados. Por otro lado, se procedió a obtener los valores RCEI de los distintos fármacos empleados para el tratamiento de la patología con el objetivo de proporcionar información que ayudase a la selección del tratamiento más eficiente.

Los artículos han sido publicados en revistas del área de economía de la salud.

Esta tesis tiene dos partes adecuadamente diferenciadas, en primer lugar, la revisión sistemática y metaanálisis en red cuyo objetivo será la revisión de la evidencia disponible y la obtención de los datos de eficacia. En segundo lugar, la realización del estudio coste-efectividad a partir de los datos previamente obtenidos con el objetivo de comparar las alternativas estudiadas.

Revisión sistemática y meta-análisis en red

En las dos primeras publicaciones (Publicación 1 y Publicación 2) no fue necesaria la realización de revisión sistemática ni meta-análisis en red. Ello se debió a que tanto para osimertinib (Publicación 1) como para dacomitinib (Publicación 2), solo existían hasta la fecha un único ensayo clínico fase IIb/III controlado y aleatorizado para cada fármaco que comparase la eficacia y toxicidad de un único TKI con otro TKI como tratamiento de primera línea en pacientes con CPNM EGFR+ (Soria et al., 2018b; Wu et al., 2017b).

Para la realización de la Publicación 3, se empleó una revisión sistemática que recopilara los ensayos clínicos más importantes y relevantes para cada uno de los TKIs, analizándose su calidad y la posible existencia de sesgos (Holleman et al., 2019b). Para mejorar dicha revisión sistemática, se añadieron los datos de SG maduros procedentes del estudio FLAURA, los cuales habían sido publicados posteriormente a la revisión sistemática (Ramalingam et al., 2020). La selección de ensayos clínicos que comparasen los fármacos TKI de primera línea entre sí, habría sido la mejor opción. Sin

embargo, debido a la ausencia de ensayos clínicos directos (head-to-head) que comparasen estos cinco TKIs entre sí, se optó por realizar un meta-análisis en red asumiendo una heterogeneidad moderada en las características de los pacientes. Mediante el empleo de los meta-análisis en red se alcanza la comparación de más de dos alternativas de manera simultánea, lo que supone una ventaja para las evaluaciones económicas. Además, en el ámbito de la toma de decisiones médicas, los meta-análisis en red se emplean habitualmente en las evaluaciones de tecnologías sanitarias que preparan las agencias gubernamentales o las empresas farmacéuticas relacionadas con las solicitudes de aprobación de dichas tecnologías (Sutton et al., 2008). En este contexto, suponen una herramienta importante capaz de proporcionar pruebas fiables y coherentes sobre la eficacia y la seguridad de los fármacos evaluados. Finalmente, los resultados de supervivencia obtenidos pueden incorporarse a los modelos de coste-efectividad.

Uno de los principales aspectos novedosos de nuestro meta-análisis en red fue el empleo de la metodología de las fracciones polinómicas, a través de la cual obtuvimos los valores de supervivencia SLP y SG para cada fármaco. Así pues, mientras en el meta-análisis tradicional (enfoque Bayesiano) se asume que los valores de hazard ratio son constantes y por tanto no varían a lo largo del tiempo. Al utilizar el método de las fracciones polinómicas, obtenemos una estimación más precisa de los datos de supervivencia de los ensayos clínicos pivotales mediante la modelización de la hazard ratio en función del tiempo, permitiendo la obtención de valores de eficacia para los estudios de coste-utilidad de los fármacos TKI de forma más ajustada a los datos, reduciendo de esta manera los sesgos (Schulz et al., 2019).

Las variables principalmente evaluadas en el meta-análisis fueron: SLP, SG y la probabilidad de aparición de efectos adversos grado 3 y 4. Los resultados obtenidos demostraron que osimertinib era significativamente más efectivo en términos de SLP en comparación con el resto de los fármacos. Dacomitinib resultó ser el segundo TKI más efectivo en términos de SLP en comparación con gefitinib, erlotinib y afatinib. Osimertinib también demostró ser más eficaz en términos de SG en comparación con el resto de TKIs. Por lo que se refiere a probabilidad de los efectos adversos, éstos se presentaron con mayor frecuencia en los fármacos TKI de segunda generación (dacomitinib y afatinib) en comparación con los otros tratamientos.

Estudios coste-utilidad

A partir de la información de eficacia y seguridad obtenida en el meta-análisis en red, se desarrolló un estudio de coste-utilidad de los medicamentos autorizados para CPNM EGFR+ estadio avanzado en España (Publicación 3). Con anterioridad, se elaboraron dos estudios coste-utilidad con el objetivo de validar el modelo de Markov diseñado (Publicación 1 y 2). En la Publicación 1, se demostró que osimertinib era más efectivo en términos de AVAC (0,20) respecto a erlotinib-gefitinib. En la Publicación 2, dacomitinib fue ligeramente más efectivo en términos de AVAC (0,06) en comparación con gefitinib. Sin embargo, ninguno de los dos fármacos ofrecía una buena relación coste-eficacia, debido a que tanto los valores de RCEI de osimertinib (273.895€/AVAC) como de dacomitinib (111.048€/AVAC) fueron mayores que el valor umbral comúnmente aceptado en España de 24.000€/AVAC (Vallejo-Torres et al., 2018). En la Publicación 3, se demostró que osimertinib era más efectivo en términos de AVAC que gefitinib (0,20), seguido por dacomitinib (0,05), afatinib (0,04) y erlotinib (0,03). Ninguno de los fármacos estudiados en la Publicación 3 resultó ser coste-efectivo, ya que superaba el umbral aceptado en España de 24.000€/AVAC.

Los tres estudios se diferencian en varios aspectos. Por un lado, en la Publicación 1 y 2 sólo se tuvieron en cuenta los dos únicos ensayos clínicos pivotales publicados hasta la fecha de las dos alternativas estudiadas, osimertinib (Publicación 1) y dacomitinib (Publicación 2). En ambas publicaciones, los fármacos empleados como comparadores fueron fármacos de primera generación (erlotinib y gefitinib) al ser los que más comúnmente recomendaban las guías clínicas como *standard of care* para pacientes con CPNM avanzado y EGFR+ (Dearden et al., 2013; NICE, 2013; Wu, Saijo, et al., 2017). Sin embargo, en la Publicación 3 se compararon los diferentes fármacos TKI procedentes de las tres generaciones existentes hasta la fecha. La quimioterapia basada en platino fue excluida como terapia estándar de primera línea, así como comparador en nuestro estudio porque los TKIs han mostrado una mejor tolerancia y una mayor prolongación de la SLP, como se ha demostrado en diferentes estudios (Maemondo et al., 2010; Wu et al., 2014; Zhou et al., 2011).

Gracias a los modelos de Markov realizados en nuestras publicaciones, hemos conseguido representar el curso natural del CPNM avanzado EGFR+ mediante el cálculo de las probabilidades de transición en cada estado de salud a partir de los

valores de SLP y SG extraídos de los ensayos clínicos pivotales. Sin embargo, además de la "asunción markoviana", los modelos de Markov presentan otra limitación relacionada con la duración de los ciclos, en particular cuanto más largos sean. Ello es debido a que en modelos de Markov las transiciones entre estados de salud tienen lugar en determinados periodos de tiempo, mientras que, en la práctica clínica diaria, los pacientes pueden transitar de un estado de salud a otro en cualquier momento. Por tanto, para evitar la suposición de que los pacientes sólo se van a desplazar entre estados de salud al principio o al final de cada ciclo, se procede a aplicar la corrección de medio ciclo tanto a los costes como a los resultados en salud en el primer ciclo y en el ciclo final, sobre todo en modelos como el que hemos elaborado, puesto que el horizonte temporal comprende la duración total de la vida del paciente (Barendregt et al., 2009).

Los sistemas nacionales de salud actuales se enfrentan a un importante desafío: cuanto están dispuesto a invertir en fármacos y tecnologías sanitarias novedosas de manera que sea asumible por el propio sistema. Para ello, se emplea el umbral coste-efectividad, que en España está establecido en 24.000€/AVAC (Vallejo-Torres et al., 2018). Según un meta-análisis previamente publicado en el que se describen los "umbrales oficiales" de 17 países, el umbral de 24.000€/AVAC español resultaría ser mucho más bajo que los "umbrales oficiales" utilizados en otros países como Portugal (31.890€/AVAC), Suecia (50.173€/AVAC) o Países Bajos (80,000€/AVAC) (Cameron et al., 2018). Aunque el valor umbral seleccionado para España pueda considerarse excesivamente bajo para permitir que las alternativas estudiadas sean coste-efectivas, este valor es similar al utilizado en otros estudios realizados en el mismo entorno (Carcedo-Rodriguez et al., 2021; Navarro et al., 2020; Taxonera et al., 2022). A pesar de que la adopción de un valor umbral implica un cierto grado de incertidumbre, éste es compensado mediante la evaluación de las curvas de aceptabilidad llevadas a cabo en el análisis de sensibilidad probabilístico.

Dado que los sistemas sanitarios nacionales tratan de maximizar los beneficios en salud para los pacientes en función del presupuesto que tienen a su disposición, y que las evaluaciones económicas tratan de determinar qué opción terapéutica resulta más coste-efectiva, el hecho de disponer de métodos como los análisis de sensibilidad (AS) que reduzcan o eviten la incertidumbre mediante la simulación de escenarios en

función de las variables modificadas, nos va a permitir obtener resultados más fiables y válidos que ayudarán en la toma de decisiones.

Nuestros AS univariantes mostraron que fueron incluidas todas las variables que podían tener un impacto significativo en los resultados. Las variables que menos influyeron en el valor de RCEI fueron los valores de utilidad (estable y progresión), descuento y costes de últimos meses de vida (*end-of-life-care cost*).

Por otro lado, las variables que más influyeron en los AS univariante fueron los costes de adquisición de los fármacos y el valor de SG. El coste de adquisición de los fármacos es un parámetro clave en las evaluaciones económicas, por lo que su variación en el AS puede conducir a cambios significativos en el RCEI. El valor de coste de adquisición empleado procede de los precios notificados, el cual se obtiene del PVL más el IVA (4%) y los descuentos oficiales determinados por el Ministerio de Sanidad. Sin embargo, en la Publicación 2, el coste de dacomitinib no estaba disponible todavía en España, por lo que se seleccionó el valor procedente de la Guía de evaluación tecnológica de la NICE (NICE, 2019). Aunque este inconveniente se evalúa adecuadamente en el análisis de sensibilidad realizado en dicha publicación, el valor que finalmente se aprobó en España y que ya fue seleccionado en la Publicación 3 (2.424€) no varió en exceso con el obtenido de la NICE (3.023€).

Sin embargo, los precios finalmente facturados al SNS no son los mismos que los precios notificados. En al ámbito hospitalario, el valor del fármaco que finalmente acaba abonando el SNS al laboratorio es un valor inferior y no suele ser público. Este hecho se produce gracias a los acuerdos alcanzados a nivel de Comunidad Autónoma y/o del propio hospital para favorecer o rechazar determinadas alternativas terapéuticas. Por lo tanto, no es conveniente utilizar los costes reales de los medicamentos, por lo que la aplicación de descuentos mediante el AS univariante es una medida que resulta mucho más realista y cercana a la práctica clínica diaria. La reducción de los costes de adquisición aumenta sin duda la eficiencia de los tratamientos. En la Publicación 1, para que osimertinib fuera considerado una alternativa coste-efectiva, era necesario al menos un 60% de descuento en el precio notificado para obtener un valor de RCEI inferior al umbral de 24.000 €/AVAC aceptado en España. En la Publicación 2, dacomitinib requería una reducción del 25% en el valor del precio notificado. Finalmente, en la Publicación 3 se requería una

reducción del 40% en el coste de erlotinib, gefitinib y dacomitinib, así como del 70% para osimertinib. El elevado descuento en el caso de osimertinib es debido a que en la Publicación 3 fueron seleccionadas presentaciones genéricas para los fármacos erlotinib y gefitinib. En este sentido, la incorporación de presentaciones genéricas al arsenal terapéutico del paciente supone una reducción de los costes de adquisición, conservando la misma eficacia que el fármaco original y contribuyendo a la sostenibilidad del sistema sanitario.

A pesar de que el valor umbral de coste-efectividad de 24.000€/AVAC que hemos citado anteriormente puede considerarse excesivamente riguroso, en los últimos años un grupo de expertos en evaluación económica en España comienza a considerar valores comprendidos entre 24.000-60.000€/AVAC como razonables según cumplan diversos criterios (gravedad de la enfermedad, existencia de alternativas, etc.) (Sacristán et al., 2020). En otros estudios, el valor de un AVAC en oncología se valoró a partir de encuestas (disposición a pagar). En una encuesta realizada a oncólogos españoles, un tercio de los encuestados consideraba aceptable un coste por AVAC de entre 30.000-60.000€, mientras que otro tercio indicaba un valor de entre 60.000-100.000€; el tercio restante consideró unos valores por encima de los 100.000€/AVAC (Camps-Herrero et al., 2014). El estudio *Oncovalor*, el primero que compara la disposición a pagar en cuatro colectivos tales como decisores sanitarios, población general, pacientes y oncólogos, estimó unos valores 57.471€, 66.074€, 73.520€ y 106.000€ por AVAC, respectivamente (Dilla et al., 2016). En todos los casos, los valores estuvieron por encima de los 24.000€/AVAC, asumidos en nuestro estudio.

La eficacia potencial de osimertinib, el primer EGFR-TKI de tercera generación aprobado, para mejorar la supervivencia fue clave para los resultados clínicos y económicos de nuestro estudio. Hasta el año 2018 en Europa, las directrices de la ESMO recomendaban indistintamente el tratamiento en primera línea con cualquiera de las tres generaciones de TKIs (erlotinib, gefitinib, afatinib, dacomitinib u osimertinib), sin especificar preferencia por ninguno de ellos (Planchard et al., 2018). Sin embargo, en la versión actualizada publicada el 15 de Septiembre de 2020, el Cómite de Directrices de la ESMO ya recomienda osimertinib como la opción preferida para los pacientes con CPNM avanzado EGFR+ previo a mutación T790M, en lugar de los EGFR-TKI de primera y segunda generación (ESMO, 2020). Tanto en la Publicación 1

como en la Publicación 3, osimertinib fue el fármaco que mejores resultados en supervivencia y calidad de vida proporcionaba respecto a las anteriores generaciones de TKIs. Sin embargo, el elevado coste de adquisición de este fármaco provocaba que el resultado obtenido fuera no coste-efectivo y hubiese que aplicar altos descuentos en los PVLs notificados.

En nuestro modelo de Markov elaborado para cada una de las publicaciones, los fármacos TKIs únicamente se empleaban en el estadio inicial, es decir, enfermedad estable. Debido a ello, los costes más elevados se producían en este estadio, ya que en el siguiente estadio ("enfermedad en progresión") se aplicaban costes de segunda línea con fármacos tales como quimioterapia a base de platino, PD-1/PD-L1, anti-VEGF y otras terapias dirigidas, cuyo coste de adquisición resultaba muy inferior al de los TKIs.

Respecto a la utilidad, se trata de un parámetro que refleja la preferencia de un paciente por el estado de salud que presenta, y adopta un valor entre cero y 1, siendo cero el peor estado de salud posible, y 1 el mejor. Los diferentes métodos de cálculo de la utilidad asumen las preferencias de los pacientes y, por esta razón, tienen un componente subjetivo, por lo que los valores obtenidos por cada uno de los métodos existentes no son idénticos. En la Publicación 1, los valores de utilidad considerados en el modelo se extrajeron de un estudio validado y publicado en la población del Reino Unido (Nafees et al., 2017), cuyo valor de utilidad seleccionado para progresión de la enfermedad (0,17) podrían ser inferiores a los valores de utilidad obtenidos en 2008 por el mismo autor (0,473) (Nafees et al., 2008), los cuales fueron seleccionados para las Publicaciones 2 y 3. Esta diferencia se debe al cambio de metodología empleado para calcular estos valores de utilidad. En el estudio de Nafees *et al.* de 2008 (Nafees et al., 2008) los autores emplearon el método *standard gamble*, mientras que en el estudio de 2017 los autores emplearon el método de *time-trade-off* (Nafees et al., 2017). Por ello, se puede concluir que estos dos métodos no son iguales estimando los valores de utilidad, produciendo el método de *time-trade-off* valores de utilidad inferiores (Stiggelbout et al., 1994). Para determinar la influencia de los valores de utilidad en los resultados definitivos del ICER, se realizaron variaciones de ±20% en los análisis de sensibilidad univariante de cada una de las publicaciones, comprobándose que no influían significativamente como para alcanzar el umbral de eficiencia. Destacar

a sí mismo, que los valores de utilidad empleados fueron extraídos de estudios verificados y publicados en la población del Reino Unido pero no de España, debido a que, hasta la fecha, estos datos no están disponibles (Nafees et al., 2008; Nafees et al., 2017).

El consumo de medicamentos oncológicos va aumentando año a año en España. En 2021, el precio medio a PVL de los medicamentos oncológicos incluidos en la prestación farmacéutica española fue de 1.222,90€, lo que supone unas 15 veces más que el precio medio de los medicamentos financiados (177,86€) (Ministerio de Sanidad, 2022). En 2021 el gasto en medicamentos oncológicos a través de hospitales y oficinas de farmacia fue de 3.110 millones de euros, lo que supone un 16,91% sobre el total de medicamentos (Ministerio de Sanidad, 2022). Por lo que se refiere al consumo a nivel hospitalario de medicamentos oncológicos, éste ha supuesto un valor de 2.898 millones de euros, representando un 29,35% sobre el total del consumo hospitalario y un crecimiento respecto a 2020 del 18,3%. Si se compara dicho consumo con respecto a 2016, el incremento asciende a un 105,9%. Por ello, en la actualidad, el establecimiento de diferentes algoritmos de compra innovadores, como el Pago por Resultados o Pay for Performance (P4P), se aplica cada vez más en los sistemas sanitarios de los países desarrollados, entre ellos España. Estos algoritmos han demostrado promover mejoras en la calidad asistencial y en la reducción de los costes de adquisición de diferentes terapias innovadoras (Epstein, 2012; M. Sutton et al., 2012). Este sistema de pago por resultados se utiliza ya en el SNS y es la forma de financiación actualmente en más de diez medicamentos. Un ejemplo es Alofisel (darvadstrocel), indicado para el tratamiento de las fístulas perianales complejas, así como el primer anticuerpo conjugado en linfoma B que llegó a España, concretamente, el medicamento Polivy (polatuzumab vedotina).

Por lo tanto, los resultados obtenidos en las evaluaciones económicas pueden ser útiles para los diferentes estamentos integrantes del SNS español (Dirección General de Cartera Básica del SNS y Farmacia, Direcciones Generales de Farmacia de las CC. AA., comité de evaluación de nuevos medicamentos en atención primaria y comités de farmacia y terapéutica en los hospitales) y los responsables políticos en las negociaciones de los precios de fármacos o tecnologías sanitarias con la industria farmacéutica, así como por la propia industria para alcanzar acuerdos que permitan

promover la sostenibilidad del SNS mediante una mejor asignación de los recursos existentes.

CONCLUSIONES

- Los resultados obtenidos tras la realización del meta-análisis en red demostraron que, por lo que respecta a la eficacia, osimertinib puede considerarse la mejor alternativa terapéutica para el tratamiento de CPNM estadio IIIb/IV EGFR+ en primera línea. En cuanto a la seguridad, afatinib y dacomitinib resultaron ser los fármacos con un perfil de reacciones adversas grado 3/4 más frecuente.
- Las fuentes de información utilizadas para obtener los datos de costes, consumo de recursos y calidad de vida necesarios para el estudio coste-utilidad se obtuvieron de la literatura, Ministerio de Sanidad y departamento de contabilidad de Osakidetza.
- Para los análisis de coste-utilidad, se desarrolló un modelo de Markov con tres estados de salud que describen la progresión de CPNM EGFR+ estadio IIIb/IV en pacientes sin tratamiento previo con fármacos TKIs, con un horizonte temporal de 15 años.
- El modelo de Markov realizado permitió convertir las variables intermedias de eficacia, como son supervivencia libre de progresión (SLP) y supervivencia global (SG), en resultados en salud (AVAC), medida que combina eficacia y calidad de vida.
- Se calculó el valor RCEI para cada una de las comparaciones. En la Publicación 1, se estimó que osimertinib resultaba no coste-efectivo en comparación con erlotinib-gefitinib. En la Publicación 2, se determinó que dacomitinib no era coste-efectivo en comparación con gefitinib. Por último, en la publicación 3, ninguno de los fármacos TKIs estudiados resultó ser coste-efectivo en comparación con gefitinib. El valor umbral de eficiencia empleado en todas las publicaciones fue de 24.000 €/AVAC.
- Las variables identificadas que mayor impacto ejercieron en el RCEI fueron el coste de adquisición de los fármacos, los valores de utilidad de los estados de salud definidos en el modelo y los valores de descuento temporal.
- La curva de aceptabilidad obtenida tras la realización del AS probabilístico demostró que para el umbral de 24.000 €/QALY definido, erlotinib resultaba el

fármaco más coste-efectivo, seguido de afatinib, dacomitinib y osimertinib. Sin embargo, para valores umbral superiores a 125.000 €/QALY, osimertinib resultaba ser la estrategia más coste-efectiva.

- La negociación de descuentos en los costes de adquisición de los fármacos TKIs, resultaría una alternativa válida para aproximarnos al valor umbral de referencia en España de 24.000 €/QALY.

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ANEXO I

Research Article

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Journal of **Comparative Effectiveness Research**

Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost–effectiveness analysis

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Aim: osimertinib improves progression-free survival in first-line epidermal growth factor receptor mutation–positive (EGFR) in non-small-cell lung cancer. **Materials & methods:** a Markov cohort model including costs, utilities and disutilities, was conducted to estimate quality-adjusted life-year (QALY) and incremental cost–effectiveness ratio when treating with osimertinib vs standard first-line tyrosine kinase inhibitors (TKIs). **Results:** Osimertinib presented higher QALYs (0.61) compared with standard EGFR-TKIs (0.42). Osimertinib costs were €83,258.99, in comparison with €29,209.45 for the standard EGFR-TKIs. An incremental cost–effectiveness ratio of €273,895.36/QALY was obtained for osimertinib. **Conclusion:** Osimertinib was more effective in terms of QALYs gained than comparators (erlotinib–gefitinib). However, to obtain a cost–effectiveness alternative, a discount greater than 60% in osimertinib acquisition cost is required.

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Keywords: cost–effectiveness • EGFR-TKI • Markov • non-small-cell lung cancer • osimertinib

Epidermal growth factor receptor (EGFR) mutations are the most usual oncogenic mutation in patients with non-small-cell lung cancer (NSCLC) with adenocarcinoma. Detection of EGFR mutations are found in about 10–15% of Western patients and 30–35% of Asian patients [1]. In Spain, the mutation detection rate in advanced-NSCLC patients was found to be 11.6% in the REASON study (82.6% presenting in-frame deletions in exon 19 and 17.4% presenting L858R mutation in exon 21) [2]. The first-generation EGFR-tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are highly active against cancers with two EGFR common sensitizing mutations (in-frame deletions in exon 19 or L858R mutation in exon 21) [1].

Nevertheless, more than half of the patients with NSCLC with EGFR-activating mutations develop tumor resistance despite the initial beneficial response to first-generation TKIs (erlotinib and gefitinib), generally 9 to 14 months after treatment initiation target [3–8]. Disease progression while on therapy with first-generation EGFR-TKIs is associated with a T790M acquired mutation in the EGFR gene. Consequently, T790M resistance mutation reduces binding of first and second-generation EGFR-TKIs to the target receptor and forces a change of treatment [9–11]. Osimertinib is an oral, third generation, irreversible EGFR-TKI that is currently employed in NSCLC EGFR T790M resistance mutations, with successful results [11–14]. Additionally, FLAURA study has demonstrated the clinical benefit of osimertinib in EGFR-TKI-sensitizing mutations [15]. In FLAURA study, the median progression-free survival (PFS) in patients with untreated EGFR mutated NSCLC was demonstrated to

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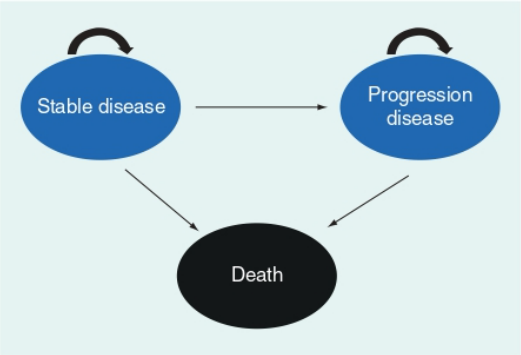

Figure 1. Structure of Markov model.
Markov model health states.

be significantly longer with osimertinib than with standard first-line EGFR-TKIs (18.9 vs 10.2 months) with a similar safety profile and lower rates of serious adverse events [15].

To date, only two prior studies have been published evaluating the cost–effectiveness of osimertinib [16,17]. A decision analytic model analysis over a 10-year time horizon has been published evaluating the cost–effectiveness of osimertinib in first-line EGFR-positive NSCLC [17]. Another cost–effectiveness analysis containing a probabilistic Markov model has been published recently, comparing osimertinib versus the first-generation employed EGFR-TKI in Canada [16]. Therefore, a complete Markov pharmacoeconomic model analysis in a European country with a public healthcare system including a deterministic and a probabilistic model of osimertinib in first-line EGFR positive NSCLC adenocarcinoma could provide extremely valuable information for medical decision makers to facilitate the optimization of healthcare resources in Europe. The aim of this study is to evaluate the incremental cost–effectiveness ratio (ICER) of osimertinib versus standard EGFR-TKIs (erlotinib and gefitinib), in order to determine which is the most efficient drug in first line.

Materials & methods

Cost–effectiveness analysis (CEA): Markov model

Design & perspective analysis

A Markov model was adopted to estimate the costs, the quality-adjusted life-years (QALYs) and ICER of two different treatment strategies (osimertinib vs standard EGFR-TKIs) in two hypothetical cohorts of patients with EGFR-positive sensitizing mutations advanced NSCLC. The model was developed from the Spanish National Health System perspective. The threshold for determining whether a strategy is cost-effective was €24,000/QALY [18]. All the costs were estimated in euros (€) 2018, and a discount rate of 3% was used for costs and effects throughout the model. The Markov model was developed in Microsoft Excel 2011 (Microsoft Corp., WA, USA), using a 15-year time horizon. The results were presented in terms of costs (€), QALYs gained and ICER.

Markov model structure

The model included three mutually exclusive health states: stable disease (SD), progressive disease (PD) and death. Each health state was associated with costs, health effects and the probability of moving to any other state. The structure and transitions allowed in the model are shown in Figure 1. Initially, all patients were on SD and received one of the two treatment strategies.. On each 28-day simulation cycle, the hypothetical cohort of patients could remain on SD, experience PD or death. Patients in SD continued treatment with the initial TKIs until progression occurred. When progression, patients were changed to a second-line regimen. After PD occurred, patients could remain in this state or die. PD was simulated until all patients died. Death of patients from any cause were included in this state.

Treatment alternatives

Each cohort was treated with osimertinib (at a dose of 80 mg once daily) or a standard oral EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily), according to FLAURA clinical trial [15].

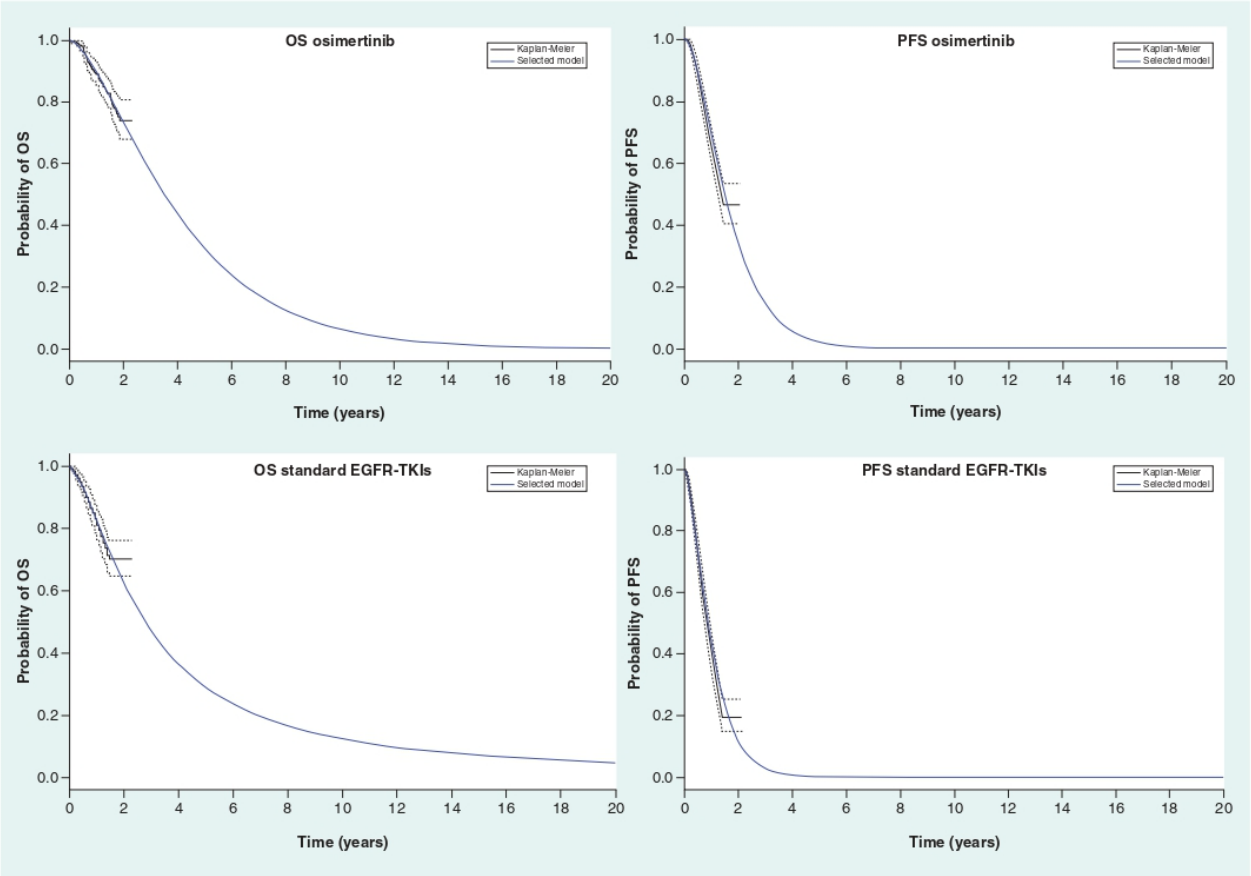

Figure 2. Overall survival and progression-free survival Kaplan–Meier plot and selected fitted curves.
EGFR: Epidermal growth factor receptor; OS: overall survival; PFS: Progression-free survival; TKI: tyrosine-kinase inhibitor.

Transitional probability data

Transition rates between different states were estimated based on progression of disease and survival values estimated from FLAURA clinical trial [15]. The method of Guyot *et al.* was employed to recreate the patient level data [19]. Due to the short follow-up of FLAURA trial, Overall Survival (OS) and PFS were not fully observed, therefore, results were extrapolated by using survival functions. In order to determine the most appropriate parametric survival curve, a goodness-of-fit analysis was conducted based on the best fit model among gamma, log-logistic, Weibull, lognormal, Gompertz, exponential, Royston-Parmar, generalized F and generalized gamma parametric distributions. These analyses were assessed using parametric plots, long-term projections and statistical tests (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) (Supplementary Figure1 and 2 & Supplementary Table 1). We used visual inspection of the Kaplan-Meier curves, goodness-of-fit statistics and clinical plausibility to determine the optimal parametric distribution with the best fit. The OS data is still immature (only complete in 25%). For this reason, a single parametric model (gamma) has been selected for all the treatment arms.

Transition probabilities from SD and PD to death were obtained based on OS and PFS as shown in Figure 2. Finally, the difference between the OS and PFS curves was employed to calculate the probability of the patient remaining on PD state.

Costs estimation

Only direct medical costs were calculated (drugs, disease management, adverse events (AE) and second-line treatment). The cost of erlotinib, gefitinib and osimertinib were calculated according to the officially notified listed prices ([drug price - 7.5% official discount in Spain] × Value added tax [VAT]) (Table 1) [20,21]. Disease

Table 1. Model input parameters.

Management of NSCLC	Cost per 28-day cycle and patient	Ref.
– Erlotinib/Gefitinib	€1,836,48	[20,21]
– Osimertinib	€5447.36	
Second-line cost osimertinib	€9294	[20,21]
– Scheme (29% of total patients)		
– EGFR-TKI scheme erlotinib/gefitinib (21%)		
– Platinum-based chemotherapy schemes (36%)		
– Non platinum-based chemotherapy schemes (35%)		
– Others therapies (8%)		
Second-line cost standard EGFR-TKIs	€15,310	[20,21]
– Scheme (47% of total patients)		
– EGFR-TKI scheme treated with osimertinib (46%)		
– Platinum-based chemotherapy schemes (13%)		
– Non platinum-based chemotherapy schemes (12%)		
– Others therapies (4%)		
Grade III–IV adverse events	Median cost/cycle	[23]
– Diarrhea	€924.11	
– Decreased appetite	€1375.31	
– Dry skin	€26.2	
– Paronychia	€341.41	
– Stomatitis grade 3	€2,332.14	
– Stomatitis grade 4	€5,325.7	
– Pruritus	€341.41	
– Fatigue	€106.78	
– Anemia	€992.22	
– Vomiting	€681.51	
– Rash	€341.41	
– AAT elevation grade 3	€559.91	
– AAT elevation grade 4	€1799.09	
– AAT elevation	€559.91	
Utilities scenario	Value	[24]
– On treatment with no side effects	0.84	
– Diarrhea	0.32	
– Vomiting	0.25	
– Rash	0.15	
– Stomatitis	0.25	
– Dry skin	0.15	
– Decreased appetite	0.41	
– Paronychia	0.15	
– Anemia	0.41	
– Fatigue	0.41	
– Disease progression	0.17	

management costs were estimated according to an expert panel's advice. Disease management cost per patient and cycle was calculated multiplying the cost of healthcare resources employed by the unit cost of each resource consumed over a 15-year time horizon.

The second-line therapy regimens were obtained from Supplementary Table 3 of FLAURA study [15] as is shown in Table 1. In osimertinib second-line arm, 21% of the patients were re-challenged with standard EGFR-TKI (erlotinib-gefitinib), 36% with platinum-based chemotherapy, 35% with non-platinum-based chemotherapy and 8% with other therapies (PD-1/PD-L1, anti-VEGF and others targeted therapies). In standard EGFR-TKIs second-line arm, 46% of the patients were treated with another EGFR-TKI including osimertinib, 13% with

platinum-based chemotherapy, 12% with non-platinum-based chemotherapy and 4% with others therapies (PD-1/PD-L1, anti-VEGF and others targeted therapies). To calculate second-line costs, patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m^2. As PFS second-line treatment curves were not available in FLAURA clinical trial, we employed AURA3 clinical trial PFS2 curves to calculate second-line treatment duration [14]. We estimated the Area Under the Curve (AUC) in the PFS AURA3 trial curve comparing osimertinib versus platinum-pemetrexed in NSCLC patients who had disease progression after first-line EGFR-TKI therapy to obtain second-line treatment duration. We employed Guyot *et al.* method to simulate the best survival curve [19]. In order to obtain the best adjusting method, this survival curve was fitted with a Weibull distribution.

Unit costs were obtained from an official database published in Spain [22]. Side effects management costs in Spain (Table 1) were obtained from an internal database [23]. Adverse effect (grade III–IV events) frequencies associated with osimertinib and gefitinib-erlotinib treatments were obtained from FLAURA study [15]. Model costs are presented in Euros (€) 2018 (Table 1).

Utilities estimation

Health state utility inputs and disutility values for the base case were obtained from recent data published from UK [24]. Different utilities values were applied considering the different health states (SD and PD) and are summarized in Table 1. A health utility of zero was applied to the health state of death.

Disutilities estimation

Only disutility values associated with grade III–IV were addressed. To calculate the disutility values associated with grade III–IV in SD, disutilities parameters of each AE extracted from Nafees *et al.* was multiplied by the relative frequency of the corresponding event obtained from FLAURA trial to calculate a weighted average disutility value for each event profile. Disutility values calculated for each grade III–IV AE were subtracted from utility values while patients remained in SD.

Univariate sensitivity analysis

A deterministic univariate sensitivity analysis (DUSA) was performed to address the uncertainty of the ICER estimated value. In DUSA a single parameter in the model (drug costs, utilities or discounts) was modified to examine the effect on the ICER result. Drug costs were modified in three different ranges (±20%, ±40% and ±60%). Utilities values were varied in a range of ±15%. The 2008 utility value (0.473) in progression disease employed in previous article of quality of life [25], was used in order to determine if the ICER value is modificated. Discount values in the DUSA model were varied in a percentage of 0 and 6%.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the uncertainty of the estimated results in the DUSA. The analysis was performed using 10,000 Monte Carlo simulations. Different parameters (side effects managements costs, disease management cost, second-line treatment costs, acquisition drug costs, utilities and transition probabilities) of the model were varied to determine the robustness of the model. In addition, the PSA was employed to obtain acceptability curves, showing the probability of each alternative being cost-effective across a range of possible values of willingness to pay for an additional QALY [26].

According to the characteristics of each variable, different types of probability distributions were employed to variate the model parameters [27]. Gamma distributions were applied for costs, beta for utilities and Dirichlet distributions for transition probabilities.

Results

Under base-case assumptions, the total QALYs were 0.61 and 0.42, for osimertinib and standard EGFR-TKIs, respectively. Osimertinib provided a 0.20 increase in QALYs compared with the standard EGFR-TKIs. For osimertinib arm, the mean costs of the intervention were €83,258.99 discounted over the 15-years horizon, in comparison with the €29,209.45 for the standard EGFR-TKIs. These costs and QALY values yielded an incremental ICER of €273,895.36/QALY for osimertinib compared with standard EGFR-TKIs. The results of the baseline scenario analysis are shown in Table 2. Additionally, the net gain in life-years (LYG) in osimertinib group compared with

Table 2. Cost–effectiveness results.

Variable	Strategy	
	Standard EGFR-TKIs	Osimertinib
Total Cost/pt	€29,209.45	€83,258.99
– Treatment cost/pt	€19,214.00	€74,651.43
– Disease management/pt	€2307.05	€2638.15
– Adverse events costs/pt	€35.30	€55.01
– 2L cost /pt	€7653.10	€5914.40
QALY gained /pt	0.42	0.61
ICER (€/QALY) Osimertinib vs Erlotinib–Gefitinib	€273,895.36/QALY	

2L: Second-line pt: patient; EGFR: Epidermal growth factor receptor; ICER: Incremental cost–effectiveness ratio; TKI: Tyrosine-kinase inhibitor; QALY: Quality-adjusted life year.

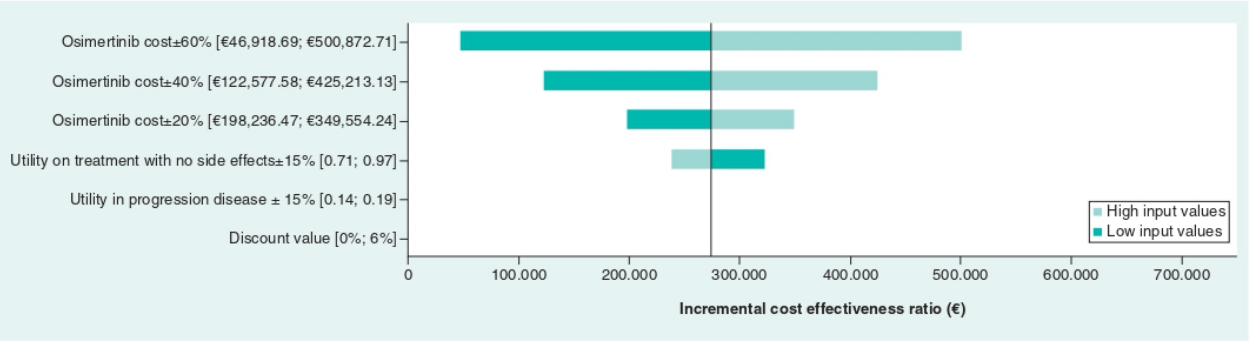

Figure 3. Tornado diagram (deterministic sensitivity analysis).

standard EGFR-TKI group was 0.25 (1.05 life-years vs 0.80 life-years for osimertinib and standard EGFR-TKIs, respectively).

The DUSA showed significant changes in the ICER after modifying osimertinib costs, utilities and discount values as is shown in Tornado diagram (Figure 3) and Supplementary Table 2. Hence, the results of the DUSA showed that discounts greater than 60% in drug acquisition cost produced an ICER value below the threshold of 24,000€ per QALY gained fixed in Spain.

Furthermore, the PSA results were consistent with the base-case analyses. According to the cost–effectiveness plane shown in Figure 4, standard EGFR-TKIs were more effective and less costly in 62.28% of the iterations in the simulation. Only in 37.72% of the iterations, osimertinib was more effective and less costly than standard EGFR-TKIs.

Finally, the likelihood of osimertinib being considered cost-effective was determined for a range of acceptability ratios, as shown in the acceptability curve. At the base-case scenario, there is a 42.94% probability of osimertinib being cost-effective at a threshold of €24.000/QALY (Figure 5).

Discussion

Recently, osimertinib has demonstrated a clinically meaningful benefit in patients with EGFR T790M mutation who have developed acquired resistance to TKIs [12–14]. Additionally, FLAURA study has demonstrated the clinical benefit of osimertinib in EGFR-TKI-sensitizing mutations. Therefore, we developed a complete cost–effectiveness analysis to compare osimertinib versus standard first-line EGFR-TKIs (erlotinib–gefitinib) in patients with previously untreated, EGFR mutation–positive advanced NSCLC, based on FLAURA study [15]. We demonstrated that osimertinib is considered more effective in comparison with standard TKIs in sensitizing EGFR mutations, in terms of QALYs gained (0.20). However, our study showed that osimertinib was not cost-effective compared with EGFR-TKIs because the ICER (€273,895.36/QALY) was higher than the commonly accepted threshold in Spain

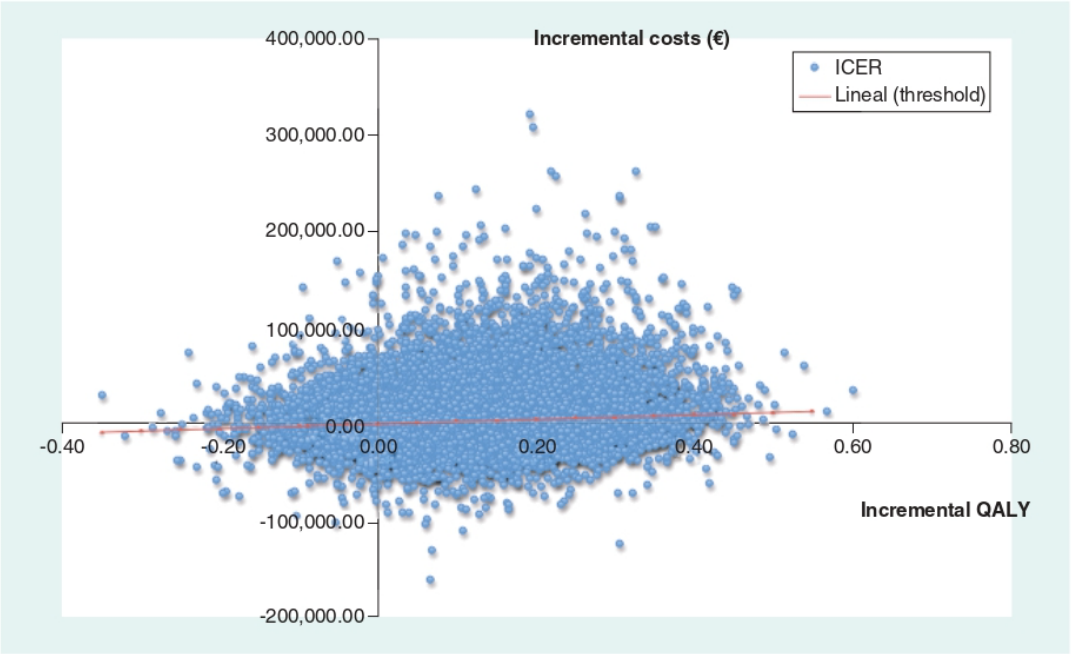

Figure 4. Scatter plot of Monte Carlo probabilistic sensitivity analysis for osimertinib versus first-line epidermal growth factor receptor-tyrosine kinase inhibitors (erlotinib–gefitinib).
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

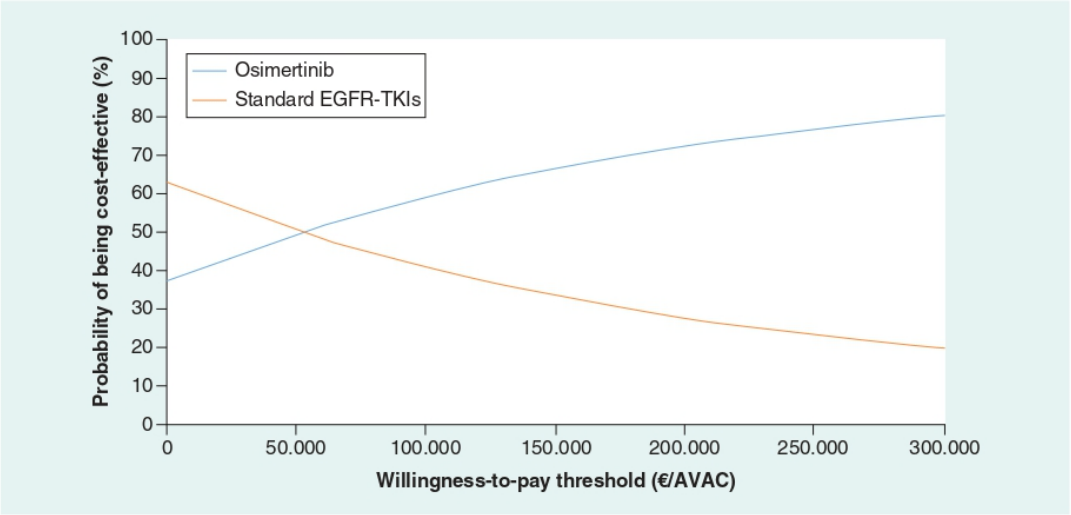

Figure 5. Cost–effectiveness acceptability curve osimertinib versus first-line epidermal growth factor receptor-tyrosine kinase inhibitors (erlotinib–gefitinib).
Graph plot willingness to pay (WTP) scenario (x-axis) versus the likelihood in percentage that the treatment would be considered cost-effective (y-axis).
ICER: Incremental cost–effectiveness ratio.

of €24,000/ QALY [18]. In addition, in our study, we established that discounts greater than 60% are crucial in the osimertinib acquisition costs to be considered a cost-effective alternative.

To date, only four different studies have compared the cost–effectiveness of osimertinib [16,17,28,29]. However, two of these studies are not comparable because they only compare osimertinib versus pemetrexed-platinum based chemotherapy in patients with demonstrated T790M mutation [28,29]. In the study published by Wu *et al.* [29] they estimated that osimertinib was not cost–effectiveness in the USA due to the high acquisition cost of osimertinib drug as we demonstrated. In addition, we can conclude that ICER value obtained (scenario 3 patients without metastasis) in USA by Wu *et al.* [29] is really approximate to ours with $222,030/QALY. In the recently published article by Aguiar *et al.* [17], the authors performed an innovative decision analytic-model over a 10-year time horizon to evaluate the cost–effectiveness of osimertinib from data collected from FLAURA study. The authors compared two different strategies: the first one comparing osimertinib in second-line in patients who harbor T790 mutation versus chemotherapy or immunotherapy in patients without this mutation; the second strategy they addressed in the aim of the study was similar to our purpose and consisted of the comparison of osimertinib in first-line continued by a standard second-line therapy at disease progression. The results obtained in the USA by Aguiar *et al.* are really in concordance with ours in Spain, obtaining an approximate ICER of $230.000/QALY, a QALY value for osimertinib of 2.12 and a 0.594 incremental number of QALY gained compared with the standard EGFR-TKIs (gefitinib–erlotinib–afatinib) in first-line. However, in the study recently published by Aguiar *et al.*, the authors only performed a DUSA over a 10-year time horizon. Generally, to reinforce the results obtained in the DUSA a PSA is frequently performed [30]. Therefore, in our study, the deterministic results obtained are complemented with a PSA to demonstrate the robustness of the ICER values obtained and to indicate accurately the osimertinib cost–effectiveness thresholds. Additionally, to improve the quality of the analysis, we changed the lifetime horizon in our study from the classical 10-year to a 15-year lifetime horizon analysis. Nonetheless, Aguiar *et al.* conclude that high cost of the drug makes osimertinib a not so cost-effective alternative, unlike the superior values of PFS or OS obtained.

To our knowledge, this is the first complete economic study in Europe to provide a direct comparison of osimertinib against the first-line standard of care (gefitinib–erlotinib) for the patients with EGFR mutated NSCLC. To reinforce our obtained results, another recently published Markov analysis by Ezeize *et al.* in Canada showed a similar non cost–effectiveness analysis with an incremental gain of 0.79 QALYs and an incremental ICER of 223.133$/QALY [16]. Therefore, our findings show that the choice of treatment in this study should be essentially determined by the drug acquisition cost. Considering the efficacy and the quality of life, osimertinib should be the treatment of choice. Osimertinib is expected to provide an incremental 0.20 QALYs gained in the study. However the acquisition cost was higher compared with the cost of standard EGFR-TKI, resulting in a difference of €55,437.43 per patient.

In addition, the acceptability curve of WTP obtained in our study shows a range of threshold values, as an aid for context-dependent decision making. We demonstrated that with standard WTP thresholds, osimertinib may be considered not cost-effective in Spain due to the high price of drug acquisition. Currently, the defined cost–effectiveness threshold in the Spanish setting is €24,000/QALY [18].

Nowadays, the establishment of different innovative purchasing algorithms such as pay-for-performance (P4P) are increasingly implemented in developed healthcare systems. These algorithms have demonstrated promoting improvements in healthcare quality and to reduce the acquisition costs of different innovative therapies [31,32]. To facilitate physician prescribing decision, different institutions such as European Society for Medical Oncology (ESMO) [33] or American Society of Clinical Oncology (ASCO) [34] have recently created pharmacoeconomic tools. Therefore, these results may be useful for health administrators and policy-makers in negotiations of prices with drug manufacturers, as also by the drug manufacturers themselves to consider reducing prices of this drug to encourage adoption of new generation of TKIs regimens.

There are some limitations in our study. First, common to all Markov models, there is the implicit uncertainty from combination of data from numerous sources and assumptions. Second, the result of the model could be impacted by the assumptions around curve extrapolation. Nonetheless, the algorithm used for extrapolation, Guyot *et al.* [19], provides excellent accuracy for the calculation of survival probabilities.

Thirdly, we only contemplate the payers' perspective of Spanish National Health System and not indirect costs (absenteeism, changes of individual productivity, unpaid assistance from a family member). In addition, the utility values considered in the model were extracted from a validated study published in the population of UK [24] but not from our own country, Spain, since these data were not available. The utility values of 0.17 assigned to disease progression could be lower than the utility values obtained in 2008 by Nafees *et al.* (0.473) [25]. This difference is due to the change of methodology employed to calculate these utilities values. In Nafees *et al.* study 2008 [25] authors

employed a standard gamble method, while in 2017 study a time-trade-off method was employed by the authors [24]. Different authors as Stiggelbout *et al.* [35] conclude that these two methods are not equal estimating utility values, therefore producing the time-trade-off method lower utilities values. In order to determine the influence of utility values in definitive ICER results in our model, we included the 2008 utility value employed in Nafees *et al.* study (0.473) [25] in the DUSA, to determine if the ICER value is modificated by different utility values and we concluded that there was no difference (€273,895.36 vs. €264,691.25) Fourth, individual data from erlotinib and gefitinib patients cannot be extracted from supplementary data of FLAURA study, therefore a combined arm is evaluated in this study. Fifth, when disease progression while on therapy with first-generation EGFR-TKI, a second generation TKI, afatinib, is normally prescribed [36]. However, we did not include an afatinib arm in the economic analysis, because in the FLAURA study a direct comparison between afatinib and osimertinib is not evaluated.

Conclusion

From Spanish National Health System perspective, treatment with osimertinib was more effective in terms of QALYs gained than treatment with standard EGFR–TKIs erlotinib–gefitinib. However, osimertinib has been proved not to be a cost-effective alternative in first-line therapy for advanced EGFR-mutated NSCLC patients, compared with erlotinib-gefitinib due to the high acquisition costs of the drug. Additionally, our study could also be applied to other TKIs treatments with similar efficacy rates that become available in the future.

Summary points

- In FLAURA study, the median progression-free survival in patients with untreated EGFR mutated non-small-cell lung cancer was demonstrated to be significantly longer with osimertinib than with standard first-line epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR–TKIs) (18.9 vs 10.2 months).
- Osimertinib presented higher quality-adjusted life years (QALYs) (0.61) compared with standard EGFR–TKIs (0.42).
- Osimertinib total costs of the intervention were €83,258.99, in comparison with the €29,209.45 for the standard EGFR–TKIs.
- An incremental cost–effectiveness ratio of €273,895.36/QALY was obtained for osimertinib compared with standard EGFR–TKIs.
- From Spanish National Health System perspective, osimertinib has been proved not to be a cost-effective alternative in first-line therapy for advanced EGFR-mutated NSCLC patients, compared with erlotinib-gefitinib due to the high acquisition costs of the drug.
- A discount greater of 60% in osimertinib acquisition cost could produce an incremental cost–effectiveness ratio value below the established threshold of €24,000 per QALY gained in Spain to result a cost–effectiveness alternative.

Author contributions

All the authors interpreted data, read and approved the final manuscript.

Financial & competing interests disclosure

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Dacomitinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost–effectiveness analysis

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Aim: To assess the cost–effectiveness of first-line treatment with dacomitinib compared with gefitinib in patients newly diagnosed with advanced NSCLC *EGFR*-positive in the context of Spain. **Materials & methods:** A partitioned survival model was developed including costs, utilities and disutilities to estimate quality-adjusted life-year (QALY) and incremental cost–effectiveness ratio when treating with dacomitinib versus gefitinib. **Results:** Dacomitinib presented higher QALYs (0.51) compared with gefitinib (0.45). Dacomitinib costs were €33,061 in comparison with €26,692 for gefitinib arm. An incremental cost–effectiveness ratio of €111,048 was obtained for dacomitinib. **Conclusion:** Dacomitinib was more effective in terms of QALYs gained than gefitinib. However, to obtain a cost–effectiveness alternative, a discount greater than 25% in dacomitinib acquisition cost is required.

Lay abstract: *EGFR* tyrosine kinase inhibitors represent the standard of care in patients with *EGFR* mutation-positive (*EGFRm+*) non-small-cell lung cancer. The introduction of new oncology therapies can result in financial pressure for healthcare payers. Therefore, the development of a cost–effectiveness study for assessing the gains in health relative to the costs of different health interventions is required. In this study, we compare dacomitinib with gefitinib as first-line treatment from a Spanish National Health System perspective, by estimating how much it costs to gain a unit of a health outcome, like a life year gained or quality-adjusted life-year. Dacomitinib has been proved not to be a cost-effective alternative because despite being more effective in terms of life year gained or quality-adjusted life-year than gefitinib, it was also much more expensive due to the high acquisition cost of dacomitinib.

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Keywords: cost-effectiveness • dacomitinib • economic evaluation • *EGFR*-mutated • EGFR-TKI • non-small-cell lung cancer • partitioned survival model

Lung cancer is the most common cancer and the most frequent cause of cancer death worldwide [1]. In terms of histology, non-small-cell lung cancer (NSCLC), being diagnosed in 80–85% of cases, is the most widespread type of lung cancer [2]. *EGFR* mutations are reported to be associated in approximately 14–19% of Western patients and 40–48% of Asian patients with NSCLC with adenocarcinoma [3,4]. In Spain, the REASON study revealed that the mutation detection rate in advanced NSCLC patients was found to be 11.6% (17.4% presenting L858R mutation in exon 21 and 82.6% presenting in-frame deletions in exon 19) [5].

EGFR tyrosine kinase inhibitors (TKIs) are the standard treatment for patients with NSCLC harboring an *EGFR* mutation [6]. To date, three first-line TKIs are normally used in clinical practice: erlotinib, gefitinib and afatinib.

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These TKIs have demonstrated significantly improved progression-free survival (PFS) as the first-line treatment compared with platinum-based therapy [7–14].

Recently, based on the ARCHER 1050 study [15], the US FDA approved dacomitinib, a second-generation EGFR-TKI, for the first-line treatment of patients with metastatic NSCLC with *EGFR* mutation-positive [16]. This study showed that dacomitinib was superior to gefitinib in terms of PFS and overall survival (OS). A seven-month improvement in OS was shown in the dacomitinib arm compared with gefitinib [17]. Nonetheless, second-generation EGFR TKIs are frequently associated with EGFR-mediated toxicities due to the relatively potent *EGFR* inhibition. Therefore, in the ARCHER 1050 study, a dose reduction was performed on the dacomitinib arm. Additionally, in another study, tolerability guided dose modifications enabled patients to continue with dacomitinib and benefit from PFS and OS improvement [18].

Although dacomitinib caused more side effects than gefitinib, these were considered manageable. Therefore, on April 2019, the EMA decided that the benefits of dacomitinib are greater than its risks, and it was authorized for use in the European Union. Consequently, dacomitinib could be considered one of the standard first-line options for patients with advanced *EGFR*-mutated NSCLC. Additionally, a new network meta-analysis comparing OS have demonstrated that treatment with dacomitinib could be considered a first-line treatment option in comparison with other standard EGFR TKIs as afatinib (hazard ratio [HR] 0.87; 95% CI: 0.61–1.24), erlotinib (HR: 0.79; 95% CI: 0.44–1.42), gefitinib (HR: 0.75; 95% CI: 0.59–0.95) and osimertinib (HR: 0.94; 95% CI: 0.68–1.29) [19].

To our knowledge, no prior incremental cost–effectiveness analysis (ICER) has been performed comparing dacomitinib versus gefitinib in Spain. This study aims to evaluate the cost–effectiveness of first-line treatment with dacomitinib compared with gefitinib in patients newly diagnosed with advanced NSCLC *EGFR*-positive in the context of Spain. Our study could help clinicians and policymakers in the decision-making process to promote the sustainability of the Spanish National Health System.

Material & methods

Cost–effectiveness analysis: partitioned survival model

Design & perspective analysis

A partitioned survival model model was constructed using clinical data from the ARCHER 1050 randomized study [15]. The quality-adjusted life-years (QALYs), the costs, and ICER of two different treatment strategies (dacomitinib vs gefitinib) were estimated in two hypothetical cohorts of patients with newly diagnosed advanced NSCLC and one *EGFR* mutation (exon 19 or Leu858Arg). We modeled the health states of patients with similar criteria to those enrolled in the ARCHER 1050 study: patients in IIIB/IV stage, with new or recurrent diagnosis, and histological or cytopathological confirmation. The presence of at least one documented *EGFR* mutation (exon 19 deletion or the Leu858Arg mutation, with or without the Thr790Met mutation) was required. The model was developed from the perspective of the Spanish National Health System. The threshold for determining the cost–effectiveness of a strategy was €24,000/QALY [20]. All the costs were estimated in euros (€) 2019, and a discount rate of 3% was used for costs and effects throughout the model. The partitioned survival model was developed in Microsoft Excel 2011 (Microsoft Corp., WA, USA) using a 15-year time horizon, which was selected because it was sufficient to collect all the costs and benefits generated in the model. The results were presented in terms of costs (€), QALYs gained and ICER.

Partitioned survival model structure

The model included three mutually exclusive health states: stable disease, progressive disease and death. As shown in Figure 1, all patients were initially on stable disease and received one of the two treatment strategies (dacomitinib or gefitinib). On each 28-day simulation cycle, the model redistributes the hypothetical cohort of patients among the three health states according to the transition probabilities. On progressive disease, the patients received a second-line regimen, and after the occurrence of progressive disease, they could remain in this state or die. Progressive disease was simulated until all the patients died. A half-cycle correction was applied.

Treatment alternatives

The model cycle length was 28 days (4 weeks), consistent with the labeled dose frequency of the two treatments. Patients in the dacomitinib group were treated with oral dacomitinib 45 mg once daily in 28-day cycles. Of the patients in this group, 66% experienced a dose reduction, 38% received the lowest dose of 30 mg/day and 28%

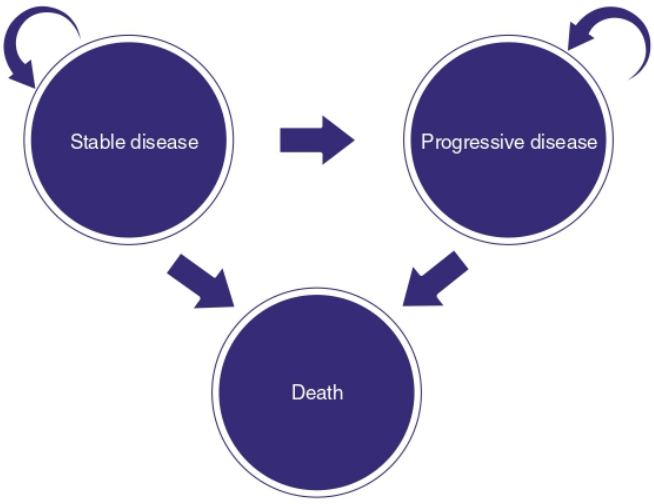

Figure 1. Structure of the partitioned survival model. Partitioned survival model health states.

received the lowest dose of 15 mg/day, according to the ARCHER 1050 trial [15]. The patients in the gefitinib group received gefitinib 250 mg orally once daily in 28-day cycles.

Transitional probability data

The clinical effectiveness data of PFS and OS were obtained from the ARCHER 1050 trial [15,17], via the techniques outlined in Guyot *et al.* [21]. WebPlotDigitizer was used to recreate Kaplan–Meier graphs to project outcomes to the end of the 15-year time horizon using Flexurv, an R package for the fully parametric modeling of survival data [22,23] (R version 3.3.3). The following parametric distributions were considered to determine the most appropriate parametric survival curve as recommended by the NICE Decision Support Unit [24]: gamma, log-logistic, Weibull, lognormal, Gompertz, exponential, generalized F and generalized gamma. The distributions were selected based on statistical tests (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual inspection of fit to Kaplan–Meier plots, goodness-of-fit statistics and clinical plausibility. (Figure 2 & Supplementary Table 2).

For PFS and OS, a log-logistic distribution was selected. This distribution has the best visual and statistical fit; the hazards consistent with the observed hazards in the ARCHER 1050 trial [15], do not yield implausible projections with the survival curves for the two arms crossing (Supplementary Material & Figures 1–4). For each TKI, the probability that patients remain in stable disease at each time is determined by the values of the PFS curve at that time. In addition, the probability of patients to achieve the death state is determined as 1 minus the OS curve at that time. From this, the probability of patients in progressive disease follows, as the three states together should always add up to 100%.

Cost estimation

Table 1 outlines the calculated costs. Direct medical costs include treatment costs, disease management costs, end-of-life care costs, adverse events costs and second-line treatment costs. The cost of gefitinib and dacomitinib were calculated according to the officially notified listed prices ([drug price – 7.5% official discount in Spain] x Value added tax [VAT]) [25,26]. The cost of dacomitinib can be considered part of the problem because up to the date of publication of this article, an official Spanish price for this drug has not been published, and it has been obtained from NICE guidance [27].

Disease management costs were estimated according to an expert panel's advice. Disease management cost per patient and cycle was calculated by multiplying the cost of healthcare resources employed by the unit cost of each resource consumed over a 15-year time horizon. The unit costs were obtained from an official database published in Spain [32].

End-of-life care costs were applied to each patient entering the death state and were obtained from an article published in Spain [28].

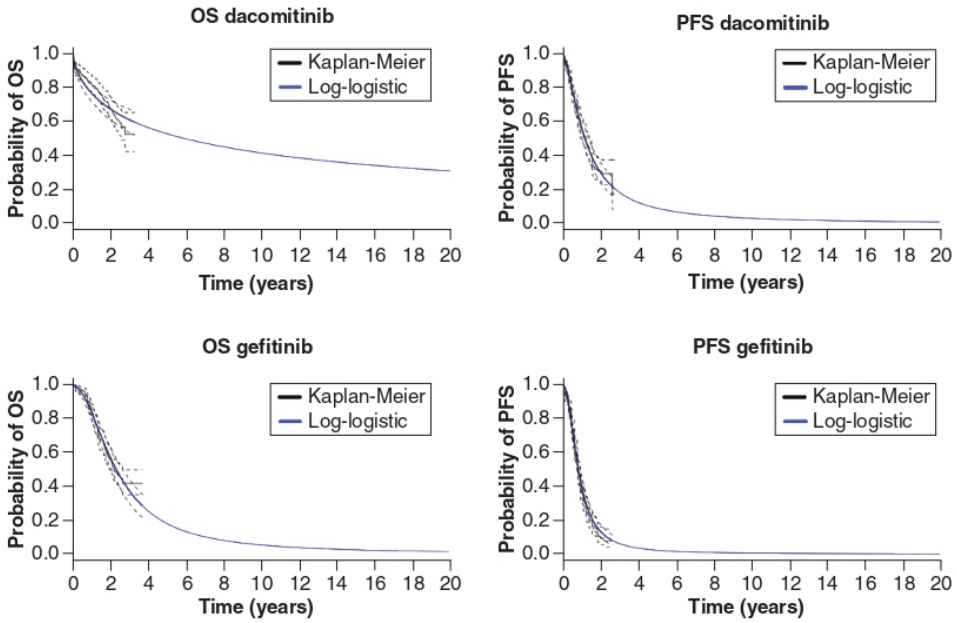

Figure 2. Overall survival and progression-free survival Kaplan–Meier plot and selected fitted curves.
PFS: Progression-free survival; OS: Overall survival.

The costs of side effects management from the perspective of the Spanish National Health System (Table 1) were obtained from published articles [29,30]. Adverse effect (grade 3/4 events) frequencies associated with dacomitinib and gefitinib treatments and reported in at least 3% of patients were obtained from the ARCHER 1050 study [15].

The second-line therapy regimens were obtained from Supplementary Table 1 ARCHER 1050 study [15] as is shown in Table 1. In dacomitinib second-line arm, 23.8% of the patients were treated with pemetrexed, 13.7% with carboplatin, 13.2% with cisplatin and 7.9% with osimertinib. In gefitinib second-line arm, 25.9% of the patients were treated with pemetrexed, 13.8% with carboplatin, 17.9% with cisplatin and 12.9% with osimertinib. The patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m^2.

All cost inputs from prior years were inflated to 2019 Spanish values using the Consumer Price Index. The model costs are presented in Euros (€) 2019 (Table 1).

Utilities estimation

The ARCHER 1050 study has not reported health state utilities. Thus, utility inputs and disutility values for the base case were estimated from the recent data published in the literature [30,31]. In order to estimate QALYs, utility and disutility values were applied considering the different health states (stable disease and progressive disease) and are summarized in Table 1. A health utility of zero was applied to the health state of death.

Disutilities estimation

The disutility values associated with grade 3/4 adverse events while the patients remained in stable disease were adopted from a recently published international study that evaluated the disutilities and complications for advanced NSCLC in different countries like the UK, France, Australia and Republic of China by employing a time trade-off technique [33]. To calculate the disutility values associated with grade 3/4 in stable disease, the disutility parameters of each adverse event extracted from Nafees *et al.* were multiplied by the relative frequency of the corresponding event obtained from the ARCHER 1050 trial to calculate a weighted average disutility value for each event profile as is shown in Supplementary Table 1. The disutility values calculated for each grade 3/4 adverse event were subtracted from the utility values while the patients remained in stable disease.

Table 1. Model input parameters.

Management of NSCLC	Cost per 28-day cycle and patient	Distribution	Ref.
Gefitinib	€2045	Gamma	[25–27]
Dacomitinib	€3023	Gamma	
Second-line cost gefitinib			
– Scheme (43.8% of total patients)	€1233	Triangular	[15,25,26]
– Permetrexed (25.9%)			
– Carboplatin (13.8%)			
– Cisplatin (17.9%)			
– Osimertinib (12.9%)			
– Median number of postprogression systemic treatments per patients in gefitinib arm	1 (1–6)		[15]
Second-line cost dacomitinib			
– Scheme (59% of total patients)	€1854	Triangular	[15,25–27]
– Permetrexed (23.8%)			
– Carboplatin (13.7%)			
– Cisplatin (13.2%)			
– Osimertinib (7.9%)			
– Median number of postprogression systemic treatments per patients in dacomitinib arm	2 (1–5)		[15]
End-of-life care cost	€12,909	Gamma	[28]
Grade III–IV adverse events (frequency >3%)	Median cost/cycle		[29,30]
– Diarrhea	€1552	Gamma	
– Dermatitis acneiform	€2.11	Gamma	
– Stomatitis	€1352	Gamma	
– Rash	€2.11	Gamma	
– Maculopapular rash	€2.11	Gamma	
– Postular rash	€2.11	Gamma	
– ALT elevation	€68	Gamma	
– AST elevation	€68	Gamma	
Utilities scenario	**Value**		[30,31]
– On treatment with no side effects	0.65	Beta	
– Diarrhea	0.32	Beta	
– Dermatitis acneiform	0.15	Beta	
– Stomatitis	0.25	Beta	
– Rash	0.15	Beta	
– Maculopapular rash	0.15	Beta	
– Postular rash	0.15	Beta	
– ALT elevation	0	Beta	
– AST elevation	0	Beta	
– Disease progression	0.47	Beta	

NSCLC: Non-small-cell lung cancer.

Univariate sensitivity analysis

Deterministic sensitivity analysis (DSA) was performed to explore the impact of the essential variables on the ICER estimated value. Thus, a single parameter in the model (drug costs, utilities or discounts) was varied to test the effect on the ICER result. The utilities values were varied in a range of ±20%. The drug acquisition costs were modified in three different ranges (±15, ±20 and ±25%). The end-of-life care costs were varied in two different ranges (±10 and ±20%), and the discounts values in the DSA were modified in a percentage of 0 and 6%. The transition probability values of PFS and OS were varied in a range of ±5. The results of the DSA were presented in a tornado diagram.

Table 2. Cost–effectiveness results.

Variable	Strategy	
	Gefitinib	Dacomitinib
Total cost/pt	€26,692	€33,061
Treatment cost/pt	€11,120	€22,833
Disease management/pt	€2,219	€1,869
Adverse events costs/pt	€63	€87
Ee end-of-life care cost	€12,785	€7,229
2L cost/pt	€505	€1,043
QALY gained/pt	0.45	0.51
ICER (€/QALY) Dacomitinib vs gefitinib	€111,048/QALY	

pt: Patient; 2L: Second-line; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

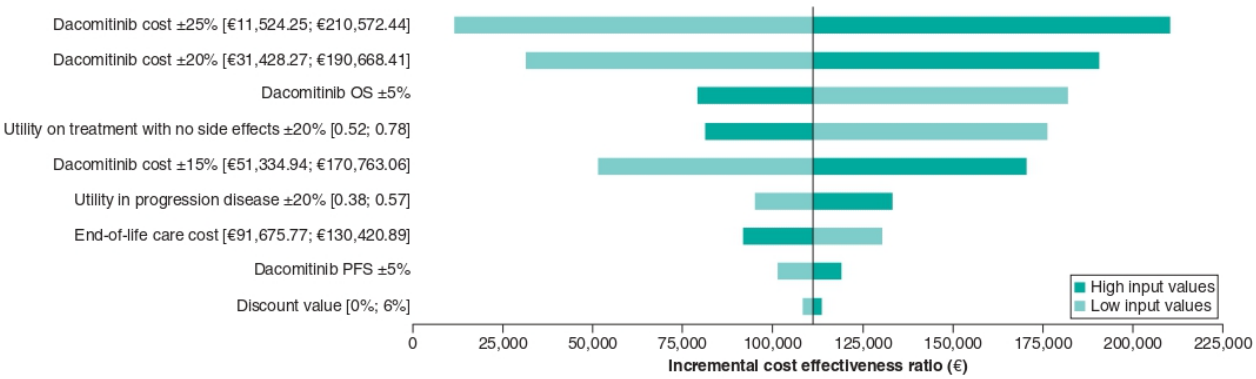

Figure 3. Tornado diagram (deterministic sensitivity analysis).
OS: Overall survival; PFS: Progression-free survival.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the influence of parameter uncertainties using 10,000 Monte Carlo simulations. Different parameters (side effects management costs, disease management costs, second-line treatment costs, acquisition costs, end-of-life care costs, utilities and transitions probabilities) of the model were varied to determine the robustness of the model. The results of the PSA was employed to obtain the cost–effectiveness acceptability curves, showing the probability of each alternative being cost-effective across a range of possible values of willingness-to-pay (WTP) for an additional QALY [34].

The different types of probability distributions were applied to variate the model parameters according to the characteristics of each variable [35]. Gamma distributions were employed for costs, beta for utilities and Dirichlet distributions for transitions probabilities. The number of postprogression systemic treatments per patient were assumed to follow a triangular distribution.

Results

The base-case cost–effectiveness results for dacomitinib and gefitinib are reported in Table 2. The total QALYs were 0.51 and 0.45 for dacomitinib and gefitinib, respectively. The incremental number of QALYs gained with dacomitinib compared with gefitinib was 0.06. The number of incremental life-years gained in the base case was 0.06 (0.86 life-years vs 0.80 life-years for dacomitinib and gefitinib, respectively). The mean costs for dacomitinib arm were €33,061 discounted over the 15-years horizon and €26,692 for the gefitinib arm, resulting in an additional cost of €6369. These costs and QALY values yielded an incremental ICER of €111,048 for dacomitinib compared with gefitinib.

The results from the DSA showed significant changes in the ICER after modifying dacomitinib acquisition costs, end-of-life care costs, utilities and discount values as shown in the Tornado diagram (Figure 3) and Supplementary

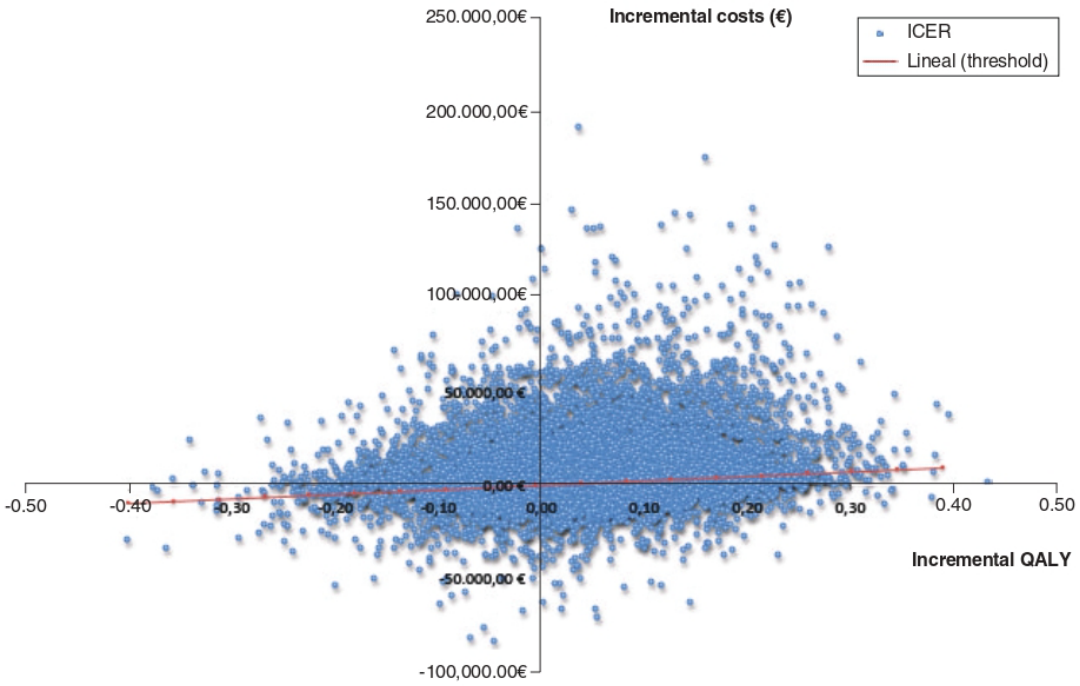

Figure 4. Scatter plot of Monte Carlo probabilistic sensitivity analysis for dacomitinib versus gefitinib.
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

Table 3. The model outcome was sensitive to the drug acquisition cost of dacomitinib, showing that discounts greater than 25% produced an ICER value below the threshold of 24,000€ per QALY gained fixed in Spain.

As shown in Figure 4, the PSA results were consistent with the base-case analyses. Dacomitinib was non cost-effective in 46.63% of the simulations, dominated in 17.84%, cost-effective in 16.11% and dominant in 19.42%.

Finally, the results plotted in a cost–effectiveness plane (Figure 4) were used to construct the cost–effectiveness analysis curve, which shows the probability that dacomitinib becomes cost-effective for different WTP thresholds. Therefore, in the base-case scenario, there is a 35.53% probability of dacomitinib being cost-effective and dominant at a threshold of €24.000/QALY (Figure 5).

Discussion

Recently, the European Commission has approved dacomitinib for the frontline treatment of adult patients with locally advanced or metastatic NSCLC [36]. Dacomitinib has demonstrated superiority over gefitinib in both PFS and OS in Phase III head-to-head comparison study [15,17]. Additionally, a recent network meta-analysis demonstrated treatment with dacomitinib versus gefitinib (HR: 0.75; 95% CrI: 0.59–0.95), afatinib (HR: 0.87; 95% CrI: 0.61–1.24), erlotinib (HR: 0.79; 95% CrI: 0.44–1.42) and osimertinib (HR: 0.94; 95% CrI: 0.68–1.29) trended directionally toward improved OS, in patients with advanced or metastatic *EGFR*+ NSCLC [19]. However, the published meta-analysis is not showing a significant difference, CrIs are very wide due to the low number of studies included.

The lack of comparative long-term efficacy data can pose challenges for health technology appraisals. Therefore, we developed a complete cost–effectiveness analysis to compare dacomitinib versus gefitinib in patients with newly diagnosed advanced NSCLC and one *EGFR* mutation based on the ARCHER 1050 study [15]. Over a 15-year time horizon, we demonstrated that dacomitinib is considered slightly more effective in comparison with gefitinib in terms of QALYs gained (0.06). Nonetheless, our study showed that dacomitinib was not cost-effective compared with EGFR-TKIs because the ICER (€111,048/QALY) was higher than the commonly accepted threshold in Spain of €24,000/QALY [20]. Thus, the base case results indicate that discounts greater than 25% are crucial for the dacomitinib acquisition costs to be considered cost-effective.

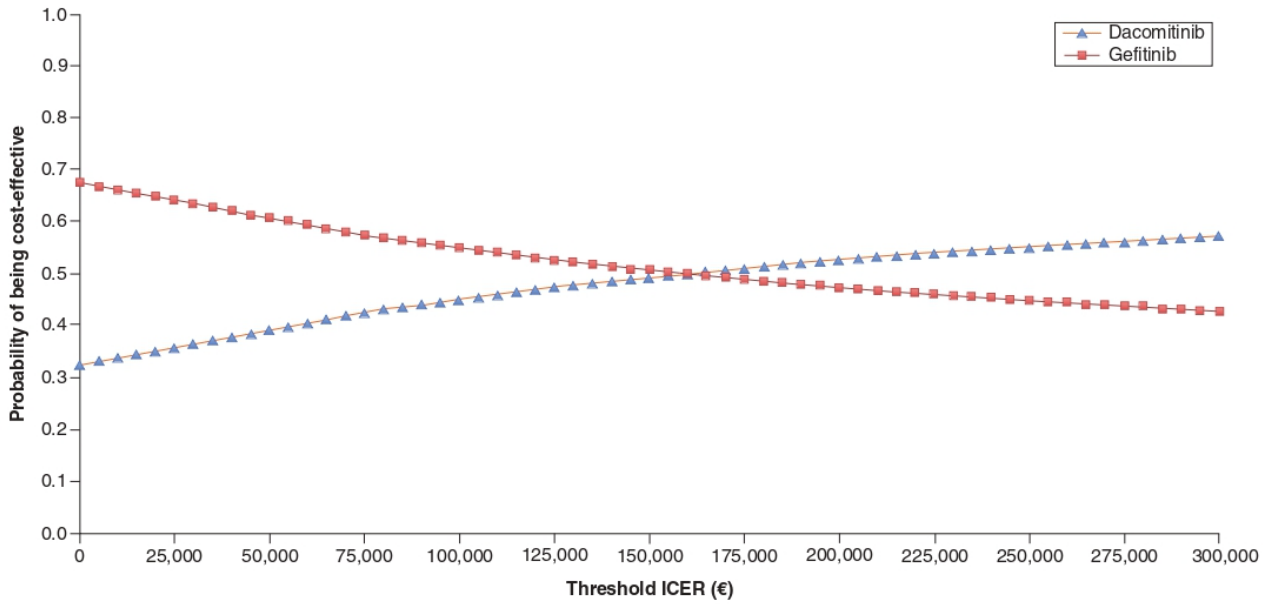

Figure 5. Cost–effectiveness acceptability curve dacomitinib versus gefitinib. Graph plot WTP scenario (x-axis) versus the likelihood in percentage that the treatment would be considered cost-effective (y-axis).
ICER: Incremental cost–effectiveness ratio; WTP: Willingness-to-pay.

At the time of the investigation, this is the first cost–effectiveness analysis to contribute a direct comparison of dacomitinib against the first-generation EGFR-TKI (gefitinib) for patients with newly diagnosed advanced NSCLC *EGFR*-mutated.

NICE has recommended dacomitinib for locally advanced or metastatic *EGFR* mutation-positive in adults. The evidence review group of NICE constructed a fixed-effects network meta-analysis using data from the ARCHER 1050 for dacomitinib and from LUX-Lung 7 for afatinib [37,38]. The results of this study showed that PFS and OS might be better for dacomitinib than afatinib, although there was no significant difference between the two treatments (PFS, HR: 0.80; 95% CI: 0.57–1.12; OS, HR: 0.88; 95% CI 0.61–1.29).

In our study, the small difference in the incremental QALY values (0.06) is mainly attributable to the differences in efficacy between the two drugs. The decrease in utility values due to adverse reactions does not have a relevant impact on the model. This fact can be seen in the DSA, where the drug is not able to be cost-effective, despite the decrease of 20% in the utility value of dacomitinib in stable disease.

In our study, dose modifications are needed to reduce the incidence and severity of treatment-related adverse events [18]. However, adjustment to dose reduction is not expected to have a large impact on the cost–effectiveness results since the price of the different doses of dacomitinib are uniformly based on NICE guidance [27].

In addition, a cost–effectiveness acceptability curve was constructed based on the results plotted in a cost–effectiveness plane to obtain the probability that dacomitinib is cost-effective compared with gefitinib for a different WTP threshold. We demonstrated that, with the defined cost–effectiveness threshold in Spain of €24,000/QALY [20], dacomitinib may be considered not cost-effective due to the high price of drug acquisition.

Lung cancer morbidity and mortality have a significant economic impact on the healthcare system and society. The poor long-term prognosis and high healthcare cost highlight the need to balance patient access to best treatment with healthcare sustainability and societal burden, particularly in the advanced NSCLC setting [39]. Economic evaluations, like the present cost–effectiveness analysis, are widely used to inform policymakers and health administrators about which treatment innovations should be reimbursed or promoted and to consider reducing prices in the drug acquisition cost.

Our study has some limitations. First, we employed a partitioned survival model, a theoretical model which, by definition, constitutes a simplified simulation of reality. Second, the utility values in the analysis model were extracted from a verified study published in the population of UK [31] but not from Spain because, to date, these

data are not available. Third, until the publication of this article, the acquisition cost of dacomitinib has not yet been approved in Spain. Therefore, the value obtained by NICE was selected [27]. Fourth, patients with brain metastases were excluded from participation in the ARCHER 1050 study because the brain penetration of dacomitinib was not known at the time of the study and this could affect the final QALY values [40].

Conclusion

This study showed that, from Spanish National Health System perspective, treatment with dacomitinib was more effective in terms of QALYs gained than treatment with gefitinib. However, dacomitinib has been proved not to be a cost-effective alternative in first-line therapy for advanced *EGFR*-mutated NSCLC patients in Spain because the ICER (€111,048/QALY) appears to be too high given the Spanish threshold. The price of dacomitinib should be reduced by 25% to become a cost-effective alternative.

Summary points

- In ARCHER 1050 study, the median progression-free survival in patients with newly diagnosed advanced non-small-cell lung cancer (NSCLC) and one *EGFR* mutation (exon 19 deletion or Leu858Arg) was demonstrated to be significantly longer with dacomitinib than with gefitinib (14.7 vs 9.2 months).
- Dacomitinib presented higher quality-adjusted life years (QALYs; 0.51) compared with gefitinib (0.45).
- Dacomitinib total costs of the intervention were €33,061, in comparison with the €26,691.88 for gefitinib arm.
- An incremental cost–effectiveness analysis of €111,048/QALY was obtained for dacomitinib compared with gefitinib.
- Dose modifications are needed to reduce the incidence and severity of treatment-related adverse events.
- From Spanish National Health System perspective, dacomitinib has been proved not to be a cost-effective alternative in first line therapy for advanced *EGFR*-mutated NSCLC patients, compared with gefitinib due to the high acquisition costs of the drug.
- A discount greater of 25% in dacomitinib acquisition cost could produce an incremental cost–effectiveness ratio value below the established threshold of €24,000 per QALY gained in Spain to result a cost–effectiveness alternative.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0233

Author contributions

All the authors interpreted data, read and approved the final manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Our study used mathematical modeling and was not an active clinical trial; therefore, no approval was required from the Institutional Research Ethics Board.

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ORIGINAL RESEARCH

Cost-effectiveness analysis of the first-line EGFR-TKIs in patients with advanced EGFR-mutated non-small-cell lung cancer

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ABSTRACT

Aim: To evaluate the cost-effectiveness of first-line treatments, such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib, for patients diagnosed with stage IIIB/IV NSCLC harboring EGFR mutations.

Materials & methods: A partitioned survival model was developed to estimate quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER) from the perspective of the Spanish National Health System. Two Bayesian NMAs were performed independently, by using the polynomial fraction method to fit Kaplan–Meier curves for overall survival and progression-free survival. Deterministic and probabilistic sensitivity analyses were performed to evaluate the uncertainty.

Results: The ICER was calculated for the four first-line treatments by comparing them with gefitinib, and the ratios obtained were as follows: €166,416/QALY for osimertinib, €183,682/QALY for dacomitinib, €167,554/QALY for afatinib, €36,196/QALY for erlotinib. It was seen that patients who received osimertinib presented higher QALYs (0.49), followed by dacomitinib (0.33), afatinib (0.32), erlotinib (0.31), and gefitinib (0.28).

Conclusions: Gefitinib is the most cost-effective treatment. In terms of QALYs gained, Osimertinib was more effective than all other TKIs. Nevertheless, with a Spanish threshold of €24,000/QALY, the reduction in the acquisition cost of osimertinib will have to be greater than 70%, to obtain a cost-effectiveness alternative.

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1. Introduction

Lung cancer is one of the most commonly diagnosed types of cancer and the leading cause of cancer-related mortality worldwide [1]. From 2008 to 2013, lung cancer was the fourth most commonly diagnosed cancer, after colorectal, prostate, and breast cancers, among the sexes with a five-year survival rate of 12.7% in men and 17.6% in women [2].

Lung cancer is further divided into small-cell and non-small -cell lung cancer (NSCLC). NSCLC is the most widespread type of lung cancer that has been diagnosed in approximately 85% of all lung cancer cases [3]. The presence of somatic mutations in the gene encoding the epidermal growth factor receptor (EGFR) could be associated in approximately 14–19% of Western patients and 40–48% of Asian patients suffering from NSCLC with adenocarcinoma [4,5]. In Spain, EGFR mutations were detected in 11.6% of NSCLC patients, out of which 17.4% presented L858R mutation in exon 21 and 82.6% presented in-frame deletions in exon 19, which is discussed later [6]

Until a few years ago, four to six cycles of platinum-based doublet chemotherapy had been selected as standard first-line treatment for patients with advanced NSCLC [7]. However, it provides limited benefits with regard to survival, with nearly one-year median overall survival (OS) [8–10]

In recent years, patients with NSCLC and activating somatic EGFR mutations have shown better clinical outcomes in both progression-free survival (PFS) and OS, when treated with EGFR tyrosine kinase inhibitors (TKI) than with chemotherapy [11,12]. Actually, three generations of EGFR TKIs have been developed (first generation: gefitinib and erlotinib; second generation: afatinib and dacomitinib, and third generation: osimertinib) [13]. However, more than half of the patients diagnosed with NSCLC EGFR-positive developed resistance to treatment with first-generation and second-generation EGFR TKIs, which is associated with an acquired mutation, T790M, in the EGFR gene [14–16]. Consequently, the T790M mutation forces a change in a third-generation drug such as osimertinib, which is currently employed with successful results [17–21]. The European Society for Medical Oncology (ESMO) guidelines recommend first-line treatment with an EGFR TKI for patients with advanced NSCLC EGFR-positive; for patients who initiate treatment with first- or second-generation EGFR TKI and develop resistance through the T790M mutation, second-line osimertinib is recommended [22,23].

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Supplemental data for this article can be accessed here.

However, since there are no direct comparative randomized controlled trials (RCTs) for all EGFR TKI, different network meta-analyses (NMA) have been published [24–32]. In our study, we have selected the NMA published by Holleman et al. [26] to obtain efficacy data.

The management of morbidity and mortality in lung cancer has a significant economic impact on the healthcare system and society. In Spain, the mean cost per patient in NSCLC ranged between €13,218 and €16,120 [33]

To the best of our knowledge, no prior cost-effectiveness analysis (ICER) has been developed to compare the three generations of EGFR TKIs (erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib). Hence, this study aims to evaluate the cost-effectiveness of first-line treatments such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib, for patients diagnosed with stage IIIB/IV NSCLC harboring EGFR mutations, in the context of Spain. Our study could provide valuable information for clinicians and medical decision makers in order to promote the sustainability of the Spanish National Health System.

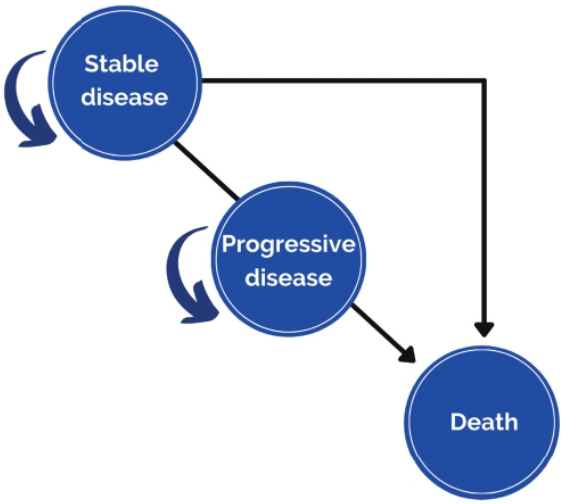

Figure 1. Structure of the partitioned survival model. Partitioned survival model health states.

2. Material & methods

2.1. Model structure and settings

The cost-utility analysis was performed using a partitioned survival model. It was constructed to select which of the five main TKIs used as first-line treatment is the most cost-effective, for patients diagnosed with stage IIIB/IV NSCLC harboring EGFR mutations. To assess cost-effectiveness, the incremental cost per quality-adjusted life-year (QALY) gained, the incremental cost per life-year (LY) gained, and the incremental costs were set as the main outcome measures. The model was developed from the perspective of the Spanish National Health System. The threshold for establishing the cost-effectiveness of an alternative was €24,000/QALY, as recommended in Spain [34]. Health outcomes and costs were discounted at a rate of 3%, in line with the Spanish guidelines [35]. All the costs were estimated in euros (€) 2021. The partitioned survival model was created in Microsoft Excel 2021 (Microsoft Corp., WA, USA). A 15-year time horizon was employed as it comprehensively captures the expected costs and health outcomes of patients over their remaining lifetime from the initiation of first-line treatment. The results were presented in terms of costs (€), QALYs gained, and ICER.

The three mutually exclusive health states chosen to conduct the study on were progression-free disease (PFS), progressive disease (PD), and death. The OS was split into alive with PFS and alive with PD. The proportion of alive with PFS was calculated by the area under the PFS curve. The proportion of alive with PD was estimated by the difference between the OS and PFS curves.

According to the transition probabilities, shown in Figure 1, for each 28-day simulation cycle, it was assumed that all patients entered the model with a stable disease and they could only transition from one health state to another or stay in the same state during a cycle. Patients in both stable and progressive disease states could transition to the death state in any cycle. In progressive disease state, the patients received a second-line regimen. Progressive disease state was simulated until all the patients died, after which a half-cycle correction was applied.

2.2. Target population

The target population from the NMA, by Holleman [26], was simulated in this model, and we have added the final OS results for osimertinib [36]. In this NMA, gefitinib was studied in eight RCTs (NEJ002, WJTOG3405, IPASS, First-SIGNAL, Lux-Lung 7, CTONG0901, ARCHER1050, and FLAURA) [21,36–43]. Erlotinib was studied in four RCTs (OPTIMAL, EURTAC, ENSURE, and CTONG0901) [42,44–47]. Afatinib was studied in three RCTs (Lux-Lung 3, Lux-Lung 6, and Lux-Lung 7) [41,48–50]. Dacomitinib was studied in one RCT (ARCHER 1050) [43,51] and osimertinib in one RCT (FLAURA) [21,36] .

2.3. Comparators

The comparator used in this analysis was gefitinib. Platinum-based chemotherapy was excluded as a standard first-line therapy in our study because TKIs have shown a better tolerance to and a longer prolongation of PFS, as demonstrated in several studies [37,38,44,45,48,49,52]

2.4. Effectiveness estimates

Erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib efficacy (PFS and OS) were estimated through a NMA based on 13 RCTs [26]. A Bayesian NMA was carried out using Markov chain Monte Carlo (MCMC) methods, based on the methodology proposed by Dias et al. [53]. First, using WebPlotDigitizer, we digitized individual patient data from the Kaplan–Meier curves for PFS and OS based on the 13 RCTs [54]. The individual patient data (IPD) was reconstructed according to an algorithm proposed by Guyot [55]. A pseudo-IPD was used to estimate the number of patients with events in each time interval. With fractional polynomials, we

modeled the hazard over-time from each study arm to achieve an overall set of estimated parameters for each treatment. This approach relaxes the proportionality of risks and fits better with the available data [56]

Two NMAs were conducted independently, one each for OS and PFS. The Bayesian NMAs were performed using R statistical software (version 3.6.3) and the rjags package [57]. Posterior sampling was conducted using Markov chain Monte Carlo method, where four chains of 15,000 samples were held after discarding a burn-in of 5,000 iterations. Models of both fixed-effect and random-effect were fitted to the data. Vague prior distributions were assigned to all stochastic parameters. First-order and second-order fractional polynomials were evaluated. A set of five values (−2. −1, 0, 1, 2) was selected for the exponents p1 and p2. Based on the deviance information criterion (DIC) (Table 1) and the visual inspection, the best-fitting model was selected to plot the pooled survival curves with lower DIC values being preferred. Fixed-effects, first-degree, and 0-exponent models were selected for both overall survival and progression-free survival (*supplementary annex, figure S1 and figure S2)*.

2.5. Cost estimations

All the results were expressed in euros (€). All costs from prior years were inflated to 2021 for Spanish values using the consumer price index (CPI). Table 2 outlines the calculated costs. Direct costs include treatment costs, disease management costs, end-of-life care costs, adverse event costs, and second-line treatment costs. The costs of the five TKIs were calculated according to the officially notified listed prices ([drug price − 7.5% official discount in Spain] + 4% Value added tax [VAT]) [58,59]. When compared to other EGFR-TKIs, there is a substantial difference seen in the costs of gefitinib and erlotinib because we have considered the generic drug values of these drugs.

Disease management costs were calculated based on an expert panel's advice. This cost per patient cycle was estimated by multiplying the cost of health-care resources incurred with the unit cost of each resource consumed over a 15-year time horizon. The unit costs of each resource were extracted from an official database published in Spain [60]

The costs endured in managing side effects were obtained from published articles [61,62]. Costs of severe adverse events (grade 3/4) included the total costs of the treatment for an adverse event per patient and were multiplied by the probability of each adverse event obtained in the NMA [26]

The second-line therapy regimens were obtained from supplementary Table 3 of FLAURA study [21]. In the osimertinib second-line arm, 21% of the patients were re-challenged with standard EGFR–TKI (erlotinib–gefitinib), followed by 36% with platinum-based chemotherapy, 35% with non-platinum-based chemotherapy, and 8% with other therapies (PD-1/PD-L1, anti-VEGF and others targeted therapies). For the four other TKI second-line arms (erlotinib, gefitinib, dacomitinib, and afatinib), 46% of the patients were treated with another EGFR–TKI including osimertinib, 13% with platinum-based chemotherapy, 12% with non-platinum-based chemotherapy, and 4% with other therapies (PD1/PD-L1, anti-VEGF, and others targeted therapies). To calculate the second-line costs, patients were assumed to have a body height of 170 cm and a weight of 70 kg, resulting in a body surface area of 1.73 m2. Since the second-line treatment curves corresponding to PFS were not available in the FLAURA clinical trial, we employed the PSF2 curves available in the AURA3 clinical trial to calculate the duration for the second-line treatment [20]. For this, we estimated the area under the curve (AUC) in the PFS2 AURA3 trial curve by comparing osimertinib

Table 1. Goodness-of-fit statistics for modeling PFS and OS. OS: overall survival; PFS: progression-free survival; DIC: deviance information criterion; NC: non convergence.

Order	Exponents	Random effects	DIC SLP	DIC OS
1	2	FALSE	5490.3	14,745.9
1	1	FALSE	4547.2	5122.4
1	0	FALSE	4025.4	4885.3
1	−1	FALSE	3851.2	NC
1	−2	FALSE	NC	NC
1	2	TRUE	5787.4	NC
1	1	TRUE	4489.8	5124.4
1	0	TRUE	3961.1	4885
1	−1	TRUE	3799.7	NC
1	−2	TRUE	NC	NC
2	2, 2	FALSE	16092.1	48,760.9
2	1, 2	FALSE	6396.8	20,477.9
2	0, 2	FALSE	5299.4	15,400.3
2	−1, 2	FALSE	4640.1	13,574.7
2	−2, 2	FALSE	4656.5	13,970.4
2	2, 1	FALSE	6576.5	20,114.4
2	1, 1	FALSE	3955.5	5805.5
2	0, 1	FALSE	3824.8	4872
2	−1, 1	FALSE	3855.2	4882.8
2	−2, 1	FALSE	NC	4924.5
2	2, 0	FALSE	5218.4	14,775.5
2	1, 0	FALSE	3830.1	4872.1
2	0, 0	FALSE	3848.2	4852.9
2	−1, 0	FALSE	NC	NC
2	−2, 0	FALSE	NC	NC
2	2, −1	FALSE	4678.8	14,029.6
2	1, −1	FALSE	3869.2	4894
2	0, −1	FALSE	3867.1	NC
2	−1, −1	FALSE	NC	NC
2	−2, −1	FALSE	NC	NC
2	2, −2	FALSE	4765.1	14,654.8
2	1, −2	FALSE	NC	NC
2	0, −2	FALSE	NC	NC
2	−1, −2	FALSE	NC	NC
2	−2, −2	FALSE	NC	NC
2	2, 2	TRUE	11755.5	NC
2	1, 2	TRUE	6509.9	16,284.4
2	0, 2	TRUE	5679.1	17,959.5
2	−1, 2	TRUE	5006.6	NC
2	−2, 2	TRUE	4950.4	NC
2	2, 1	TRUE	6742.8	17,223.1
2	1, 1	TRUE	3915.3	5918.7
2	0, 1	TRUE	3780	4889.4
2	−1, 1	TRUE	3804.3	4889.5
2	−2, 1	TRUE	NC	4912.1
2	2, 0	TRUE	5537.2	17,568.3
2	1, 0	TRUE	3777.4	4876.1
2	0, 0	TRUE	3799.8	4849.4
2	−1, 0	TRUE	3815.3	NC
2	−2, 0	TRUE	NC	NC
2	2, −1	TRUE	4889.3	NC
2	1, −1	TRUE	3806.2	4906.2
2	0, −1	TRUE	3807.1	NC
2	−1, −1	TRUE	NC	NC
2	−2, −1	TRUE	NC	NC
2	2, −2	TRUE	4877	NC
2	1, −2	TRUE	NC	4930.4
2	0, −2	TRUE	NC	NC
2	−1, −2	TRUE	NC	NC
2	−2, −2	TRUE	NC	NC

Table 2. Model input parameters.

Management of NSCLC	Cost per 28-day cycle and patient	Distribution	References
Erlotinib	€494	Gamma	[56,57]
Gefitinib	€292	Gamma	
Dacomitinib	€2,424	Gamma	
Afatinib	€1,714	Gamma	
Osimertinib	€5,447	Gamma	
Second-line cost osimertinib	€11,880	Weibull	[21,56,57]
Scheme (29% of total patients)			
EGFR-TKI scheme erlotinib/gefitinib (21%)			
Platinum-based chemotherapy schemes (36%)			
Non platinum-based chemotherapy schemes (35%)			
Others therapies (8%)			
Second-line cost erlotinib, gefitinib, afatinib and dacomitinib	€15,310	Weibull	[21,56,57]
Scheme (47% of total patients)			
EGFR-TKI scheme treated with osimertinib (46%)			
Platinum-based chemotherapy schemes (13%)			
Non platinum-based chemotherapy schemes (12%)			
Others therapies (4%)			
End-of-life care cost	€12,947	Gamma	[61]
Grade III–IV adverse events (frequency >3%)	**Median cost/cycle**		[59,60]
Diarrhea	€1,556	Gamma	
Dermatitis acneiform	€2.11	Gamma	
Stomatitis	€1,352	Gamma	
Rash	€2.11	Gamma	
Maculopapular rash	€2.11	Gamma	
Postular rash	€2.11	Gamma	
Alanine aminotransferase elevation	€68	Gamma	
Aspartate aminotransferase elevation	€68	Gamma	
Fatigue	€176	Gamma	
Neutropenia	€1,910	Gamma	
Decreased appetite	€10.31	Gamma	
Paronychia	€2.11	Gamma	
Weight decreased	€10.31	Gamma	
Dyspnea	€176	Gamma	
Asthenia	€176	Gamma	
Utilities scenario	**Value**		[62,63]
On treatment with no side effects	0.65	Beta	
Diarrhea	0.32	Beta	
Dermatitis acneiform	0.15	Beta	
Stomatitis	0.25	Beta	
Rash	0.15	Beta	
Maculopapular rash	0.15	Beta	
Postular rash	0.15	Beta	
Alanine aminotransferase elevation	0	Beta	
Aspartate aminotransferase elevation	0	Beta	
Fatigue	0.41	Beta	
Neutropenia	0.46	Beta	
Decreased appetite	0.41	Beta	
Paronychia	0.03	Beta	
Weight decreased	0.41	Beta	
Dyspnea	0.41	Beta	
Asthenia	0.41	Beta	
Disease progression	0.47	Beta	

with platinum/pemetrexed-based chemotherapy in NSCLC for patients who experienced a progression in the disease after receiving first-line EGFR–TKI therapy. We employed the method proposed by Guyot et al. to simulate the best survival curve [55], which was then fitted with a Weibull distribution to obtain the best adjusting method.

End-of-life care costs were applied to each patient entering the death state and were obtained from an article published in Spain [63].

2.6. Utility estimates

To estimate QALYs, values of utilities for stable disease and progressive disease were estimated from data published in the literature [64]. A health utility of zero was applied to the health state of death. By employing a time trade-off technique, the disutility values associated with grade 3/4 adverse events were obtained from an international study for advanced NSCLC conducted in different countries such as the UK, France, and Australia [65].

2.7. Univariate sensitivity analyses

Deterministic sensitivity analyses (DSA) was conducted to estimate the impact of the essential variables on the ICER value. Hence, different parameters in the model, such as drug costs, utilities, and discount rates, were varied to test their influence on the ICER results. The results of the DSA were presented in a tornado diagram.

2.8. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to quantify the impact of combined uncertainty of all model-input parameters using 10,000 Monte Carlo simulations, and the results were plotted on a cost-effectiveness plane. Different parameters of the model, such as disease management costs, side effects management costs, second-line treatment costs, drug costs, end-of-life care costs, and utilities, were varied to determine the robustness of the model. The cost-effectiveness acceptability curve was calculated after the PSA results were obtained, showing the probability of each TKI drug being cost-effective across a range of possible values of willingness-to-pay (WTP) for an additional QALY [66]. Depending on the characteristics of each variable, different types of probability distributions were applied, namely gamma distributions for costs, beta for utilities, and Dirichlet for transition probabilities.

3. Results

3.1. Base-case analysis

Effectiveness and costs were outlined according to each treatment and were summarized in Table 3. The highest QALY per patient was observed in patients who received osimertinib (0.49), followed by patients who received dacomitinib (0.33), afatinib (0.32), erlotinib (0.31), and gefitinib (0.28). Furthermore, afatinib was associated with the lowest total costs (€22,859) and osimertinib with the highest total costs (€56,881). It was seen that in Spain, no treatment strategy was cost-effective with a WTP threshold of €24.000/QALY. When compared to gefitinib, the most cost-effective therapy was erlotinib with an ICER of €36,196 per QALY gained, followed by osimertinib with an ICER of €166,416/QALY.

3.2. Deterministic sensitivity analysis

The results of the DSA for each drug are represented in the four tornado diagrams in Figure 2. The DSA showed significant changes in the ICER, after modifying acquisition costs and OS values in each drug. However, only when the acquisition cost is reduced by 40% for erlotinib and 70% for osimertinib, do we obtain an ICER value below the threshold of 24,000€ per QALY gained, which is fixed in Spain? For all other parameter variations, when the acquisition cost is reduced by 40% the ICER of each drug comparison exceeded the WTP per QALY for Spain.

Figure 3 shows the four scatter plots of Monte Carlo probabilistic sensitivity analysis. For erlotinib versus gefitinib, about

Table 3. Cost-effectiveness results.

	Treatment cost/pt	Disease management cost/pt	Adverse events cost/pt	End-of-life care cost/pt	2 L cost/pt	Total Cost/pt	LYG/ pt	QALY/ pt	ICER (€/QALY)
Gefitinib	22,859	1,114	16	12,922	7,655	44,566	0.48	0.28	-
Erlotinib	23,994	1,071	6	12,912	7,655	45,638	0.52	0.31	36,196
Afatinib	29,672	1261	49	12,905	7,655	51,542	0.45	0.32	167,554
Dacomitinib	31,850	975	36	12,922	7,655	53,438	0.47	0.33	183,682
Osimertinib	56,881	2008	6	12,807	5,935	77,637	0.64	0.49	166,416

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; 2 L: second-line; pt: patient.

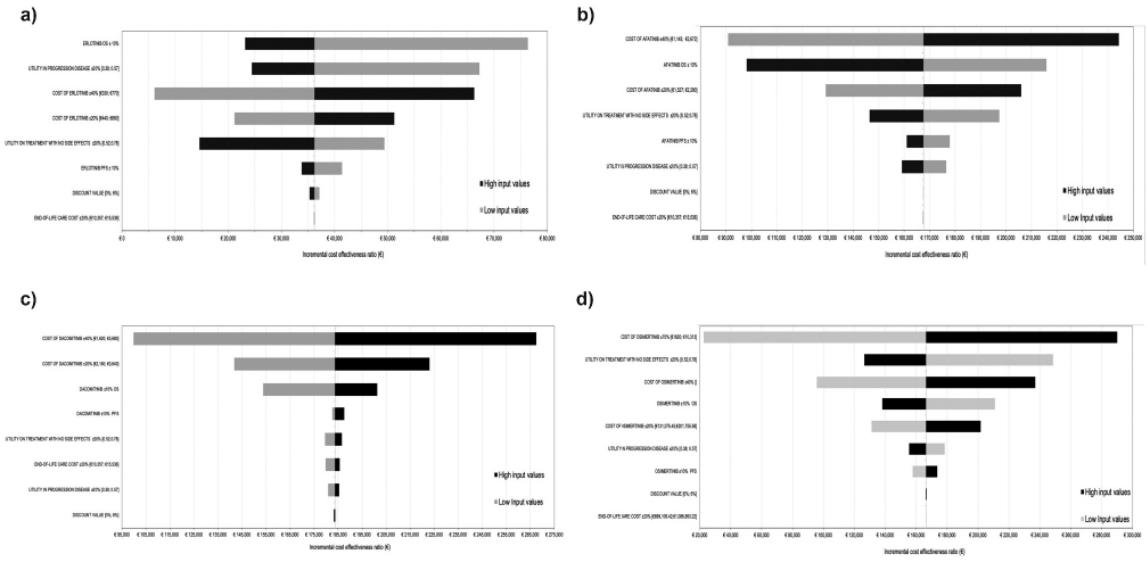

Figure 2. Tornado diagram representing one-way sensitivity analyses with changing baseline parameters. Comparisons represented: (a) erlotinib vs. gefitinib, (b) Afatinib vs. gefitinib, (c) dacomitinib vs. gefitinib and (d) osimertinib vs. gefitinib.

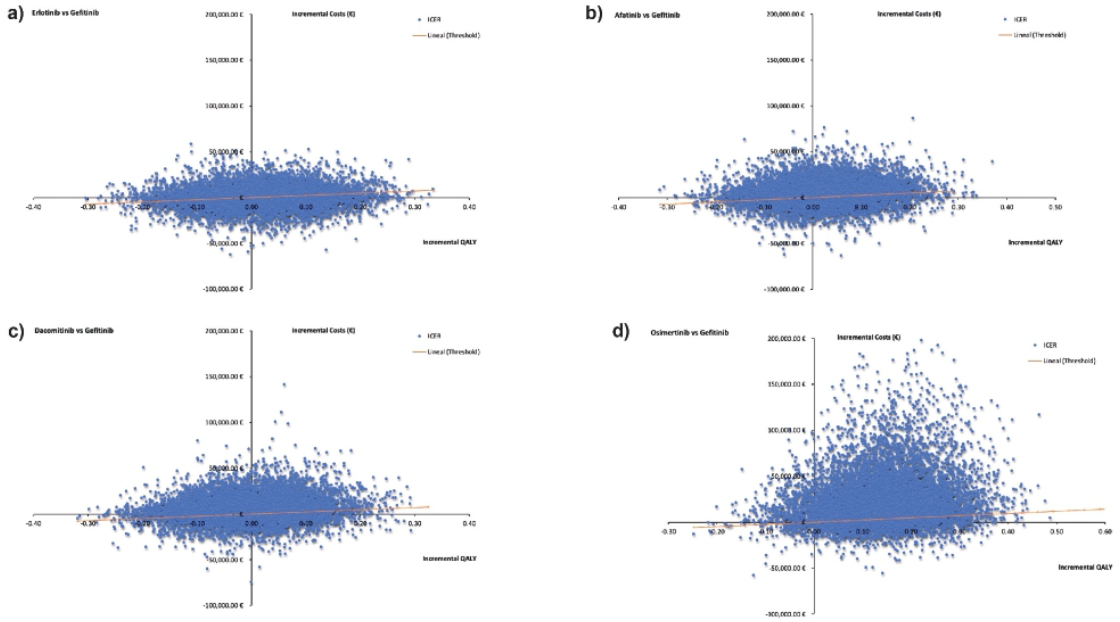

Figure 3. Scatter plot of monte carlo probabilistic sensitivity analysis for (a) erlotinib vs. gefitinib, (b) afatinib vs. gefitinib, (c) dacomitinib vs. gefitinib, and (d) osimertinib vs. gefitinib.

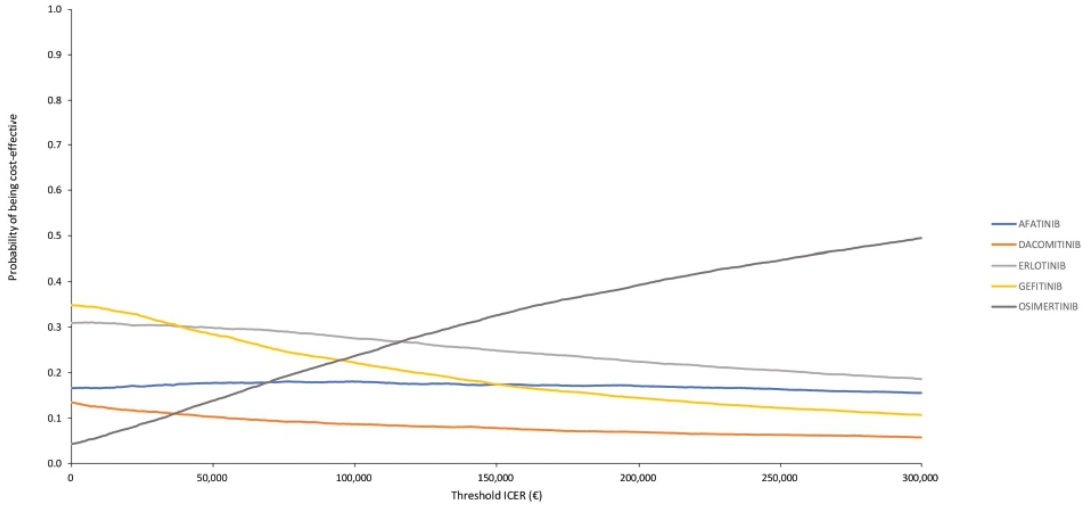

Figure 4. Cost-effectiveness acceptability curve demonstrating the probability at different WTP levels for erlotinib vs. gefitinib (a), afatinib vs. gefitinib (b), dacomitinib vs. gefitinib (c), and osimertinib vs. gefitinib (d). Graph plot WTP scenario (x-axis) vs. Likelihood in percentage that the treatment would be considered cost-effective (y-axis). ICER: incremental cost-effectiveness ratio; WTP: willingness to pay.

25.70% of the PSA iterations were dominant, 23.54% of the PSA iterations were cost-effective, 19.91% were dominated, and 30.85% were non-cost-effective.

The cost-effectiveness acceptability curve (CEAC) is shown in Figure 4 for varying values of WTP. It showed that with a Spanish threshold of €24,000/QALY, gefitinib had the highest probability of being cost-effective (32.56%). Meanwhile, erlotinib, afatinib, dacomitinib, and osimertinib had a probability of 30.43%, 16.96%, 11.49%, and 8.56%, respectively. Finally, at a threshold of €300,000/QALY, osimertinib demonstrated a 50% probability of being cost-effective.

4. Discussion

In the context of limited resources, the economic evaluation of the impact of different treatments for NSCLC EGFR+ could

become an essential tool for clinicians and policymakers to select the best cost-effectiveness treatment for patients and sustainability of the Spanish National Health System. At the time of this study, this was the first cost-effectiveness analysis that compared first-line gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib in patients with stage IIIB/IV NSCLC EGFR-mutated in the context of Spain. Our study demonstrated that over a 15-year time horizon, osimertinib was slightly more effective in terms of QALYs gained than gefitinib (0.20), followed by dacomitinib (0.05), afatinib (0.04), and erlotinib (0.03). Nevertheless, the results showed that with the current WTP threshold in Spain (€24,000/QALY), none of the TKIs were cost-effective when compared to standard first-generation EGFR-TKI, gefitinib, for patients diagnosed with advanced NSCLC EGFR-positive. Although the ICER threshold selected can be considered rigorous, this value is similar to that used in other studies conducted in the same setting [67–70]. According to the study conducted by Cameron et al. describing the 'official thresholds' for 17 countries, €24,000 per QALY threshold appears to be much lower than the 'official thresholds' used in other countries such as Portugal (€31,890), Sweden (€50,173), or The Netherlands (€80,000) [71]. However, it is difficult to compare these thresholds across countries because they have been calculated using different methodologies and techniques.

The findings from our study confirm the results of other cost-effectiveness studies, such as Holleman et al. [72], where osimertinib was shown to be the most effective, followed by afatinib, erlotinib, and gefitinib in The Netherlands. However, afatinib was found to be cost-effective (ICER €22,514/QALY) and gefitinib dominant, when compared to gefitinib, respectively. A major difference with respect to our study is that Holleman et al. included only four TKIs and excluded dacomitinib. In line with our results, several economic evaluations published in other countries have shown that osimertinib would not be as cost-effective as a first-line treatment when compared to first-generation and second-generation EGFR TKIs [73,74–77,78]. In two different studies that were conducted, dacomitinib was observed to be cost-effective in China and dominant compared to gefitinib in Portugal [79,80]. However, in our recent study published in Spain, dacomitinib was found not to be cost-effective when compared to gefitinib [81]. For afatinib, our results differ from other economic evaluations published in France, China, and Canada, which showed afatinib to be cost-effective when compared to gefitinib as a first-line treatment in patients with EGFRm NSCLC [82–84].

Our one-way sensitivity analysis showed that all variables that could have a significant impact on the results were included. The two parameters that most influenced the results were OS values and first-line drug treatment costs, which were modified by increasing or decreasing them using the upper or lower boundaries. Hence, only significant changes in those variables would potentially modify the results of the ICER.

Based on the results obtained in the cost-effectiveness plans for each of the EGFR-TKIs, we constructed a cost-effectiveness acceptability curve to determine the probability of cost-effectiveness of each drug for different WTP thresholds. It was deduced from the curve that, with the established cost-effectiveness threshold in Spain (€24,000/QALY) [32], none of the EGFR-TKIs evaluated in this study could be considered cost-effective due to the high acquisition cost of the drugs.

An important strength of our study is that we have selected an NMA that compiles the most important and relevant clinical trials for each of the EGFR TKIs [26], in addition to this, we have updated the mature OS results of osimertinib from the FLAURA study [36]. Furthermore, a novel aspect of our current study was the use of the polynomial fraction methodology using which we obtained the survival values of OS and PFS for each TKI, which could be fitted closely to our data. Hence, assuming constant ratio of hazards implies a constant difference in effectiveness through time; fractional polynomial method can be selected as a better approach over traditional NMA, to assess relative efficacy of TKIs [85]

This study has several limitations. First, due to the lack of head-to-head clinical trials comparing these five first-line TKIs, an NMA in this study was selected for an indirect comparison, although moderate heterogeneity in patient characteristics which was assumed. Second, some key clinical inputs, such as utility values, were extracted from a verified study published in the population of the UK [64] because when the study was conducted, these values were not available in Spain. However, the sensitivity analyses demonstrated only slight impacts on this value. Third, in our study, we have not assessed the cost-effectiveness of TKIs by subgroups (age and sex). This is because the 13 clinical trials we have used were generally similar, both clinically and methodologically, and included only patients with activating EGFR mutations, with the percentage of males ranging from 11% to 47% and the median age range being 56–65 years. Fourth, the comparator chosen for our study has been gefitinib, because it is the alternative with lesser efficacy. Fifth, for second-line treatment we selected the scheme followed in the FLAURA trial because till date, no valid scheme has been established in our country by the Spanish National Health System. Sixth, in our study, we have not evaluated the penetration of EGFR-TKIs into the central nervous system (CNS). Owing to the high incidence of EGFR mutation positivity among patients with brain metastases, ranging between 44 and 63% as opposed to the usually reported 10% incidence of EGFR mutation in all patients diagnosed with NSCLC [86], this could be considered an important limitation. Osimertinib demonstrated better CNS efficacy and activity against both parenchymal brain metastases and leptomeningeal disease and a greater reduction in the risk of CNS progression, as compared to first-generation EGFR-TKIs [21,87,88]. To make further observations, a comprehensive study of this subgroup of patients would be required.

The potential effectiveness of osimertinib, the first third-generation EGFR-TKI, to improve survival was a decisive determinant of clinical and economic results of our study. In Europe, ESMO guidelines recommended first-line treatment with monotherapy of other treatments such as erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib (ESMO

2018). However, in the updated version published on 15 September 2020, the ESMO Guidelines Committee recommended osimertinib as the preferred option for NSCLC patients with sensitizing EGFR mutations instead of first-generation and second-generation EGFR-TKIs [22,23]. However, our findings demonstrated that in the context of Spain, osimertinib could not be considered as a cost-effective option compared to first-generation and second-generation TKIs. Therefore, for osimertinib to be cost-effective in Spain, the acquisition costs of osimertinib will have to be reduced.

5. Conclusion

This study showed that, from the perspective of the Spanish National Health System, none of the treatments proved to be cost-effective for a Spanish threshold of €24,000/QALY. The most effective drug was osimertinib, when compared to gefitinib. However, the ICER obtained for osimertinib versus gefitinib (€166,415/QALY) appears to be too high, for the given Spanish threshold. The price of osimertinib should be reduced by 70%, for it to become a cost-effective alternative.

Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

Our study used mathematical modeling and was not an active clinical trial; therefore, no approval was required from the Institutional Research Ethics Board.

Author contributions

All the authors interpreted the data, read, and approved the final manuscript.

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