JUAN ZAFRA MARTÍN

STEREOTACTIC ABLATIVE RADIOTHERAPY AND IMMUNOTHERAPY IN OLIGOPROGRESSIVE METASTATIC CANCER: CLINICAL RESULTS AND SEARCH FOR BIOMARKERS

DOCTORAL THESIS

Supervised by

Dra. Isabel Barragán Mallofret and Dr. Rodolfo Chicas Sett

Academic Tutor

Dr. Emilio Alba Conejo

PhD Program in Biomedicine, Translational Research and New Health Technologies
Faculty of Medicine

MÁLAGA, 2024

AUTOR: Juan Zafra Martín

https://orcid.org/0000-0003-4778-4271

EDITA: Publicaciones y Divulgación Científica. Universidad de Málaga

UNIVERSIDAD DE MÁLAGA

ANDALUCÍA TECH
Campus de Excelencia Internacional

DECLARACIÓN DE AUTORÍA Y ORIGINALIDAD DE LA TESIS PRESENTADA PARA OBTENER EL TÍTULO DE DOCTOR

D. JUAN ZAFRA MARTÍN
Estudiante del programa de doctorado BIOMEDICINA, INVESTIGACIÓN TRASLACIONAL Y NUEVAS TECNOLOGÍAS EN SALUD de la Universidad de Málaga, autora de la tesis, presentada para la obtención del título de doctor por la Universidad de Málaga, titulada: STEREOTACTIC ABLATIVE RADIOTHERAPY AND IMMUNOTHERAPY IN OLIGOPROGRESSIVE METASTATIC CANCER: CLINICAL RESULTS AND SEARCH FOR BIOMARKERS.
Realizada bajo la tutorización del Dr. EMILIO ALBA CONEJO y dirección de la Dra. ISABEL BARRAGÁN MALLOFRET y el Dr. RODOLFO CHICAS SETT

DECLARO QUE:
La tesis presentada es una obra original que no infringe los derechos de propiedad intelectual ni los derechos de propiedad industrial u otros, conforme al ordenamiento jurídico vigente (Real Decreto Legislativo 1/1996, de 12 de abril, por el que se aprueba el texto refundido de la Ley de Propiedad Intelectual, regularizando, aclarando y armonizando las disposiciones legales vigentes sobre la materia), modificado por la Ley 2/2019, de 1 de marzo.
Igualmente asumo, ante a la Universidad de Málaga y ante cualquier otra instancia, la responsabilidad que pudiera derivarse en caso de plagio de contenidos en la tesis presentada, conforme al ordenamiento jurídico vigente.

En Málaga, a 22 de JUNIO de 2024

Fdo.: JUAN ZAFRA MARTÍN Doctorando	Fdo.: EMILIO ALBA CONEJO Tutor
Fdo.: ISABEL BARRAGÁN MALLOFRET Directora	RODOLFO CHICAS SETT Director

D. Emilio Alba Conejo (tutor),
Catedrático de Oncología del Área de Medicina y Dermatología de la Facultad de Medicina de la Universidad de Málaga

Dra. Isabel Barragán Mallofret (directora),
Investigadora Senior del Programa de Refuerzo de Unidades de Gestión Clínica adscrita al Área de Oncología de la Facultad de Medicina de la Universidad de Málaga

Dr. Rodolfo Chicas Sett (co-director),
Doctor en Medicina por la Universidad Católica de Valencia "San Vicente Mártir" y Especialista en Oncología Radioterápica en el Hospital Universitari i Politècnic La Fe de Valencia

CERTIFICAMOS que D. JUAN ZAFRA MARTÍN
ha obtenido y estudiado personalmente bajo nuestra dirección los datos clínicos necesarios para la realización de su Tesis Doctoral, titulada: "Stereotactic Ablative Radiotherapy and Immunotherapy in Oligoprogressive Metastatic Cancer: Clinical Results and Search for Biomarkers", que consideramos que tiene el contenido y rigor científico necesarios para ser sometido al superior juicio de la Comisión que nombre la Universidad de Málaga para optar a grado de Doctor.

Y que las publicaciones que avalan la presentación de esta tesis en formato de compendio de publicaciones y cuyas referencias son:

1. Chicas-Sett, R., Zafra, J. (equally contributed) (2023). Combination of Stereotactic Ablative Radiotherapy and Systemic Therapy in Oligoprogressive Non-small Cell Lung Cancer. Interdisciplinary Cancer Research. Springer, Cham. https://doi.org/10.1007/16833_2023_171
2. Chicas-Sett R, Zafra J (equally contributed), et al. Combination of SABR With Anti-PD-1 in Oligoprogressive Non-Small Cell Lung Cancer and

Melanoma: Results of a Prospective Multicenter Observational Study. Int J Radiat Oncol Biol Phys. 2022;114(4):655-665. doi:10.1016/j.ijrobp.2022.05.013

3. Zafra J, Onieva JL, et al. Novel Blood Biomarkers for Response Prediction and Monitoring of Stereotactic Ablative Radiotherapy and Immunotherapy in Metastatic Oligoprogressive Lung Cancer. Int. J. Mol. Sci. Int. J. Mol. Sci. 20 Apr. 2024, doi:10.3390/ijms25084533

no han sido utilizadas en tesis anteriores ni en la Universidad de Málaga ni en otras Universidades.

Y para que conste, en cumplimiento de las disposiciones vigentes, expedimos el presente certificado en Málaga el 22 de JUNIO de 2024.

Firman

Directora: Isabel Barragán Mallofret Director: Rodolfo Chicas-Sett

Tutor: Emilio Alba Conejo

AGRADECIMIENTOS

Ya sea en los créditos de una película o un disco, o en una tesis doctoral como la que nos ocupa, percibo que se acostumbra a aprovechar este espacio de agradecimientos de una manera, en cierto sentido, reivindicativa. El que escribe no se libra de ser culpable de esto ocasionalmente. Pero uno, al fin y al cabo, lleva dedicándose ya un número razonable de años a esto de la oncología y ha logrado entender que, por muchos reveses que te haya podido dar la vida, nada se acerca ni remotamente al temor existencial que experimentan las personas que se sientan al otro lado de la mesa en la consulta del hospital. Por eso no quiero caer en la autocomplacencia de asimilar estos años predoctorales a un "viaje del héroe" (soy más de comedia *indie* americana que de tragedia griega). Porque esto no va de hablar de mí, sino de todas las personas que me han ayudado a que pueda estar escribiendo ahora estas palabras.

Agradezco la existencia de esta tesis doctoral en primer lugar, y siempre en primer lugar, a los pacientes y a sus familias. Acudir a la consulta de un oncólogo buscando una solución para una enfermedad grave y salir de allí habiendo aceptado participar en un estudio con la esperanza de beneficiar a pacientes futuros es un acto de una generosidad absoluta. Sin su colaboración, todas estas páginas estarían en blanco. Gracias a todos y cada uno de ellos.

A Isabel Barragán, directora de esta tesis, persona más trabajadora del mundo, mejor jefa sin pretender serlo, farmacéutica que más sabe de oncología radioterápica, y espectadora que acierta todos los años la película ganadora del Festival de Cine de Málaga. Necesitaré bastante tiempo para devolverte una fracción de lo que me has dado, así que espero que sigamos trabajando juntos muchos años.

A Rodolfo Chicas, co-director, mentor, amigo y, en general, modelo vital a seguir. Qué suerte haber coincidido durante cuatro años en una isla en mitad del Atlántico. Decenas de profesores universitarios no consiguieron despertar

en mí una vocación investigadora en seis años y tú lo hiciste en una tarde. Tengo clarísimo que si no te hubiera conocido sería un oncólogo radioterápico muy diferente.

A Emilio Alba, tutor de este doctorado. Me he cruzado con mucha gente buena en estos años en Málaga, pero si hubo una condición primordial y necesaria para ello es que tuvieras la generosidad de querer escucharme cuando era un residente con una idea algo abstracta en la cabeza.

A todos los miembros del Grupo de Investigación Traslacional en Inmunoterapia del Cáncer de IBIMA. A Juanlu por tratar los datos de una forma que sólo se puede definir como hacer magia. A Alberto, que va camino de ser otro mago. A Javi por tener respuesta para todo. A Eli por ser como es. A Bea, Laura, María, Andrea, Jaime y toda la gente que ha pasado por el laboratorio. A las enfermeras que sacan las muestras por aceptar siempre que suba un paciente más. A Antonio Rueda por su apoyo, sus buenos consejos y sus aportaciones fundamentales al proyecto como jefe de grupo.

A la Asociación Española Contra el Cáncer por concederme su Ayuda Clínico Junior, que ha sido imprescindible para abrirme las puertas del mundo de la investigación oncológica. Gracias a todo el personal de la Fundación Científica y de todas las sedes regionales.

A mis compañeros de oncología médica y radioterápica por prestar atención a este *oncólogo equidistante*. A todo el servicio de oncología radioterápica del Hospital Clínico Universitario Virgen de la Victoria. Gracias a médicos, enfermeros, técnicos, radiofísicos, auxiliares, administrativas… Gracias a José Antonio Medina, responsable de despertar mi vocación oncológica hace años y, cosas de la vida, mi actual jefe. Supongo que cuando me animó a ser oncólogo no se imaginó que algunos años después tendría que hacer frente él mismo a una avalancha de pacientes complejos inasumible por ningún servicio que no esté tan bien organizado como el que él dirige (haberlo pensado antes).

A mis amigos de toda la vida: Alberto(s), Chema, Sergio, Jorge, Juan Carlos, Lucía, Gonzalo. A los amigos que han venido después: Juan, Elisa, Laura, Andrés. A mis profesores del colegio *Granada College*. A mis compañeros de oncología radioterápica del Hospital Universitario de Gran Canaria Doctor Negrín por ayudarme a encontrar mi propio camino. A todos los profesionales que han colaborado en los artículos que aquí se presentan.

A mis padres, por enseñarme desde que nací, y todos los días desde entonces, que lo más importante en la vida es ser buena persona. Gracias a los dos por darme todo lo que hay en la vida salvo respuestas simples a preguntas complejas.

A mi hermana Esperanza, la persona más interesante que conozco y, seguramente, la menos autoconsciente de ello.

A mi abuela Victoria, que no pudo verme hacer nada realmente importante, pero en vida me trató como si todos los días completara una tesis doctoral. A mi abuelo Juan, por hacerme sentir orgulloso de llevar su nombre.

A Marta, por permitirme descubrir con ella el lado bueno (y bonito) de las cosas.

"I don't want to achieve immortality through my work. I want to achieve it through not dying".

Woody Allen

RESUMEN EN ESPAÑOL

A pesar de los importantes avances realizados en las últimas décadas, el cáncer continúa siendo una de las principales causas de muerte a nivel mundial. En este contexto, uno de los principales retos es el tratamiento del cáncer metastásico, que actualmente se sigue considerando una enfermedad incurable en la que la terapia sistémica tiene un papel protagonista, pero paliativo. Además, existen tipos tumorales como el cáncer de pulmón no microcítico o el melanoma en los que las quimioterapias tradicionales no han sido útiles para controlar la enfermedad de manera efectiva, resultando en cifras de supervivencia extremadamente bajas.

Afortunadamente, en la última década se ha producido un cambio de paradigma en el tratamiento del cáncer metastásico con la aparición de dos terapias diferentes pero complementarias: la radioterapia estereotáxica ablativa (SABR o SBRT, en sus siglas en inglés) y la inmunoterapia basada en inhibidores de puntos de control inmune (ICI).

Radioterapia estereotáxica ablativa

La radioterapia es una de las modalidades más ampliamente utilizadas en el tratamiento del cáncer. Ideada hace más de 100 años, consiste en la administración de radiación ionizante de manera localizada sobre el tumor con el objetivo de dañar el ADN de las células cancerosas provocando su destrucción. Este enfoque localizado y no invasivo en lo que respecta a su modalidad más extendida (la conocida como radioterapia externa) ha tenido que ir necesariamente acompañado de un desarrollo tecnológico muy pronunciado. Esto ha convertido a la radioterapia moderna en un tratamiento altamente especializado, preciso, hecho a la medida de cada paciente y con un perfil de efectos secundarios muy reducido respecto a otras terapias. La máxima expresión de esta especialización en el campo de la Oncología Radioterápica es la SABR o SBRT, en la que se aprovechan las ventajas en cuanto a control local del hipofraccionamiento extremo junto con una precisión milimétrica en la administración del tratamiento. Estas dos características han convertido a la SABR en una opción curativa equivalente a la cirugía en tumores

como el cáncer de pulmón localizado, pero también en una opción en un novedoso e intrigante campo como es el de la enfermedad oligometastásica.

Enfermedad oligometastásica

El concepto de oligometástasis surge en los años 90 como un estado intermedio entre la enfermedad localizada y diseminada y, por tanto, potencialmente curable con tratamientos sistémicos y/o ablativos locales. Con el desarrollo de la SABR en el siglo XXI, esta definición vuelve a generar interés dado que empieza a ser factible tratar a pacientes metastásicos de forma ablativa sin causar efectos secundarios graves ni interrupciones del tratamiento sistémico. Aunque, al tratarse de un concepto novedoso, no existe aún una evidencia clara acerca de dónde se debe establecer el límite de una enfermedad oligometastásica, los consensos más recientes de las principales sociedades científicas establecen un máximo de cinco lesiones en un máximo de tres órganos, independientemente del tumor primario, basándose en la mejor evidencia disponible hasta la fecha. Adicionalmente, el término oligometástasis ha ido ampliándose recientemente para distinguir situaciones clínicas diferenciales que podrían beneficiarse de añadir un tratamiento local. De esta manera, y en oposición al concepto clásico de oligometástasis sincrónica o de novo, surgen conceptos como oligorrecurrencia, oligopersistencia y oligoprogresión. Aunque todos están siendo objeto de ensayos clínicos, la situación de oligoprogresión es aún más novedosa y plantea una hipótesis disruptiva: ¿puede la SABR ayudar al tratamiento sistémico a que resulte más efectivo? Por definición, una enfermedad oligoprogresiva es aquella en la que, durante un tratamiento sistémico activo, el paciente experimenta una progresión limitada (entre 1 y 5 lesiones) sin repercusión clínica que, de manera estándar, obligaría a suspender el tratamiento e iniciar una nueva línea. Esto puede suponer un perjuicio importante para el paciente al tener que cambiar a un tratamiento que probablemente resultará más tóxico y de efectividad limitada. Es por ello que alargar el beneficio clínico del tratamiento sistémico es fundamental para intentar cronificar la enfermedad metastásica durante el mayor tiempo posible. Este enfoque de tratar de forma ablativa una clona tumoral resistente ya ha sido testado en ensayos clínicos de SABR y terapias

dirigidas para el cáncer de pulmón no microcítico en situación de oligoprogresión, con resultados favorables para la combinación. En el caso de la suma de SABR e inmunoterapia, las potenciales sinergias inmunogénicas entre las dos terapias la convierten en una modalidad de especial interés.

A pesar de que tradicionalmente se ha considerado la radioterapia como un tratamiento únicamente local, existen evidencias de un efecto sistémico adicional desde hace décadas. En los años 50, se acuñó el término "efecto abscopal" para definir una situación clínica en la que un paciente metastásico experimenta una regresión de un tumor no radiado después de recibir radioterapia sobre una lesión a distancia. Este intrigante fenómeno, a pesar de su impacto, era particularmente poco frecuente hasta hace una década. Sin embargo, estudios preclínicos durante décadas acabaron llegando a la conclusión de que este efecto está mediado por la inmunidad, hasta el punto de que existen modelos murinos en los que es posible desencadenar un efecto abscopal de manera reproducible. Sin embargo, este hallazgo en humanos continuó siendo extremadamente raro hasta la aparición de los ICI.

Inmunoterapia

Los ICI son un tipo de inmunoterapia que "levanta el freno del sistema inmune". Para progresar en el organismo, las células tumorales son capaces de aprovechar los mecanismos fisiológicos de tolerancia inmune para evadir a los linfocitos T. Estos puntos de control inmunitarios (PD-1/PD-L1, CTLA-4) son bloqueados por estos fármacos inmunoterápicos, de forma que se interrumpe la interacción inhibitoria, favoreciendo así el efecto citotóxico de los linfocitos. Los ICI se han convertido en el tratamiento de elección en varios tipos de cáncer metastásico, logrando respuestas duraderas nunca vistas anteriormente en muchos tipos tumorales. Sin embargo, existen aún importantes retos por resolver. De entrada, los ICI en monoterapia son inefectivos en hasta el 80% de los pacientes. Además, incluso los pacientes que inicialmente responden pueden desarrollar resistencias secundarias a lo largo del tratamiento. En muchos casos, una vez agotada la opción de la inmunoterapia, las líneas sucesivas son las mismas quimioterapias que tan pobres resultados han ofrecido tradicionalmente. Es por esto que, en el caso de los ICI, es especialmente

importante tratar de mejorar la respuesta sistémica para alargar el beneficio clínico el mayor tiempo posible. Para ello, están surgiendo múltiples combinaciones con inmunoterapia, siendo la adición de SABR una opción particularmente interesante.

Combinación de SABR e inmunoterapia

La radioterapia, especialmente en forma de SABR, es capaz de producir una muerte celular inmunogénica en el tumor radiado, lo cual provoca reclutamiento de células inmunitarias al microambiente tumoral y facilita la presentación antigénica, estimulando de esta manera la activación de linfocitos T citotóxicos. Este efecto inmunomodulador posee sinergias con el mecanismo de acción de los ICI. Esto se ha evidenciado tanto a nivel preclínico como en recientes estudios clínicos que han mostrado mejores tasas de respuesta con la combinación que con inmunoterapia en exclusiva. En el escenario de la oligoprogresión, la posibilidad de reactivar sistema inmune con SABR puede extender el beneficio de los ICI a través de este efecto abscopal y, en el mejor de los casos, lograr respuestas completas duraderas. Sin embargo, la evidencia inicial muestra todavía resultados contradictorios, e incluso en las series más favorables, no todos los pacientes se benefician de esta combinación.

En este sentido, es fundamental seleccionar qué pacientes se pueden beneficiar en mayor medida de este abordaje. No sólo en cuanto a sus variables clínicas, sino también moleculares, con el objetivo de alcanzar una Oncología verdaderamente personalizada. Con este fin, en tiempos recientes se está impulsando el uso de biopsia líquida de muestras biológicas para analizar posibles biomarcadores pronósticos y predictivos, dada la mayor facilidad en la obtención en comparación con la biopsia de tejido sólido, especialmente cuando se pretende recoger múltiples muestras a lo largo del tiempo. El análisis de diferentes parámetros genéticos, epigenéticos y celulares puede ser clave para la identificación de los mejores candidatos para esta combinación y para lograr una mejor caracterización del efecto abscopal en humanos.

Objetivos

El objetivo principal de esta tesis doctoral es describir y contribuir al conocimiento clínico y molecular de la combinación de inmunoterapia basada en ICI y SABR en el escenario de la enfermedad oligoprogresiva.

Este objetivo primario se desarrolla a través de tres objetivos específicos:

- Analizar el estado del arte del tratamiento del paciente metastásico en oligoprogresión y la utilidad de la SABR al combinarla con diferentes tipos de tratamiento sistémico, con un enfoque particular en las sinergias con la inmunoterapia en cáncer de pulmón no microcítico.
- Estudiar el beneficio clínico de la combinación de inmunoterapia y SABR en pacientes oligoprogresivos a través de un estudio prospectivo en el que se analizan variables como la tasa de respuesta objetiva, supervivencia libre de progresión, supervivencia global y toxicidad.
- Identificar biomarcadores de respuesta y/o resistencia a la combinación de inmunoterapia y SABR en oligoprogresión a través de muestras de sangre para biopsia líquida.

Publicaciones y resultados

Cada uno de estos tres objetivos específicos está representado por una publicación científica. Es por este motivo que la presente tesis se presenta en modalidad de "compendio de publicaciones". Esto es un reflejo del enfoque esencialmente práctico de los estudios que han formado parte del doctorado. Más allá de los aspectos de investigación, este proyecto se ha planteado desde su concepción con un objetivo clínico claro: tratar de buscar el beneficio clínico de los pacientes a través de una técnica de radioterapia de vanguardia y altamente especializada. Adicionalmente, y una vez establecido el aporte relevante de esta técnica oncológica, se ha planteado cómo optimizar la selección de pacientes a través del análisis en biopsia líquida de biomarcadores potencialmente relevantes para la predicción y monitorización de la respuesta. Por todo ello, la tesis se compone de tres publicaciones interrelacionadas y que son consecuencia del conocimiento adquirido en cada una de las mismas.

En primer lugar, se presenta un capítulo de libro que supone una extensa revisión del concepto de oligoprogresión metastásica, la utilidad de la SABR en este contexto, las potenciales sinergias con diferentes tipos de tratamiento sistémico y la evidencia disponible que justifica su utilización en cáncer de pulmón no microcítico. En este sentido, destaca la combinación de SABR con inmunoterapia debido a las características particulares de estos dos tratamientos y su relación con el efecto abscopal.

Como continuación de esta publicación, se describe un estudio clínico original realizado por el doctorando en colaboración con sus directores de tesis que incluye 50 pacientes con cáncer de pulmón no microcítico o melanoma metastásico tratados con la combinación de SABR e inmunoterapia tras experimentar una oligoprogresión. Tras una mediana de seguimiento de 33 meses, se obtuvo una tasa de respuesta objetiva del 42%, así como una mediana de supervivencia libre de progresión de 14,2 meses. Este último dato refleja la extensión del beneficio clínico con inmunoterapia que se puede alcanzar con dicha combinación. Hay que destacar que en esta cohorte hubo un grupo de pacientes largos supervivientes que mantuvieron una respuesta completa tras la SABR e incluso finalizaron la inmunoterapia, sin objetivar evidencia de enfermedad tras varios años. Por el contrario, otros pacientes no lograron beneficiarse de la combinación, por lo que progresaron rápidamente. Ante esta situación, no encontramos variables clínicas relevantes que permitieran identificar un perfil de paciente que se beneficia en mayor medida de la adición de SABR tras una oligoprogresión a inmunoterapia. Sin embargo, sí que encontramos que los pacientes que presentaron efecto abscopal según nuestros criterios clínicos tenían una mediana de supervivencia libre de progresión significativamente más alta que aquellos que no. Esto sugiere la existencia de este efecto abscopal inmunomediado que pueda estar determinando la respuesta clínica global en los pacientes.

Finalmente, como respuesta a estos interrogantes, surge el estudio en el que se basa la última publicación de esta tesis. Con un protocolo clínico similar al del anterior trabajo, realizamos un tratamiento de SABR e inmunoterapia en

pacientes con oligoprogresión (en este caso, con cualquier histología tumoral) y, en esta ocasión, añadimos el análisis de biomarcadores a través de biopsia líquida en muestras de sangre extraídas antes, durante y después de la SABR. Adicionalmente, y para estudiar fenómenos específicos de la SABR y de la combinación, incluimos una segunda cohorte de pacientes con oligometástasis de novo u oligorrecurrencia que reciben sólo SABR. La publicación contenida en esta tesis incluye los resultados preliminares a nivel de ADN libre circulante, células sanguíneas periféricas circulantes y vesículas extracelulares en los primeros pacientes reclutados. Aunque este estudio continúa reclutando pacientes, estos primeros datos suponen una primera orientación en torno a marcadores novedosos y no previamente descritos que pueden servir como predictores y/o pronosticadores en este contexto clínico.

Discusión

La revisión en torno al estado del arte del uso de SABR en pacientes en oligoprogresión evidencia que este tipo de radioterapia puede lograr una mejora en las tasas de respuesta ante una situación de resistencia limitada a diferentes tratamientos sistémicos: quimioterapia, terapias dirigidas e inmunoterapia. Los primeros estudios en este sentido sugieren adicionalmente un posible beneficio en supervivencia al alargar el beneficio clínico de los tratamientos sistémicos evitando o retrasando el cambio de línea. Todo esto manteniendo un perfil excelente perfil de seguridad en la mayoría de contextos clínicos y agentes sistémicos. Es por ello que las indicaciones de SABR ante estos escenarios están aumentando en los últimos años. La utilización de SABR sobre lesiones con una progresión limitada durante un tratamiento con terapia anti-EGFR ha demostrado su beneficio clínico en estudios fase II. En el caso de la inmunoterapia, los ensayos clínicos todavía se encuentran en fases más iniciales, aunque desde la publicación reciente del estudio CURB ya contamos con evidencia de un estudio aleatorizado. A pesar de esto, el interés por combinar radioterapia e inmunoterapia está creciendo exponencialmente dados los descubrimientos relevantes que se han ido produciendo en torno al efecto inmunogénico de la radioterapia a nivel preclínico, así como las primeras

evidencias clínicas de este efecto abscopal en pacientes tratados con inmunoterapia.

Aunque existen publicaciones acerca de la combinación prácticamente desde la aparición de los primeros agentes inmunoterápicos, en el momento de iniciar esta tesis doctoral las investigaciones en el escenario de oligoprogresión eran extremadamente escasas. La segunda publicación de este compendio surge con el objetivo de responder, a un nivel clínico prospectivo, a la cuestión de si la SABR puede contribuir a los resultados de pacientes en oligoprogresión a inmunoterapia que mantienen beneficio clínico a la misma y son candidatos a un tratamiento con radioterapia paliativa. En este estudio, incluimos a 50 pacientes metastásicos y en oligoprogresión a anti-PD-1 con cáncer de pulmón no microcítico o melanoma (en ese momento, las dos principales patologías con indicación de inmunoterapia). Al cierre del seguimiento, observamos una tasa de respuesta objetiva del 42% y una mediana de supervivencia libre de progresión de 14,2 meses. Esto denota una extensión del beneficio clínico de la inmunoterapia que permite mantener el mismo agente durante más tiempo. En estos tipos tumorales, es un hallazgo fundamental, dado que las líneas sucesivas suelen basarse en quimioterapias tradicionales que aportan un beneficio mucho más limitado y con una mayor probabilidad de efectos secundarios graves. Además, al tratarse de un estudio iniciado en 2017, la inmunoterapia era la segunda o incluso tercera línea de tratamiento en un porcentaje considerable de los pacientes, lo cual acentuaba aún más la importancia de mantener el mismo agente sistémico durante el mayor tiempo posible. A pesar de estos buenos resultados a nivel estadístico, lo cierto es que no todos los pacientes obtuvieron el mismo beneficio. En el extremo más favorable, un subgrupo de pacientes alcanzó una respuesta completa tras añadir la SABR, obteniendo un beneficio clínico extendido que incluso permitió la finalización de la inmunoterapia al permanecer sin evidencia de enfermedad durante varios años. Por el contrario, otros pacientes progresaron rápidamente a pesar del tratamiento radioterápico. El análisis de las variables clínicas del estudio no nos permitió extraer elementos muy concluyentes a este respecto. Sí es cierto que identificamos que los pacientes que presentaban un efecto abscopal (evaluado mediante los criterios clínicos descritos en el cuerpo del artículo)

conseguían una mediana de supervivencia libre de progresión significativamente mayor que aquellos pacientes que no lograban esta respuesta a distancia (21 vs 3 meses). Esto sugiere la participación de un efecto inmunoestimulador global que puede revertir la resistencia a la inmunoterapia y no únicamente conseguir un efecto citotóxico local sobre las lesiones radiadas.

Para intentar responder a algunas de estas incógnitas, diseñamos un nuevo estudio traslacional con el objetivo de medir biomarcadores en biopsia líquida de muestras sanguíneas obtenidas a lo largo del tiempo en pacientes metastásicos tratados con SABR (T1 basal, T2 tras la primera fracción, T3 tras la última fracción, T4 dos meses post-SABR y TP ante nueva progresión). La tercera y última publicación de esta tesis doctoral describe los primeros resultados disponibles de dicho estudio. En este caso, se incluyen dos cohortes de pacientes: la cohorte A comprende pacientes tratados con inmunoterapia en oligoprogresión a la misma, pero manteniendo la línea sistémica por beneficio clínico, mientras que la cohorte B es un grupo comparativo de pacientes tratados exclusivamente con SABR en el contexto de oligometástasis sincrónica u oligorrecurrencia. A nivel clínico, el artículo describe los resultados preliminares de los 27 primeros pacientes analizados (19 de la cohorte A y 8 de la B), en su mayor parte varones con cáncer de pulmón no microcítico y tratados sobre una única lesión frecuentemente de localización en pulmones o ganglios linfáticos. Con una mediana de seguimiento de seis meses, la última ORR evaluada fue de un 63% sumando ambas cohortes, incluyendo un 26% de respuestas completas. Se trata de una cifra elevada en comparación con otros estudios (y con nuestro anterior trabajo), aunque hay que matizar que se trata de pacientes con un seguimiento aún corto. A nivel traslacional, analizamos las células sanguíneas circulantes periféricas y el ADN libre circulante por citometría de flujo, así como los ARN pequeños contenidos en vesículas extracelulares. La concentración de ADN libre circulante se redujo de forma significativa a lo largo del tratamiento con SABR (de T2 a T3) en pacientes respondedores. Datos similares han sido publicados con análisis de ADN tumoral circulante, pero este es un biomarcador más complejo y costoso de determinar. Nuestros resultados orientan a que el ADN libre circulante podría ser un

marcador precoz de respuesta que se encuentra más ampliamente disponible en nuestro medio y con un menor coste.

Por otra parte, encontramos que los pacientes no respondedores tenían un menor porcentaje de células CD4+ y CD8+PDL1+, así como un mayor porcentaje de CD8+PD1+. Estos tres hallazgos han sido previamente descritos en la literatura y orientan hacia una activación inmune por la SABR. En cuanto a células B, los pacientes respondedores mostraron un menor porcentaje de CD19+ y un mayor porcentaje de CD20+, lo cual sugiere una participación de esta estirpe celular en la respuesta a ICI y SABR.

Por último, el análisis de ARN pequeños de pacientes con cáncer de pulmón no microcítico en la cohorte A desveló una serie de marcadores que se encontraban diferencialmente expresados de forma significativa en T2 entre respondedores y no respondedores. Entre ellos, destacan *RNU2-2P*, un pseudogen que participa en la vía *de* TATA-box binding protein *(TBP),* TATA-box binding protein associated factor 5 (*TAF5*) y general transcription factor IIB (*GTF2B*), y que ha sido descrito anteriormente en cáncer; así como *SNORD1B*, que ha sido descrito previamente como infraexpresado en cáncer de pulmón no microcítico. Finalmente, el micro ARN *hsa-miR-1-3p* contribuye a la progresión del cáncer de pulmón no microcítico y se encontraba infraexpresado en pacientes respondedores. Ninguno de estos biomarcadores de ARN ha sido descritos previamente en la combinación de inmunoterapia con SABR, por lo que suponen un primer paso en este campo y potenciales parámetros de respuesta clínica si se confirman en análisis posteriores que incluyan un mayor número de pacientes y un seguimiento de mayor duración.

Conclusiones

En definitiva, esta tesis doctoral trata un tema de gran actualidad en el campo de la oncología a través de un enfoque multidisciplinar y vanguardista, integrando la información clínica y molecular de los pacientes para identificar biomarcadores predictivos y/o pronósticos que permitan optimizar la selección de los pacientes que más se benefician de la combinación de radioterapia con inmunoterapia. A través de los estudios incluidos en esta tesis, se ha identificado un contexto clínico de oligoprogresión en el que la radioterapia

estereotáxica puede tener un rol determinante, tal y como sugieren los resultados clínicos previamente discutidos. Sin embargo, existe una necesidad imperiosa de identificar factores moleculares que puedan determinar esta respuesta. En la tercera y última publicación de esta tesis, se muestran los primeros resultados de un nuevo estudio enfocado en este objetivo, desarrollando una serie de biomarcadores sanguíneos que parecen permitir separar a los pacientes entre buenos y malos respondedores a la combinación. Si estos resultados se confirman en el futuro, junto con el análisis de otros biomarcadores que se publicarán durante la duración de este estudio, estaremos más cerca de poder predecir la respuesta de un paciente al tratamiento radio-inmunoterápico a través de una muestra de sangre. En este sentido, la presente tesis sienta las bases de esta estrategia traslacional al mismo tiempo que abre nuevas preguntas en este campo de conocimiento que podrán ser objeto de futuras investigaciones.

ABSTRACT

Introduction:

Oligoprogressive disease is a distinct clinical entity that can benefit from the addition of stereotactic radiotherapy (SABR) to systemic therapy. When combined with immune checkpoint inhibitors (ICI), both therapies can act synergistically through a radiation-induced abscopal effect. However, the variables that drive this response in humans remain unclear, and there are no current biomarkers that can help to optimize patient selection for this approach. This thesis aims to describe the current knowledge on this combination and contribute to the evidence in this field through clinical studies on oligoprogression that include biomarker analysis in liquid biopsy.

Methods:

The thesis is presented as a compendium of publications. The first publication is an in-depth review on the combination of SABR with systemic therapy in metastatic oligoprogressive non-small cell lung cancer (NSCLC).

The second publication is a prospective observational study testing the combination of SABR and ICI in oligoprogressive patients with NSCLC or melanoma. SABR is delivered concomitantly with ICI in 35 Gy in 5 fractions. The objective response rate (ORR) is evaluated two months post-SABR and subsequently every three months by RECIST criteria.

The final publication presents a prospective clinical and translational study in two cohorts. Cohort A includes tumor-agnostic patients in oligoprogression to ICI receiving SABR in 35 Gy in 5 fractions. B is a comparative cohort of oligometastatic patients treated with only SABR in ablative doses. Blood samples are gathered before SABR (T1), after the first (T2) and last fractions (T3), two months post-SABR (T4) and at further progression (TP). We assess peripheral blood mononuclear cells (PBMCs), circulating cell-free DNA (cfDNA) and small RNA from extracellular vesicles.

Results:

The review piece shows that SABR is safe and effective when combined with chemotherapy, targeted therapy, and ICI in oligoprogressive disease. The combination with ICI is especially promising given the immune implications of the abscopal effect.

In the first prospective study, 50 patients were included. With a median follow-up of 32.8 months, ORR was 42% (30% complete response and 12% partial response). Median progression-free survival (PFS) was 14.2 months (95% confidence interval, 6.9-29 months) and overall survival (OS) since SABR was 37.4 months (95% confidence interval, 22.9 months-not reached).

Finally, the translational study included the first 27 patients that could be analyzed (cohort A: n = 19; B: n = 8). With a median follow-up of 6 months, the last ORR was 63% (26% complete and 37% partial response). A decrease in cfDNA from T2 to T3 correlated with a good response. At T2, CD8+PD1+ and CD8+PDL1+ cells were increased in non-responders and responders, respectively. At T2, 27 microRNAs were differentially expressed. These are potential biomarkers of response.

Conclusions:

SABR and ICI in metastatic oligoprogressive patients is a safe combination that improves ORR and extends the clinical benefit of ICI,delaying or avoiding a change in systemic therapy. It is of paramount importance to identify clinical and molecular variables that can help in patient selection for this combined approach. PMBCs, cfDNA and EVs are sources of potential biomarkers of early response in this setting.

CONTENTS

LIST OF FIGURES

Figure 3. Heatmap for differential expression at T2 between responders and non-responders in terms of significant micro RNA (miRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA) and piwi-interacting RNA (piRNA). All molecules displayed exhibited differential expression with a p value < 0.05.

Figure 4. Longitudinal analysis of significantly differentially expressed miRNAs between time points.

Figure 5. Graphical representation of the upstream analysis of relevant small RNA in T2 according to Ingenuity Pathway Analysis. **A)** RNU-2P pathway. **B)** SNORD1B pathway.

LIST OF TABLES

GLOSSARY OF TERMS AND ABBREVIATIONS

ALK: anaplastic lymphoma kinase

AR: Abscopal response

ASTRO: American Society of Radiation Oncology

BBB: blood-brain barrier

cfDNA: cell-free DNA

CI: Confidence interval

CNS: Central nervous system

CR: Complete response

CT: Chemotherapy

ctDNA: Circulating tumor DNA

CTLA-4: cytotoxic T-lymphocyte associated protein 4

DAMPs: Damage-associated molecular patterns

ECOG*:* Eastern Cooperative Oncology Group

EGFR: epidermal growth factor receptor

EORTC: European Organization for Research and treatment of Cancer

ESTRO: European Society of Radiation Oncology

EVs: Extracellular vesicles

Fx: Fraction

GTF2B: General transcription factor IIB

HMGB1: High mobility group box 1 protein

HR: Hazard ratio

ICD: Immunogenic cell death

ICI: Immune checkpoint inhibitor

IMRT: Intensity modulated radiotherapy

IPA: Ingenuity Pathway Analysis

iRECIST: immune Response Evaluation Criteria in Solid Tumors

LC: Local control

LINAC: Linear accelerator

MHC-I: Major histocompatibility complex I

NLR: Neutrophil-to-lymphocyte ratio

NSCLC: Non-small cell lung cancer

OMD: Oligometastatic disease

OPD: Oligoprogressive disease

OS: Overall survival

PBMCs: Peripheral blood mononuclear cells

PCA: Principal Component Analysis

PD-1: programmed cell death protein 1

PD-L1: programmed cell death protein 1 ligand

PFS: Progression-free survival

piRNA: Piwi-interacting RNA

PR: partial responses

RT: Radiotherapy

SABR: Stereotactic ablative radiotherapy

SD: Stable disease

SoC: Standard of care

SRS: Stereotactic radiosurgery

TAA: Tumor-associated antigen

TAF5: TATA-box binding protein associated factor 5

TBP: TATA-box binding protein

TGF-ß: Transforming growth factor beta

TKI: Tyrosine kinase inhibitor

TME: Tumor microenvironment

TPS: Tumor proportion score

Treg: T regulatory cell

TT: Targeted therapy

TTNT: Time to next treatment

VMAT: Volumetric modulated arc therapy

WBRT: whole-brain radiotherapy

CHAPTER I: INTRODUCTION

1. The oligometastatic state

The current state of metastatic cancer

Over the last few decades, cancer survival and cures have progressively increased [1]. However, metastatic disease in particular remains a considerable challenge. Currently, it is considered an incurable disease in which systemic therapy is, albeit the primary treatment choice, merely a palliative approach [2]. Furthermore, certain tumor types such as metastatic non-small cell lung cancer (NSCLC) and melanoma are especially aggressive and unresponsive to traditional chemotherapies. For this reason, survival rates in patients with these tumors have remained extremely low for decades, with median overall survival (OS) of less than a year both in NSCLC and melanoma [3,4].

However, in the last decade there has been a true paradigm shift in the treatment of metastatic cancer with the development of two distinct but complementary therapies: stereotactic ablative radiotherapy (SABR, or SBRT) [5] and immunotherapy in the form of immune checkpoint inhibitors (ICI) [6]. These new approaches are extending cancer survival and even questioning the idea of metastatic cancer as an incurable disease, particularly in cases of oligometastasis.

Definition of oligometastasis

The concept of oligometastasis was coined in 1995 by Hellman and Weichselbaum as an intermediate stage between localized cancer and metastatic disease that could benefit from metastasis-directed therapies with curative intent [7]. These include surgery, SABR and locally ablative therapies such as thermoablation, radiofrequency ablation, etc. [8]. At present, given that there are no biomarkers available that can identify true oligometastatic disease (OMD), its diagnosis is based on imaging. The two main consensus documents define OMD as cases with up to five lesions in up to three different organs, independently of the primary tumor [9,10]. To note, the consensus of

the European Society of Radiation Oncology (ESTRO) and the American Society of Radiation Oncology (ASTRO) establish that OMD should probably not be defined by a set number of tumor sites, but rather by the ability to safely deliver SABR to all sites together with the aid of biomarkers of oligometastasis [9].

These consensus documents further subdivide the concept of OMD into distinct categories. In this regard, there is an important distinction to be made between patients with "genuine" OMD and those with prior polymetastatic disease that have become oligometastatic after systemic therapy (*induced* OMD). Moreover, patients with genuine OMD can have upfront oligometastases (*de novo* OMD) or *repeat* oligometastases after a prior history of OMD (**Figure 1**).

Based on the response during treatment, three particular cases of OMD can be defined:

- Oligopersistence: in which a limited number of lesions remain under active systemic therapy.
- Oligorecurrence: new limited lesions after a systemic therapy-free interval.
- Oligoprogression: progression in a limited number of lesions under active systemic therapy.

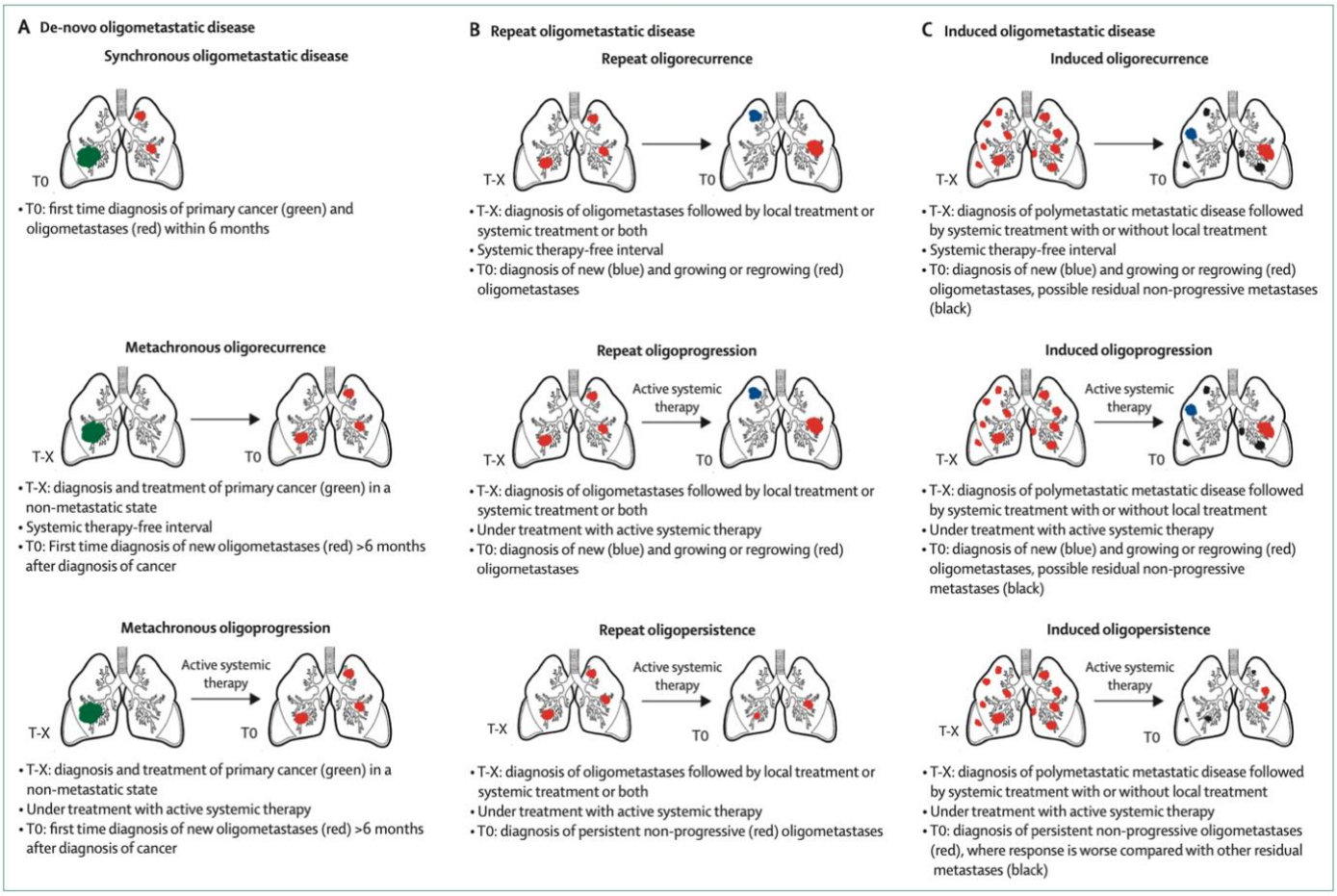

Figure 1. Illustration of the oligometastatic disease classification system [10]. (A) De-novo oligometastatic disease. (B) Induced oligometastatic disease. (C) Repeat oligometastatic disease. T0=at this current point of time. T-x=any previous point in time.

The case for oligoprogressive disease

Oligoprogression has garnered a special interest in recent years due to the advances in systemic therapy and SABR. New systemic agents offer significant advantages over traditional chemotherapy in many types of metastatic cancer, which has reinforced the need to extend the clinical benefit of systemic therapy for as long as possible. This idea has led to a groundbreaking hypothesis: could SABR to oligoprogressive sites help systemic therapy to be effective in more patients and for an extended period of time? This doctoral thesis aims to shed some light on this intriguing topic.

2. Systemic therapy in metastatic cancer

Chemotherapy

Systemic agents are the cornerstone treatment for metastatic cancer [1]. For many decades, systemic therapy has mostly been synonymous with chemotherapy. Even today, chemotherapy is still the treatment of choice in many tumor types, including breast cancer, colorectal cancer, or sarcomas [11-13]. Chemotherapy mainly possesses a cytotoxic effect through DNA damage to tumor cells [14]. However, these agents offer modest benefits in many cancers, and toxicity usually limits the continuation of treatment for an extended time [15]. For instance, three-year survival in NSCLC with standard chemotherapy is less than 5% [16].

Targeted therapy

This problem was partially overcome by the development of targeted therapies (TT) that point towards specific molecular receptors with certain alterations known as driver mutations [17]. In patients with these mutations, TT can be far more effective than chemotherapy and are currently the first line treatment in epidermal growth factor receptor (EGFR)+ and anaplastic lymphoma kinase (ALK)+ NSCLC, [18] as well as BRAF-mutated melanoma [19]. Some of these agents can even surpass the blood-brain barrier and, therefore, be effective for brain metastases, which is a considerable limitation of most chemotherapies [20]. Moreover, side effects are usually milder than those of chemotherapy, and many of these agents can be administered orally instead of intravenously, which adds to this more convenient profile [21].

Despite these advantages, patients with driver mutations usually represent less than 10% of cases, which puts into perspective the fact that TT are not widely useful across many cancers [22].

Immunotherapy

The situation is quite different for ICI. Although immunotherapies have been used in cancer for decades, the current use of the term mainly refers to drugs that target two immune-related receptors: the axis formed by programmed cell

death protein 1 (PD-1) and its ligand (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4). These molecules are known as immune checkpoints: they are part of the physiological process of immune tolerance (CTLA-4 regulates the priming of T lymphocytes in the lymph nodes and PD-1/PD-L1 regulates their cytotoxic effect) [23]. Tumor cells can take advantage of these interactions to induce immunosuppression and escape the immune system [24]. By blocking these interactions, ICI agents (anti-PD-1/L1, anti-CTLA-4) "take the brakes off" the immune system and allows for an effective T cell function [25]. These mechanisms are represented in **Figure 2**.

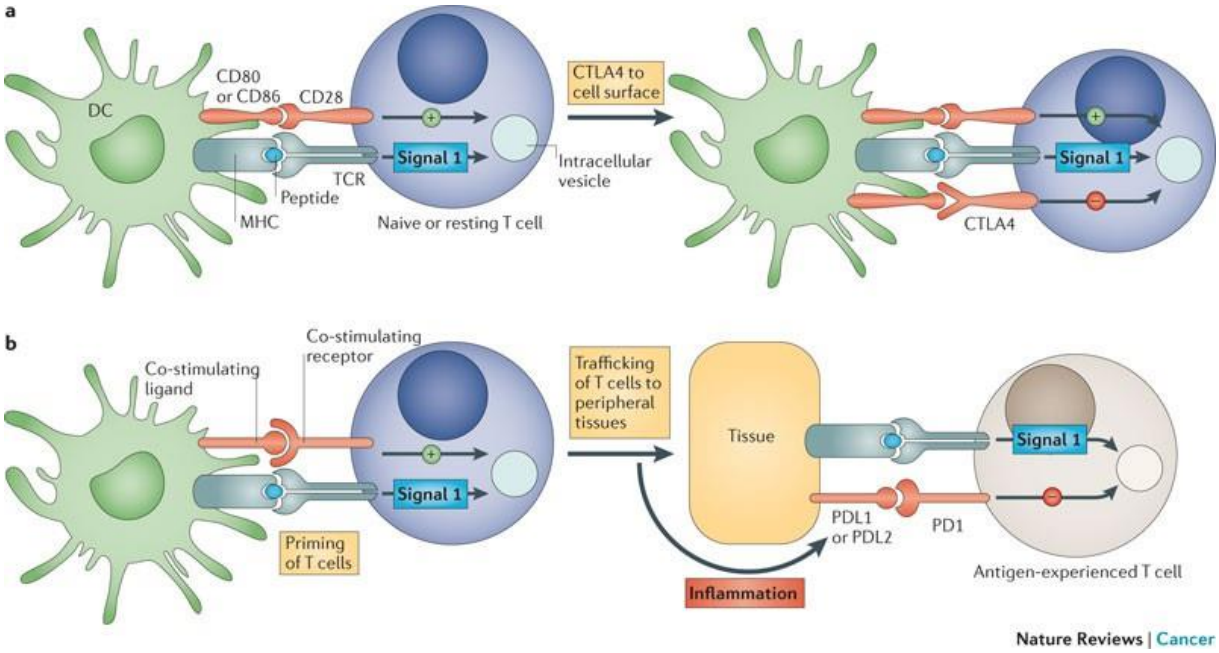

Figure 2. Biological mechanisms of the immune checkpoints CTLA-4 (a) and PD-1/PD-L1 (b) [26].

Since their introduction a decade ago, ICI have been tested in several clinical trials for different tumor types. Not only have they proven to be more effective than standard of care (SoC) systemic therapy in many metastatic cancers but has also shown a better toxicity profile (especially in the case of anti-PD-1/L1

drugs) [27]. ICI are currently the first line of therapy in NSCLC and melanoma [28,29]. Moreover, they are also effective in other tumors such as bladder, renal cell and head and neck cancer, among others [30].

Immunotherapy has revolutionized the treatment of metastatic cancer. A paradigmatic case is NSCLC, in which five-year survival with ICI has improved to more than 30% [31]. Despite these encouraging facts, ICI have introduced a new set of questions and challenges in the field of Oncology.

Limitations

The main issue with ICI is that only 20 to 30% of patients actually respond to monotherapy [32]. Moreover, many patients who do respond end up developing secondary resistances to immunotherapy over time [33]. This constitutes a very complex challenge given that, in most cases, further lines of therapy are the SoC chemotherapies of the past that did not offer favorable results. Currently, these primary and secondary resistances are trying to be overcome by combining ICI with other treatment modalities [34]. A prime example is chemotherapy, with can improve response rates compared to ICI alone, although with the corresponding increase in toxicity [35]. Double ICI is approved in certain tumor types such as melanoma, also with better response rates and higher toxicity [35]. Combinations with TT, as well as new immunotherapy agents, are being investigated in clinical trials [34]. In this regard, the combination with radiotherapy (RT), particularly in the form of SABR has shown promise due to it being an effective and safe treatment and with intriguing synergistic immune-related effects [36].

3. Stereotactic radiotherapy in metastatic cancer

Definition and history

SABR is a type of radiotherapy that delivers high doses of ionizing radiation in very few fractions (fx), usually one to five. This is performed with state-of-the-art technology that allows for an extremely precise, conformed, and non-invasive treatment that offers an excellent toxicity profile [37].

The term "stereotactic" originates from a frame-based coordinate system developed for precise neurosurgery [38]. The concept of stereotactic radiosurgery (SRS) was coined in the 50s to unite stereotaxy to radiation therapy, but was further developed during the 80s with the introduction of linear accelerators (LINACs). This allowed for the delivery of extremely high doses of RT to brain locations in a single fraction, including those not accessible by surgery. The delivery of SRS in a single fraction takes advantage of the ablative effect of radiation by transcending the principles of the traditional linear quadratic model of conventional RT, therefore destroying tumor tissue while preserving normal cells with millimetric precision [39]. SABR as a concept was established once this SRS technique was translated to extracranial sites as a form of extreme hypofractionation (generally, no more than 5 fx) [37]. This also exploits the ablative properties of RT, but with the added properties of fractionation in terms of immune modulation [40].

Clinical evidence

SABR has seen a rapid development in this century due to the progress in the technology to deliver precise RT, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) [41]. Evidence in this field first focused on localized scenarios such as early-stage lung cancer, where SBRT has demonstrated local control rates that are equivalent to surgery and is currently the standard of care in inoperable patients or those who refuse surgery [42]. More recently, a phase II study has positioned SABR as an equally effective alternative to surgery in inoperable cases of localized kidney cancer [43].

Together with these curative intent scenarios, SABR is increasingly being employed as an ablative treatment in the context of OMD [44]. In this regard, a study of paramount importance for SABR in OMD has been the SABR-COMET trial [45]. This was a phase II study that randomized 99 oligometastatic patients (up to five metastases) with different tumor types to receive either the standard of care systemic therapy or the standard of care + SABR to all metastatic sites. The extended long-term outcomes of study after eight years of follow-up showed striking results. Patients in the SABR arm had a significant benefit in 8-year OS (27.2% vs 13.2%; HR, 0.50; 95% CI, 0.30-0.84; P = 0.008). Interestingly, estimated 8-year progression-free survival (PFS) was 0% in the control group vs 21.2% in the experimental arm (HR, 0.45; 95% CI, 0.28-0.72; P < .001). Considering the long-term follow-up, these results could suggest that some of these patients may be cured from their OMD with this combined approach. This benefit is trying to be confirmed in two ongoing studies: COMET-3 (patients with up to three metastases) and COMET-10 (up to ten) [46].

Several studies focused a single tumor type have further provided positive data in this oligometastatic context: OliGomez [47] and Iyengar et al. [48] in NSCLC, ORIOLE [49] and STOMP [50] in prostate cancer, and several more trials are ongoing [51].

The innate characteristics and growing evidence of SABR make it a prime candidate to combine it with systemic therapy in OMD in terms of local control and safety [52]. But more interestingly, it offers a potential synergy with current ICI-based immunotherapies.

The abscopal effect

In the 1950s, Mole described a curious phenomenon which he called “abscopal effect” [53]. This was observed when a metastatic patient who received RT to one site of disease experimented a regression in distant metastases that had not been irradiated. This occurrence challenged the idea of RT being an exclusively local treatment. However, since the introduction of the concept, the abscopal response had been extraordinarily infrequent, with just 46 cases reported worldwide until recently [54]. Nonetheless, preclinical investigations around this phenomenon continued over the following decades, establishing

that the abscopal effect was mediated by the immune system [55]. Coincidentally, the introduction of ICI in clinical practice ten years ago saw an exponential growth of abscopal responses in the literature [56], even with subgroup analyses of pivotal immunotherapy trials suggesting improved survival in patients who received some form of RT [57]. The development of SABR in OMD, the approval of ICI in more and more types of metastatic cancer and the discovery of the immunostimulatory properties of RT and, especially, SABR have created a perfect breeding ground for the in-depth study of the potential benefits of this combination [58].

4. Combination of SABR and immunotherapy

Biological basis

At a molecular level, RT can produce two types of damage: sublethal and lethal. Sublethal damage is based on the accumulation of DNA mutations that do not allow cancer cells to divide, therefore dying by apoptosis. This damage is more characteristic of conventional RT. With higher doses per fraction as in SABR, lethal or ablative damage is more predominant, causing tumor cells to die by necrosis [59]. A third type of damage known as immunogenic cell death (ICD) has gained interest in recent years. This a kind of apoptosis that can provoke an immune response against tumor neoantigens (TAAs) contained inside tumor cells but released after their death [60]. RT, and more frequently SABR, have been shown to induce this ICD [61].

RT possesses effects both in the innate and adaptative immune systems [62]. When delivered, radiation produces inflammation that induces the release of heat shock proteins, damage-associated molecular patterns (DAMPs), high mobility group box 1 protein (HMGB1) and numerous cytokines, all which favor the recruitment of immune cells to the tumor microenvironment (TME). At this point, dendritic cells are able to identify the TAAs released at the TME after radiation-induced ICD and take them to the lymph nodes to present them to naïve T cells. These causes their activation into cytotoxic T cells than can therefore travel to distant non-irradiated sites to unleash an abscopal response. Furthermore, in the presence of ICI, T cell effector function will not be hindered, and antitumor activity will be enhanced. This phenomenon is represented in **Figure 3**. In short, RT serves as an in-situ vaccination for T-cell priming [63].

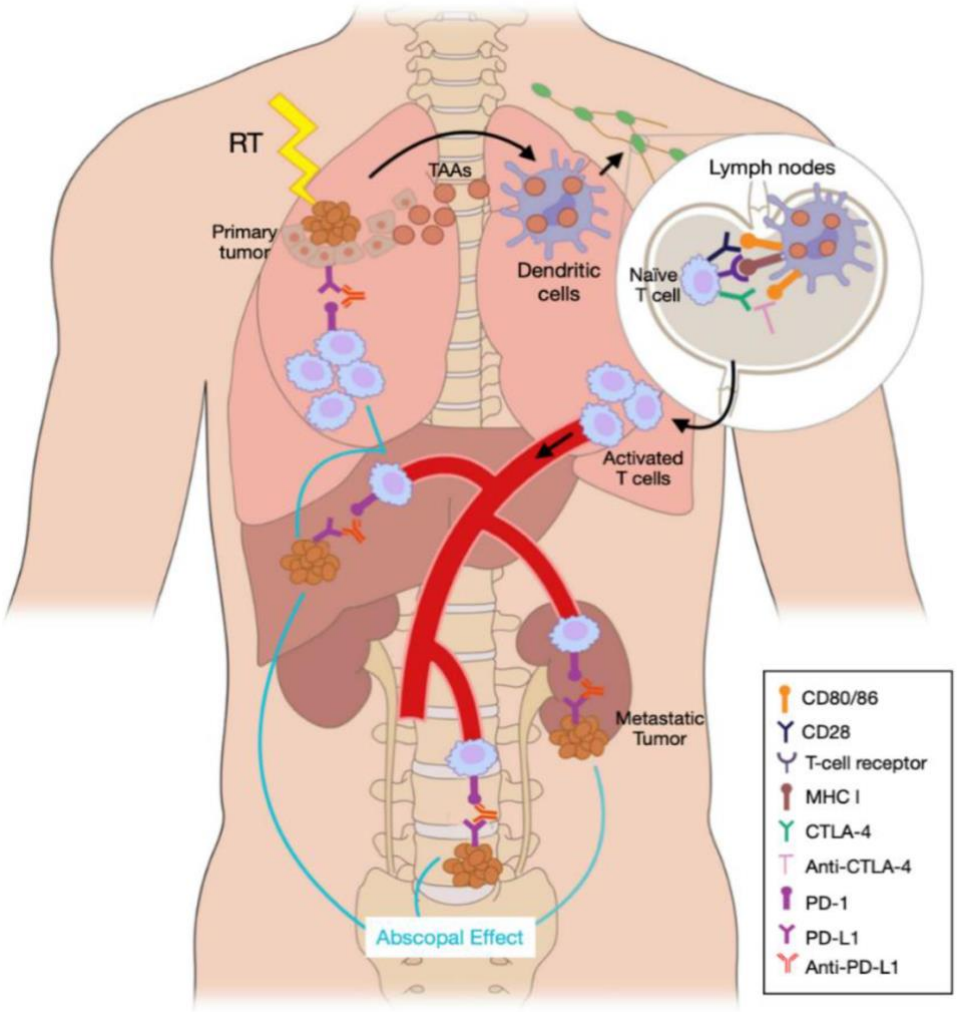

Figure 3. Visual representation of the interaction between radiotherapy and immunotherapy [36]. When delivered to the tumor, radiotherapy (RT) induces immunogenic cell death and the release of tumor-associated antigens (TAAs) nearby. Dendritic cells (DC) recognize these TAAs and carry them to the lymph nodes, where they present them to naïve $CD8^+$ T cells through the major histocompatibility complex I (MHC I) and CD80/86 and CD28 receptors. At this point, anti-cytotoxic T lymphocyte-associated antigen (CTLA)-4 agents block the CTLA-4 receptor in naïve T cells, which ceases their inhibition. Activated cytotoxic T cells are then incorporated into the bloodstream and travel to distant metastases and back to the irradiated tumor to eliminate the disease. At this stage, anti-PD-1/L1 therapy blocks the interaction between these two receptors, which allows for a stronger antitumor effect driven by T cells.

While abscopal effects can be unleashed consistently in murine models [64], this response in humans is more complex. This is partly due to the fact that radiation also possesses immunosuppressive effects. For instance, lymphocytes are very sensitive to RT and can be destroyed even with low doses [65]. Moreover, RT can also stimulate the release of transforming growth factor beta (TGF-ß) [66] and induce an increase in T regulatory cells (Tregs) [67]. Numerous factors such as dose, fractionation, treatment timing and sequence, number of treated sites and location, among others, have been described to alter the balance between these immunosuppressive and immunostimulatory effects [68].

Variables involved in the abscopal effect

One of the main limitations in the design of clinical trials that test the efficacy of SABR and ICI is the complex web of patient and treatment variables that can play a part in the outcomes of this combination. Some of these include:

- Dose and fractionation: While the optimal RT plan is not yet established, SABR has been shown to be more immunogenic than normofractionated RT due to its higher doses per fraction [69]. However, it remains unclear whether ablative doses as used in SABR treatments with curative intent are ideal in the context of the combination with ICI. Doses of >12 Gy per fraction can lead to immunosuppression by removing the trigger from the STING pathway through the upregulation of TREX1 [70]. Nonetheless, both ablative and subablative doses have been used in clinical trials with positive results, so this aspect in still under debate [36]. Recent data even suggests that RT fx of as low as 0.5 Gy could be employed to stimulate the immune response when paired with ICI [71].

- Treatment timing and sequence: Although these variables are still under investigation, concurrent SABR and ICI as opposed to sequential has shown better results in recent studies [72,73]. This is a safe approach that avoids the interruption of systemic therapy in order to deliver RT. In the case of brain metastases, upfront RT has shown an impact in

survival when followed by ICI [74] by avoiding the need for continuous high doses of corticosteroids to manage neurological symptoms [75]. SABR in non-consecutive fractions separated by at least 36 hours is preferred as it allows for lymphocyte repopulation [76].

- Location and number of lesions: Early studies evaluating the abscopal effect delivered SABR to just a single site in hope of eliciting a distant response [77]. However, this is currently considered inefficient, as treating multiple lesions may unleash the presentation of a wider variety of TAAs from a greater number of tumor subclones, therefore improving the systemic response [68]. Moreover, in patients with up to five metastases in total, evidence from clinical trials on OMD shows that SABR to all sites is the most effective course of action [9]. The location of these metastatic is also a factor to consider. Visceral lesions seem to favor a greater immune response than bone metastases [78,79]. Elective nodal irradiation has been suggested to cause immunosuppression and might explain the poor results from studies testing this combination in head and neck cancer [80]. Finally, bowel irradiation has been suggested to affect the microbiome and impact ICI response [81].

Clinical evidence

The first reports of improved ICI response and abscopal effects with SABR arrived with the introduction of the first approved ICI agent: ipilimumab. Formenti et al. conducted a phase I-II study on 39 patients with metastatic NSCLC treated with ipilimumab and SABR in 28.5 Gy in 3 fx or 30 Gy in 5 fx and reported a 31% disease control rate and a median PFS of 7.1 months. These promising results were achieved while preserving safety, with only 10.3% of grade 3 or higher adverse effects [82].

This study paved the way for a series of trials testing the combination of ICI and SABR (I-SABR), such as COSINR [72], PEMBRO-RT [77] and MDACC [83]. These last two trials were assessed in a pooled analysis. They included 148 immunotherapy-naïve NSCLC patients that were randomized to receive SABR + pembrolizumab vs pembrolizumab alone. Patients in the experimental arm had

a disease control rate of 65.3% vs 43.3% in the control arm (odds ratio 2.51, 95% CI 1.28–4.91; p=0·0071). This benefit also translated into an increased median PFS ((9 months vs 4.4 months) and OS (19.2 vs 8.7 months) in the I-SABR group, with no differences in toxicity [84]. All these trials lead to the idea that I-SABR improves ORR compared to ICI alone. Furthermore, it has a potential benefit in PFS and OS that must be confirmed in phase III studies.

Being a relatively new concept in OMD, evidence in the field of oligoprogression has been scarce for years, but this has changed with the recent publication of the final results of the CURB trial [85]. This was a randomized phase II study that included patients with metastatic NSCLC or breast cancer in oligoprogression to five or less lesions after having received at least one line of systemic therapy. The study included 106 patients who were randomized to receive SoC systemic therapy or SABR to all oligoprogressive sites + SoC and evaluated for PFS as the primary endpoint. Interestingly, patients with breast cancer did not seem to benefit from the addition of SABR, as median PFS was 4.4 months in the SABR group vs 4.2 months in the SoC group (p=0·43). In contrast, patients with NSCLC showed an impressive advantage when treated with SABR, with a median PFS of 10 months vs 2.2 months in the SoC arm (HR 0.41, 95% CI 0.22–0.75; p=0.0·0039). This a more than a four-times increase in median PFS compared to SoC systemic therapy (**Figure 4**). To note, 77% of patients with NSCLC received immunotherapy, 71% were treated with SABR to more than one lesion and 39% were polymetastatic (in the sense that they had more than five lesions in total). Despite the CURB trial being published later, these quality data from a randomized setting further supports the hypothesis and study design that was developed for the second publication in this thesis that will be explained in chapter VII. However, the fact that breast cancer patients did not benefit from the combination, together with other studies that have been negative, such as the STOP trial [86], evidence that there is a need for biomarkers that can improve patient selection.

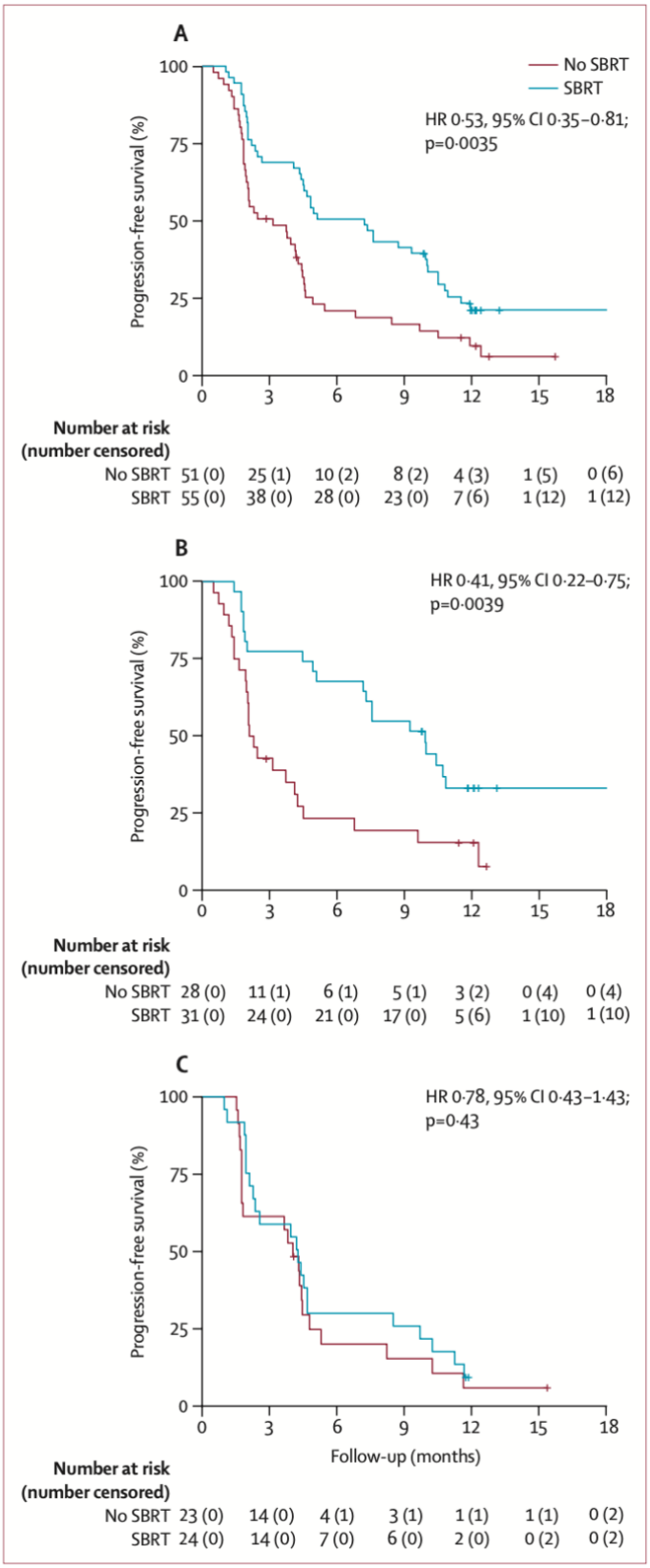

Figure 4. Progression-free survival curves in the CURB trial [85]. A) Entire cohort, B) Non-small cell lung cancer patients, C) Breast cancer patients. *Abbreviations: HR, hazard ratio; SBRT, stereotactic body radiotherapy.*

5. Biomarkers in cancer

Translational research

In the 21st century, advances in Oncology are focused on precision medicine that aims to deliver personalized treatments for each patient [87]. To this end, translational research is a key element for the discovery and generalization of new biomarkers that can improve survival in cancer [88]. Translational research communicates clinical practice with basic science and establishes a symbiotic relationship between these two apparently disconnected spheres. For this bidirectional feedback to be successful, it requires the multidisciplinary collaboration of clinical professionals (radiation and medical oncologists, surgeons, pathologists, radiologists, etc.) and basic researchers (biologists, immunologists, geneticists, bioinformaticians, lab technicians…). Furthermore, and given the large number of patients necessary to identify potentially useful biomarkers, collaborative networks between cancer centers must be established together with an efficient system for the gathering of patient samples [89]. Modern omics analyses are also costly and require adequate funding and must be handled by highly specialized personnel. In this context, it is necessary to select the most convenient type of sample to analyze and prioritize the study of the most promising candidates for biomarkers.

Liquid biopsy

Tumor tissue samples, known as solid biopsies, are the most employed in the analysis of biomarkers in cancer, both diagnostic and therapeutic [90]. However, these present several problems. They usually imply an invasive procedure that can even require hospitalization and general anesthesia, they can be difficult to access, sample quantity may be insufficient, and they might lead to complications such as bleeding and infections [91]. More importantly, these disadvantages make them practically difficult to perform clinical monitorization through longitudinal sampling over time.

For the reasons above, current efforts on the discovery of biomarkers are focusing on liquid biopsy. Liquid biopsy is a minimally invasive technique that allows for the analysis in blood or other biological fluids of cells, DNA fragments

or other molecules with diagnostic and/or therapeutical value. Compared to tissue samples, liquid biopsy is much easier and faster to gather and process, allows for longitudinal sampling, and avoids the problem of intra and intertumoral heterogeneity [92].

Candidate analytes

Despite being a very active field of cancer research, no definitive predictive or prognostic biomarkers have been identified in the context of combined ICI and SABR. Nonetheless, several cells and molecules are promising candidates (**Figure 5**):

- Peripheral blood mononuclear cells (PBMCs): Circulating immune populations can be easily assessed in liquid biopsy [93]. In previous reports, RT has been described to induce an increase in circulating CD4 and CD8 T cells, which suggests an immune activation [94,95]. A high neutrophil-to-lymphocyte ratio (NLR) before and after SABR has also been reported as a predictor of response and survival [96]. Given the considerable amount of preclinical evidence showing an involvement of several other cell types (natural killer cells, B plasma cells, macrophages, Tregs, etc.), their assessment in translational studies on humans is a promising area of research [97].

- Circulating tumor DNA (ctDNA) and cell-free DNA (cfDNA): The analysis of ctDNA as a potential diagnostic and therapeutic biomarkers is being conducted in several clinical trials [98]. In the context of SABR, pre-treatment ctDNA levels have been proposed as a predictor of PFS and OS in oligometastatic NSCLC [99]. However, ctDNA can be expensive and complex to determine in a standard laboratory [100]. For this reason, the concentration of cfDNA could be a valid surrogate that is more widely available for daily clinical practice [101].

- Extracellular vesicles (EVs): These are small vesicles that carry a series of molecules that participate in processes of cellular communication

[102]. A subtype of EVs are exosomes, which contain, among other molecules, fragments collectively known as small RNAs but that are divided in different types: micro RNAs (miRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), among others [103]. Although evidence is still limited, EVs are interesting candidates for early biomarkers of response given that their expression is rapidly influenced by radiation [104] and immunotherapy [105].

- Cytokines: As previously mentioned, the delivery of RT drives the release of several immune-related cytokines. These can be immunostimulatory, like interferon-gamma [106] and interferon type 1 [107], or immunosuppressive, like TGF-β [66]. Cytokines can be easily assessed with ELISA and are interesting biomarkers in terms of response prediction and monitoring.

- DNA methylation: Epigenetics is a very novel area of research. DNA hypermethylation results in the silencing of gene expression, whereas hypomethylation allows for gene upregulation [108]. These interactions drive several key processes in cancer development and progression, and their influence on systemic therapy and RT response is currently being analyzed [109,110].

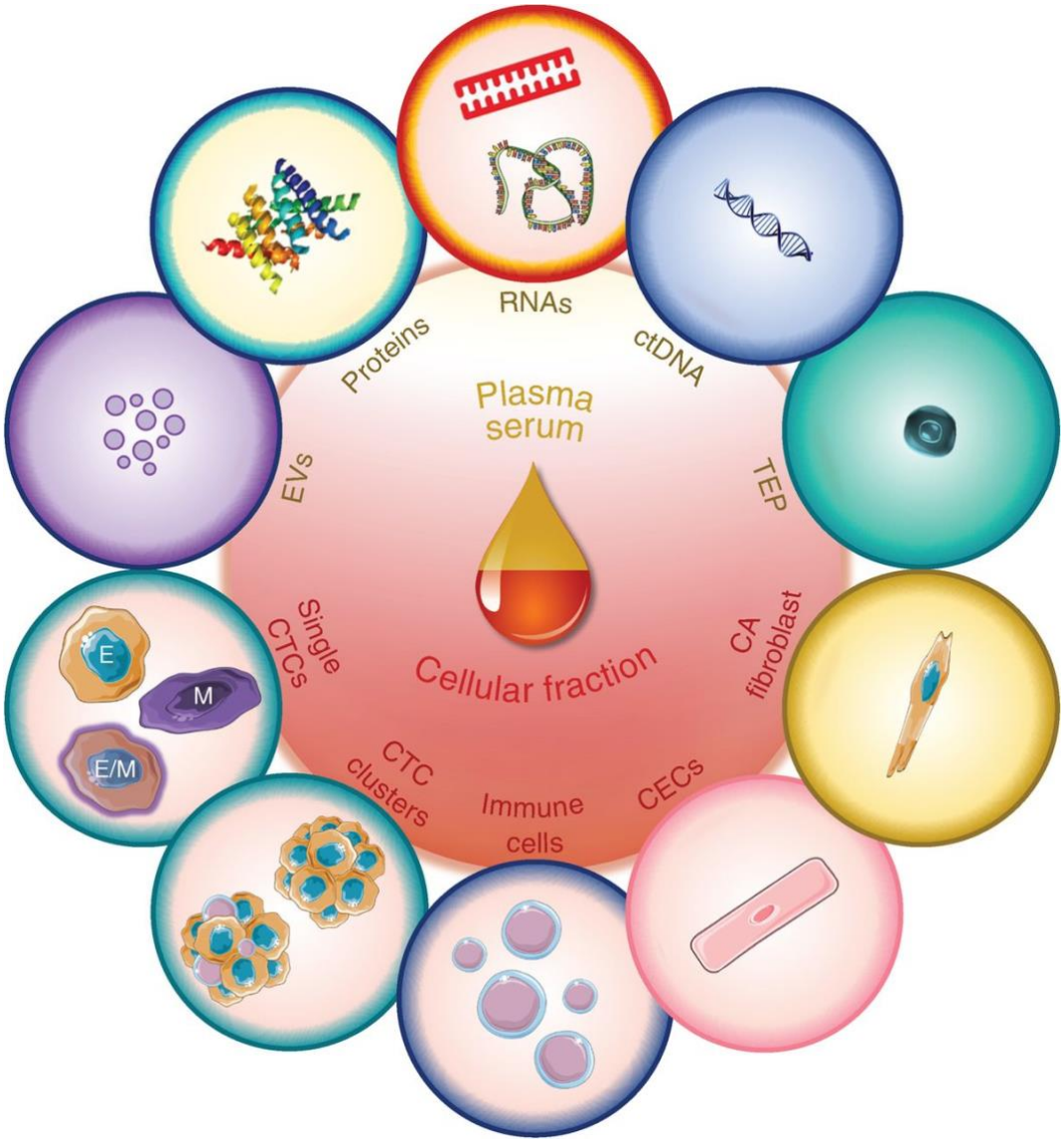

Figure 5. Possible circulating cancer biomarkers in liquid biopsy from blood [111]. *Abbreviations: E, epithelial; M, mesenchymal; EVs, extracellular vesicles; CA fibroblast, cancer-associated fibroblast; CECs, circulating endothelial cells; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; TEP, tumor-educated platelet.*

6. Our clinical and translational protocol

Why oligoprogression to immunotherapy?

Since the conceptualization of this doctoral thesis, we decided to focus our research on one specific subgroup: metastatic patients experiencing oligoprogression while under ICI and treated with SABR to these progressing lesions. As stated along this chapter, SABR may be able to extend the clinical benefit of systemic therapy. This is of paramount importance in patients treated with ICI, as immunotherapy is usually the most effective and safe systemic line. Taking NSCLC as an example, progression to ICI results in a change to successive lines of chemotherapy that offer very poor survival results [4]. To add to this issue, many patients present primary resistance to ICI or develop acquired resistances at some point [33]. In this context, SABR does not only offer excellent rates of local control at oligoprogressive sites but can also unleash a systemic response to overcome systemic ICI resistance [86]. Identifying which patients are going to benefit the most from this abscopal effect is the key aspect in this context.

Patient and treatment characteristics

The studies in this thesis include patients with metastatic cancer in oligoprogression to ICI (up to five lesions) but maintaining the same systemic line due to clinical benefit. These patients are treated with concomitant SABR (generally in 35 Gy in 5 non-consecutive fractions) to all progressing sites. The ORR is assessed two months after the end of SABR and subsequently every three months for the duration of follow-up. To evaluate the abscopal response, prior to SABR, we select up to two out-of-field lesions and assess if they shrink ≥30% two months after the end of SABR. In the third publication of this thesis, we also include a comparative cohort of oligometastatic patients treated with SABR alone in ablative doses.

Biomarker assessment

In the study described in chapter VIII, we add translational studies to this clinical protocol. We gather blood samples from patients before SABR (T1),

after the first and last SABR fx (T2 and T3), two months after SABR (T4) and in case of further progression (TP). In these samples, we conduct analyses on PBMCs, cfDNA, EVs, cytokines and epigenetics. These molecules are correlated with ORR and survival. In this doctoral thesis, we present the first results of this study in terms of PMBCs, cfDNA and EVs. A detailed description of both the clinical and translational protocols will be provided in the corresponding chapters.

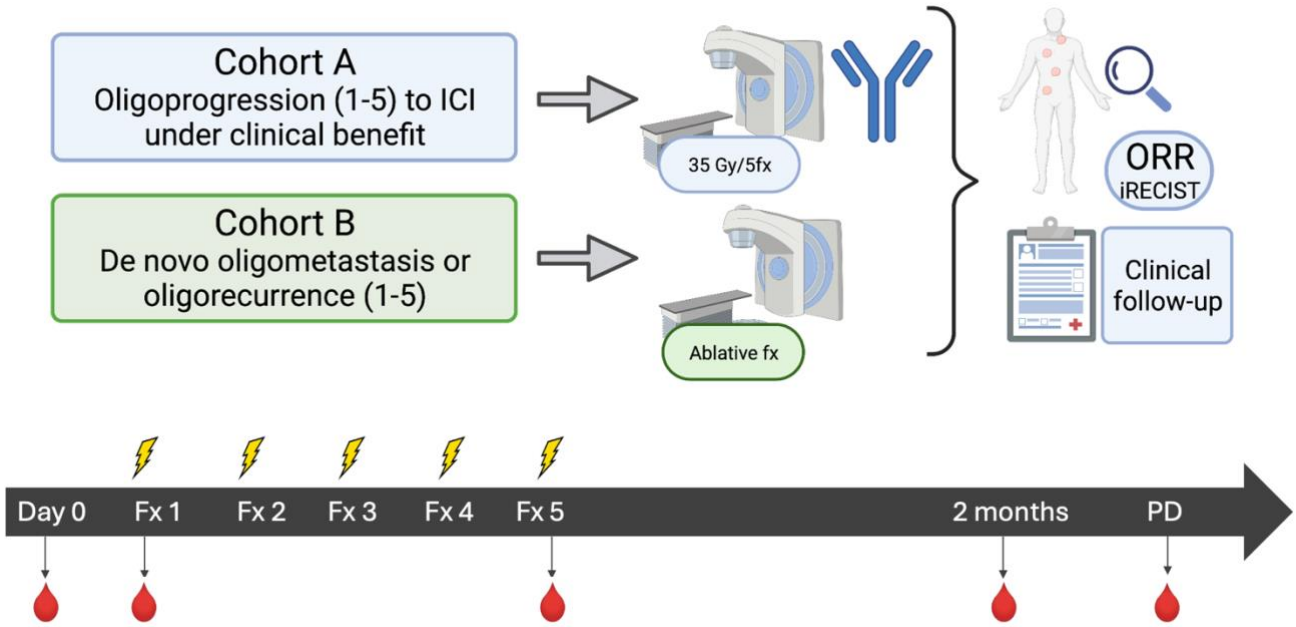

Figure 6. Clinical and translational protocol in our oligoprogression study. *Abbreviations: ICI, immune checkpoint inhibitors; fx: fractions; ORR, objective response rate, iRECIST, immune Response Evaluation Criteria in Solid Tumors; PD, progression disease*. Figure created with biorender.com.

CHAPTER II: AIM AND OBJECTIVES

The aim of this doctoral thesis is to describe the available evidence on the combination of ICI-based immunotherapy and SABR in oligoprogressive disease, as well as contribute to the clinical and molecular knowledge in this nascent field by designing and conducting prospective clinical studies. The hypothesis is that SABR can improve the clinical benefit of ICI in patients who share certain biomarkers than can be identified in liquid biopsy.

This aim is developed over three specific objectives, each of them realized through one scientific publication:

- Objective 1: To analyze the state-of-the-art in the treatment of oligoprogressive metastatic patients and the utility of SABR when combined with different types of systemic therapy. Given the current evidence, this analysis will be focused on NSCLC and the synergies between SABR and ICI. This objective is developed in chapter VI.

- Objective 2: To assess the clinical benefit from the combination of ICI and SABR through a prospective observational study on patients with metastatic NSCLC or melanoma. This benefit is measured in terms of ORR, abscopal response, PFS, OS, local control, and toxicity. This objective is carried out in chapter VII.

- Objective 3: To identify biomarkers of response and/or resistance to the combination of ICI and SABR by analyzing several molecules in liquid biopsy from oligoprogressive patients participating in a clinical prospective study. This objective is addressed in chapter VIII.

The presentation of this thesis as a compendium of publications reflects the essentially practical focus of this aim and objectives. The thesis has been designed considering this clinical focus and the three publications included are interrelated as a consequence of the acquired knowledge in each of them.

CHAPTER III: OVERVIEW OF RESULTS

The findings of this doctoral thesis are explained in detail in chapters VI, VII and VIII. In this chapter, the main results of each publication are summarized.

CHAPTER VI

This first publication is an extensive review on oligoprogressive disease in metastatic NSCLC that is published as a book chapter in the Handbook of Interdisciplinary Cancer Research (Springer, 2023). We review the definition of oligometastatic and oligoprogressive disease, the indications and limitations of current systemic therapy in NSCLC, and the available evidence at the time of writing (2022) on the addition of SABR to chemotherapy, TT and ICI in this context.

In patients with chemotherapy, only consolidative SABR after a first line of systemic therapy has been studied. A number of studies have shown that the combination is safe and effective in terms of response and survival, both with SABR in extracranial disease and SRS in brain metastases [112, 113].

When combined with targeted therapy in ALK+ and EGFR+ patients, SABR and SRS are also safe, but concomitancy is not recommended in brain metastasis or thoracic RT [114]. In extracranial disease, concomitant SABR to oligoprogressive sites was assessed in a phase II trial by Iyengar et al. in patients receiving erlotinib [115]. The combination showed a safe toxicity profile and a median PFS and OS of 14.7 months and 20.4 months, respectively.

Finally, the combination of ICI with SABR is safe and does not increase the rate of immune-related adverse effects, as shown in several studies [116]. At the writing of this review, no randomized data in the oligoprogressive setting was available. However, the PEMBRO-RT trial testing upfront ICI plus SABR had been published and reported a doubling in ORR compared to ICI alone, with a median PFS of 6.6 vs 1.9 in favor of the I-SABR arm [77]. In oligoprogressive disease,

prospective and retrospective data show promising response and survival rates [114].

CHAPTER VII

This chapter describes an original clinical study performed by the doctorate in collaboration with the thesis directors. It is a prospective observational multicenter study that includes 50 patients with metastatic NSCLC or melanoma treated with combined SABR and ICI after experiencing oligoprogression in up to five lesions.

Patients had a median age of 64 years and 64% were male. The most frequent tumor type was non-squamous NSCLC and had more than five metastases in total. Patients had received a median of two lines of systemic therapy before ICI. The current lines of ICI were either pembrolizumab or nivolumab. The most treated locations were the lungs and nodal metastases.

With a median follow-up of 32.8 months, the ORR was 42% (30% complete responses and 12% partial responses). Stable disease was reported in 10% and progression in 48%. The abscopal response was measurable in 40 patients and was observed in 26 patients (65%). At the end of follow-up, six patients were disease-free with no active treatment. Median PFS was 14.2 months and median OS since the delivery of SABR was 37.4 months. No differences between tumor type were observed. Patients with abscopal response had a significantly longer median PFS compared to those who did not present one (21.2 vs 3 months, $p < 0.0001$). This benefit was maintained in multivariate analysis, although no other variables aside from primary refractory disease and male sex (which predicted a higher risk of progression) seemed to affect PFS or OS. Only 6% of patients presented grade 3 side effects, and none of these were related to SABR.

CHAPTER VIII

The last publication of the thesis presents early results of a new study on oligoprogressive patients that incorporates biomarker analyses. This is also a prospective observational study that aims to recruit 72 patients treated with I-SABR to oligoprogressive sites (cohort A) and a comparative cohort of another 72 patients that receive only SABR to OMD (cohort B). Blood samples are gathered at baseline (T1), after the first (T2) and last SABR fx (T3), two months post-SABR (T4) and in case of new progression (TP).

Up to the writing of this thesis, 91 patients have been recruited for the study, but the publication includes the first 27 patients that had at least one imaging reevaluation after SABR at the cut-off date of November 30, 2023 (n = 19 from cohort A and n = 8 from cohort B). Median age, sex distribution and ECOG were similar between cohorts, with a predominance of males. Lung cancer was the most frequent in both cohorts (73.6% in A and 50% in B), followed by renal (15.8% and 25%, respectively). The most frequent treatment site was the lungs for both groups (40% and 60%), and most patients were treated to one lesion (62% and 75%).

With a median follow-up of 6 months (range, 3.4 – 19.8 months), last ORR considering both cohorts was 63%: 26% complete response (n = 7) and 37% partial (n = 10). Furthermore, 3.7% (n = 1) had stable disease and 33.3% (n = 9) suffered new progression. The abscopal response could be measured in 14 patients in cohort A and was 35.7% (n = 5). There were no significant differences in PFS or OS between groups. Median OS and PFS were not reached. No grade ≥3 toxicity was reported.

Fifteen patients with NSCLC were available for cfDNA and PMBCs studies. In univariate analysis, the percentage of CD8+ PD1+ cells was significantly higher in non-responders vs responders at T2 (p = 0.011). In contrast, CD8+ PDL1+ cells were higher in responders (p = 0.026). Moreover, at T3, the percentage of CD4+ was significantly higher in responders compared to non-responders (p = 0.036).

CD20+ B cells also increased in responders from T1 to T2 (p = 0.0234). In paired longitudinal analysis, the concentration of cfDNA significantly decreased in responders from T2 to T3 (p = 0.0488) but did not vary in non-responders.

Small RNA data for differential expression analysis between responders and non-responders (last ORR) were available from T1 through T4 samples of 14 patients with NSCLC in cohort A. Two patients were excluded due to being outliers. At T2, we found 27 miRNAs that were differentially expressed between responders and non-responders with p value < 0.05. Of these, three (*hsa-miR-133a-1, hsa-miR-133a-2 and hsa-miR-1-3p*) were significantly downregulated in responders with adjusted p value < 0.05.

IPA software identified four upstream regulators related to small RNA in T2. TATA-box binding protein associated factor 5 (*TAF5*), TATA-box binding protein (*TBP*) and general transcription factor IIB (*GTF2B*) were associated with *RNU2-2P*, which was downregulated in responders. In contrast, PTPRR was associated with *SNORD1B*, upregulated in responders. In longitudinal analysis, *hsa-miR-133a-3p* exhibited an increase from T2 to T4 in responders.

CHAPTER IV: GENERAL DISCUSSION

The review presented in chapter VI provides a detailed description of the reasons that warrant the use of SABR in patients with oligoprogressive cancer under systemic therapy, together with an in-depth view at the available evidence when combined with chemotherapy, targeted therapy, and immunotherapy.

These studies not only show that SABR does not add to the baseline toxicity of most of these systemic therapies, but also suggest a potential benefit in PFS and OS that is explained by the extension of clinical benefit achieved when delaying or even avoiding a change in the current line of systemic therapy to which the patient is oligoprogressing. This approach has been tested in phase II studies of TT in lung cancer. In the case of ICI, evidence used to be lacking, but this has recently changed with the publication of the CURB trial, a randomized phase II trial with very positive results for patients with oligoprogressive NSCLC that were mostly treated with immunotherapy. There is a growing interest in the combination of SABR and ICI because of the relevant discoveries that are being made both preclinically and clinically in regard to the abscopal effect of RT and the immunogenic effect that can overcome the resistance to immunotherapy.

Although there have been data on this combination practically since the introduction of the first ICI agents, at the time of conceptualization of this doctoral thesis, all the studies on the specific field of oligoprogression to ICI were retrospective. For this reason, the study contained in chapter VII was designed with the aim to answer, at a prospective clinical level, if SABR can improve the response to ICI in oligoprogressive patients that maintained the same ICI due to clinical benefit and were referred to the radiation oncology department to receive palliative SABR.

This was a prospective observational multicenter study that included 50 metastatic patients with NSCLC or melanoma (the main two tumor types in which immunotherapy was approved for clinical practice at the time) in

oligoprogression to pembrolizumab or nivolumab. At the end of follow-up (with a median of 32.8 months, the ORR was 42%, including 30% of complete responses. Even more interestingly, median PFS was 14.2 months, which means that SABR was able to delay the change of systemic line for over a year. This is a fundamental finding given that subsequent systemic lines are usually based on traditional chemotherapies that offer a very limited benefit and a higher chance of serious side effects. In the case of this study, as it started recruitment back in 2017, immunotherapy was the second or even third line in many patients, which accentuated the importance of maintaining the clinical benefit of ICI for as long as possible.

Despite the overall positive results, it is true that not all patients obtained this same benefit. In the most favorable cases, a subgroup of patients achieved an extended long-term benefit that even allowed for the discontinuation of immunotherapy, staying disease-free until the end of follow-up. In contrast, other patients progressed rapidly after SABR and died shortly after. The analysis of the clinical variables of the study was not very conclusive when trying to identify common characteristics among these two groups. Nonetheless, we observed that patients that presented an abscopal response according to our pre-specified clinical criteria of a ≥30% reduction in 1-2 non-irradiated lesions, had a significant advantage in terms of median PFS compared to patients that did not present this out-of-field response (21 months vs 3 months, $p<0.0001$). This suggests the involvement of a global immunostimulatory effect that goes beyond the local cytotoxic effects of SABR and that can revert the resistance to immunotherapy. However, there is no consensus on how to evaluate this response clinically. Moreover, the fact that this variable can only be evaluated after SABR means that it is not a helpful tool for patient selection.

To try to find answers to some of these questions, we designed a new prospective study to be conducted during the remainder of the predoctoral period and that would be centered around biomarkers. The first results of this study are detailed in chapter VIII. Given that our clinical protocol had been

successful in our previous publication, we decided to keep focusing on oligoprogressive patients. Since 2017, immunotherapy had been approved in several additional cancer types. To better reflect the current SoC in daily clinical practice, we designed the study to include patients with any type of tumor under ICI. In addition to this cohort (A) we designed a comparative cohort (B) of oligometastatic patients with de novo OMD or oligorrecurrence that received only SABR in ablative doses. Blood samples are gathered before, during and after SABR and analyzed to identify cellular, genetic, and epigenetic biomarkers and correlate them with the clinical variables.
In terms of response, the last evaluated ORR was 63% in the first 27 patients, including 26% complete responses. These are high rates compared with our previous study and others, but it must be noted that median follow-up is still quite short (6 months).

For the translational studies, we focused on patients with NSCLC in this first analysis given that it was the most frequent tumor type. The concentration of cfDNA decreased significantly across SABR treatment (from T2 to T3) in responders, but not in non-responders. Similar results have been published with ctDNA, but the latter is much more expensive and complex to determine. cfDNA has been proposed as a surrogate in previous studies but has never been analyzed in the context of I-SABR. Our results also suggest that this could be an early biomarker of response that is more widely available and inexpensive.
As for PMBCs, we found that non-responders had a lower percentage of CD4+ and CD8+PDL1+ cells, as well as a higher percentage of CD8+PD1+ compared to responders. These three findings have been previously described in the literature as related to worse outcomes in NSCLC. In terms of B cells, responders showed an increase in CD20+ and decrease in CD19+ from T1 to T2, which indicate an immune response.
Finally, small RNA analysis, which was available in 14 patients with NSCLC from cohort A, revealed 27 miRNAs that were differentially expressed in T2 between responders and non-responders. One of these is *hsa-miR-1-3p*, which was downregulated in responders and has been described as a key contributor to the progression of NSCLC. Two other small RNA, *RNU2-2P* and *SNORD1B* were

also significantly different between responders and non-responders. *RNU2-2P* is a pseudogene that is inhibited by *TBP*, *TAF5* and *GTF2B*, whereas *SNORD1B* is involved in the *PTPRR* pathway. Both of these pathways have been described to participate in cancer. Longitudinally, *hsa-miR-133a-3p* exhibited an increase from T2 to T4 in responders. This is consistent with the previously described role of this miRNA against lung adenocarcinoma progression and chemotherapy resistance. None of these biomarkers have been previously described as being involved in the response to the combination of SABR to ICI. Their discovery, if confirmed with longer follow-up and more patients, is a steppingstone in the field of biomarkers of I-SABR.

CHAPTER V: CONCLUSIONS

This doctoral thesis assesses a topic of great relevance in the field of radiation and medical oncology through a multidisciplinary and original approach, integrating clinical and molecular information from patients to identify predictive and/or prognostic biomarkers that can optimize the selection of patients that benefit the most from the combination of SABR and immunotherapy in oligoprogressive disease. Through the publications included in the thesis, we have identified a clinical context of oligoprogression in which SABR can have a decisive role by unleashing an immune-related abscopal effect than can overcome ICI resistance. The main conclusions that can be extracted from these three publications are as follows:

1) Oligometastatic disease is a distinct clinical entity that can benefit from the addition of ablative therapies such as SABR to standard systemic therapy (or even excluding systemic therapy in some cases).
2) Oligoprogression is a particular type of oligometastasis in which SABR can have a role to eliminate resistant tumor subclones and extend the clinical benefit of systemic therapy.
3) The most precise definition of oligometastasis is yet to be established and blood biomarkers may be useful in this definition.
4) SABR is safe and effective when combined with chemotherapy, targeted therapy, and immunotherapy in oligoprogressive disease. The combination of SABR with immunotherapy is especially promising given the immune implications of the abscopal effect.
5) SABR and ICI in metastatic oligoprogressive cancers such as NSCLC and melanoma is a safe combination that improves response rates and extends the clinical benefit of ICI by delaying or avoiding a change in systemic therapy. Patients who present an abscopal response have a significant improvement in PFS compared to those who do not.
6) A subgroup of patients experiences long-term response after I-SABR and can even stay disease-free with no active treatment. In contrast,

other patients do not seem to benefit at all from the addition of SABR and progress rapidly.

7) It is of paramount importance to identify clinical and molecular variables that can help in patient selection for this combined approach.
8) Liquid biopsy allows for the easy gathering of blood samples to analyze biomarkers longitudinally to perform treatment monitorization.
9) Cell-free DNA is a potential biomarker of early response, as it decreases over time in patients that respond to SABR.
10) PMBCs reflect the immune effects of SABR. Responders show higher percentages of CD4+ and CD8+PDL1+ cells and lower percentages of CD8+PD1+ cells. This indicates an immunostimulatory response driven by RT.
11) EVs are a novel tool for biomarker analysis and seem to be promising candidates for biomarkers of early response in I-SABR. Differences in expression between responders and non-responders in the *RNU2* family, *SNORD1B, hsa-miR-1-3p and hsa-miR-133a-3p* observed after the first SABR fraction are potential markers if confirmed in future analysis with more patients and longer follow-up.

To conclude, this doctoral thesis lays the foundation for a line of research focused on a highly specialized protocol, both at the clinical and translational levels, for the treatment and analysis of oligoprogressive patients treated with immunotherapy. At the same time, it provides new questions that must be assessed during the rest of the ongoing study and future translational projects and clinical trials.

CHAPTER VI: COMBINATION OF STEREOTACTIC ABLATIVE RADIOTHERAPY AND SYSTEMIC THERAPY IN OLIGOPROGRESSIVE NON-SMALL CELL LUNG CANCER

Rodolfo Chicas-Sett and Juan Zafra

Abstract

Targeted therapy (TT) and immune checkpoint inhibitors (ICI) have significantly increased survival in metastatic non-small cell lung cancer (NSCLC). The development of acquired resistances to these treatments has led the way for a new clinical scenario: oligoprogressive disease (OPD). In this context, stereotactic ablative radiotherapy (SABR) has appeared as one promising strategy to overcome these resistances. This review aims to assess the current evidence on the role of SABR in oligoprogressive NSCLC.

SABR in OPD is safe and seems to be effective for eradicating resistant tumor clones, allowing for the continuation of the same systemic line and with a possible impact in survival. The most solid evidence at the moment centers around the combination of SABR with TT, particularly in patients with EGFR and ALK mutations. SABR in combination with ICI is also a promising field which is exponentially growing.

The ability to maintain the same systemic treatment after OPD seems to be relevant, given that it allows for a continued clinical benefit and extended survival in metastatic NSCLC. The use of SABR in this setting is showing promising results in early studies. This strategy should be further investigated in randomized trials to confirm this benefit and improve patient selection and treatment optimization.

Authors Rodolfo Chicas-Sett and Juan Zafra have equally contributed to this work.

R. Chicas-Sett
Department of Radiation Oncology, ASCIRES Grupo Biomedico, Valencia, Spain
Department of Radiation Oncology, La Fe University and Polytechnic Hospital, Valencia, Spain e-mail: rchicas@ufm.edu; rchicass@ascires.com

J. Zafra
Group of Translational Research in Cancer Immunotherapy, Health and Medical Research Centre (CIMES), University of Malaga (UMA), Malaga, Spain

Department of Radiation Oncology, Virgen de la Victoria University Hospital, Malaga, Spain

Institute of Biomedical Research in Malaga (IBIMA), Malaga, Spain

Faculty of Medicine, University of Malaga (UMA), Malaga, Spain

https://doi.org/10.1007/16833_2023_171

Keywords

Immunotherapy · Metastatic disease · NSCLC · Oligoprogression · Radiotherapy

CHAPTER VII: COMBINATION OF SABR WITH ANTI-PD-1 IN OLIGOPROGRESSIVE NON-SMALL CELL LUNG CANCER AND MELANOMA: RESULTS OF A PROSPECTIVE MULTICENTER OBSERVATIONAL STUDY

Rodolfo Chicas-Sett, MD, MSc, PhD,[1,2,3] Juan Zafra, MD, MSc,[1,3,4,5,6] Delvys Rodriguez-Abreu, MD, PhD,[7] Juan Castilla-Martinez, MD, MSc,[1,8] Gretel Benitez, MD,[7] Barbara Salas, MD, PhD,[1] Samuel Hernandez, MD,[9] Marta Lloret, MD, PhD,[1] Juan Luis Onieva, MSc,[3,4,10] Isabel Barragan, PhD,[3,6,10,11] and Pedro C. Lara, MD, PhD[12,13]

[1]Department of Radiation Oncology, Dr Negrin University Hospital of Gran Canaria, Las Palmas de Gran Canaria, Spain;

[2]Department of Radiation Oncology, ASCIRES Grupo Biomedico, Valencia, Spain;

[3]Faculty of Medicine, University of Malaga (UMA), Malaga, Spain;

[4]Group of Translational Research in Cancer Immunotherapy, Health and Medical Research Centre (CIMES), University of Malaga (UMA), Malaga, Spain;

[5]Department of Radiation Oncology, Virgen de la Victoria University Hospital, Malaga, Spain;

[6]Institute of Biomedical Research in Malaga (IBIMA), Malaga, Spain;

[7]Department of Medical Oncology, Insular University Hospital of Gran Canaria, Las Palmas de Gran Canaria, Spain;

[8]Department of Radiation Oncology, ASCIRES Grupo Biomedico, Elche, Spain;

[9]Department of Medical Oncology, General Hospital of Fuerteventura, Puerto del Rosario, Spain;

[10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain;

[11]Group of Pharmacoepigenetics, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden;

[12]Centro Oncologico Integral Canario, San Roque University Hospital, Las Palmas de Gran Canaria, Spain;

[13]Universidad Fernando Pessoa Canarias, Las Palmas, Spain

Received Dec 30, 2021; Accepted for publication May 7, 2022. www.redjournal.org

Purpose: The percentage of patients with metastatic non-small cell lung cancer (NSCLC) and melanoma who benefit from anti−programmed cell death protein 1 (anti-PD-1) is low owing to resistance mechanisms. SABR has a role in oligoprogressive disease and can improve responses to anti-PD-1. This multicenter prospective observational study aimed to determine whether concomitant anti-PD-1 and SABR to oligoprogressive sites enhance tumor response in metastatic NSCLC and melanoma. Methods and Materials: Patients with metastatic NSCLC or melanoma in progression to anti-PD-1 but continuing the same line owing to clinical benefit were referred for palliative SABR. All patients received concomitant pembrolizumab or nivolumab and SABR to 1 to 5 lesions, maintaining anti-PD-1 until further progression, unacceptable toxicity, or medical/patient decision. Objective response rate—complete responses and partial responses—was evaluated during all follow-up according to Response Evaluation Criteria in Solid Tumors 1.1. The abscopal response was evaluated 8 weeks after SABR as a ≥30% reduction in 1 to 2 predefined nonirradiated lesions.

Results: Of the 61 patients enrolled, 50 could be analyzed. With a median follow-up of 32.8 months, objective response rate was 42% (30% complete responses and 12% partial responses). Median progression-free survival was 14.2

months (95% confidence interval, 6.9-29 months). Median overall survival since SABR was 37.4 months (95% confidence interval, 22.9 months- not reached). Abscopal response was 65%, evaluated in 40 patients who fulfilled the criteria.

Conclusions: Combined anti-PD-1 and SABR in oligoprogressive metastatic NSCLC or melanoma can achieve high rates of response and extend the clinical benefit of immunotherapy by delaying further progression and a new systemic therapy. This approach should be assessed in larger randomized trials.

Corresponding author: Rodolfo Chicas-Sett, MD, MSc, PhD; E-mail: rchicas@ufm.edu

Rodolfo Chicas-Sett and Juan Zafra made equal contributions to this study.

Isabel Barragan and Pedro C. Lara made equal contributions to this study.

This work was supported by Fundacion Colegio de Medicos de las Palmas (I33/20) and Fundacion Cientifica de la Asociacion Española Contra el Cancer (CLJUN211613ZAFR).

Disclosures: D.R.-A. reports the following: financial interests, institutional, invited speaker (Bristol Myers Squibb); financial interests, institutional, advisory board (Bristol Myers Squibb); financial interests, institutional, invited speaker (Merck Sharp & Dohme); financial interests, institutional, advisory board (Merck Sharp & Dohme); financial interests, institutional, invited speaker (F. Hoffmann-La Roche); financial interests, institutional, advisory board (F. Hoffmann-La Roche); financial interests, institutional, invited speaker (Pierre Fabre); financial interests, institutional, advisory board (Pierre Fabre); financial interests, institutional, invited speaker (Novartis); financial interests, institutional, advisory board (Novar- tis); financial interests, institutional, invited speaker (Boehringer Ingelheim); financial interests, institutional, advisory board (Boehringer Ingelheim); financial interests, institutional, invited speaker (Pfizer); financial interests, institutional, advisory board (Pfizer); financial interests, institutional, invited speaker (Lilly); financial interests,

institutional, advisory board (Lilly); financial interests, institutional, invited speaker (AstraZeneca); financial interests, institutional, advisory board (AstraZeneca). All other authors have declared no conflicts of interest.

Data sharing statement: Research data are not available at this time.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijrobp.2022.05.013.

Int J Radiation Oncol Biol Phys, Vol. 000, No. 00, pp. 1–11, 2022 0360-3016/$ - https://doi.org/10.1016/j.ijrobp.2022.05.013

CHAPTER VIII: NOVEL BLOOD BIOMARKERS FOR RESPONSE PREDICTION AND MONITORING OF STEREOTACTIC ABLATIVE RADIOTHERAPY AND IMMUNOTHERAPY IN METASTATIC OLIGOPROGRESSIVE LUNG CANCER

Juan Zafra [1,2†], Juan Luis Onieva [3,2†], María Garrido-Barros [3,2], Andrea González-Hernández [3,2], Beatriz Martínez-Gálvez [3], Alicia Román [4], Rafael Ordóñez-Marmolejo [4], Elisabeth Pérez-Ruiz [3], José Carlos Benítez [3], Andrés Mesas [5], Andrés Vera [6], Rodolfo Chicas-Sett [7,8], Antonio Rueda-Domínguez [3*], Javier Oliver [3†], Isabel Barragán [3,9†*]

[1] Group of Translational Research in Cancer Immunotherapy (CIMO2), Department of Radiation Oncology, Virgen de la Victoria University Hospital, Institute of Biomedical Research in Malaga (IBIMA), Málaga, Spain.

[2] University of Malaga (UMA), Málaga, Spain.

[3] Group of Translational Research in Cancer Immunotherapy (CIMO2), Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria Hospitals, Institute of Biomedical Research in Malaga (IBIMA), Málaga, Spain.

[4] Department of Radiation Oncology, Virgen de la Victoria University Hospital, Málaga, Spain.

[5] Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria Hospitals, Málaga, Spain.

[6] Department of Radiation Oncology, Dr Negrín University Hospital, Las Palmas de Gran Canaria, Spain.

[7] Department of Radiation Oncology, La Fe University Hospital, Valencia, Spain.

[8] Group of Clinical and Translational Cancer Research, Le Fe Health Research Institute, Valencia, Spain.

[9] Group of Pharmacoepigenetics, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.

***** Correspondence: A.R.D., ruedadominguez@gmail.com; I.B., isabel.barragan@ki.se

†Juan Zafra [1,2†] and Juan Luis Onieva [3,2†]. These authors contributed equally to this work and share first authorship. Javier Oliver [3†] and Isabel Barragán [3,9†]. These authors contributed equally to this work and share last authorship.

Abstract: Up to 80% of patients under immune checkpoint inhibitors (ICI) face resistance. In this context, stereotactic ablative radiotherapy (SABR) can induce an immune or abscopal response. However, its molecular determinants remain unknown. We present early results of a translational study assessing biomarkers of response to combined ICI and SABR (I-SABR) in liquid biopsy from oligoprogressive patients in a prospective observational multicenter study. Cohort A includes metastatic patients in oligoprogression to ICI maintaining the same ICI due to clinical benefit and who receive concomitant SABR. B is a comparative group of oligometastatic patients receiving only SABR. Blood samples are extracted at baseline (T1), after the first (T2) and last (T3) fraction, two months post-SABR (T4) and at further progression (TP). Response is evaluated by iRECIST and defined by the objective response rate (ORR) – complete and partial responses. We assess peripheral blood mononuclear cells (PBMCs), circulating cell-free DNA (cfDNA) and small RNA from extracellular vesicles. Twenty-seven patients could be analyzed (cohort A: n=19; B: n=8). Most were males with non-small cell lung cancer and one progressing lesion. With a median follow-up of 6 months, last ORR was 63% (26% complete and 37% partial response). A decrease in cfDNA from T2 to T3 correlated with good response. At T2, CD8+PD1+ and CD8+PDL1+ cells were increased in non-responders and responders, respectively. At T2, 27 micro RNAs were differentially expressed. These are potential biomarkers of response to I-SABR in oligoprogressive disease.

Keywords: immunotherapy, stereotactic ablative radiotherapy, oligoprogression, biomarkers, cell-free DNA, small RNA.

doi:10.3390/ijms25084533

REFERENCES

CHAPTERS I-V

[1] Santucci C, Carioli G, Bertuccio P, Malvezzi M, Pastorino U, Boffetta P, Negri E, Bosetti C, La Vecchia C. Progress in cancer mortality, incidence, and survival: a global overview. Eur J Cancer Prev. 2020 Sep;29(5):367-381. doi: 10.1097/CEJ.0000000000000594. PMID: 32740162.

[2] Ganesh K, Massagué J. Targeting metastatic cancer. Nat Med. 2021 Jan;27(1):34-44. doi: 10.1038/s41591-020-01195-4. Epub 2021 Jan 13. PMID: 33442008; PMCID: PMC7895475.

[3] Knight A, Karapetyan L, Kirkwood JM. Immunotherapy in Melanoma: Recent Advances and Future Directions. Cancers (Basel). 2023 Feb 9;15(4):1106. doi: 10.3390/cancers15041106. PMID: 36831449; PMCID: PMC9954703.

[4] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018 Jan 24;553(7689):446-454. doi: 10.1038/nature25183. PMID: 29364287.

[5] Mazzola R, Jereczek-Fossa BA, Franceschini D, Tubin S, Filippi AR, Tolia M, Lancia A, Minniti G, Corradini S, Arcangeli S, Scorsetti M, Alongi F. Oligometastasis and local ablation in the era of systemic targeted and immunotherapy. Radiat Oncol. 2020 May 4;15(1):92. doi: 10.1186/s13014-020-01544-0. PMID: 32366258; PMCID: PMC7197157.

[6] Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020 Aug;17(8):807-821. doi: 10.1038/s41423-020-0488-6. Epub 2020 Jul 1. PMID: 32612154; PMCID: PMC7395159.

[7] Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995 Jan;13(1):8-10. doi: 10.1200/JCO.1995.13.1.8. PMID: 7799047.

[8] Kim C, Hoang CD, Kesarwala AH, Schrump DS, Guha U, Rajan A. Role of Local Ablative Therapy in Patients with Oligometastatic and Oligoprogressive Non-Small Cell Lung Cancer. J Thorac Oncol. 2017 Feb;12(2):179-193. doi: 10.1016/j.jtho.2016.10.012. Epub 2016 Oct 22. PMID: 27780780.

[9] Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, Méndez Romero A, Nevens D, Palma D, Park C, Ricardi U, Scorsetti M, Yu J, Woodward WA. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020 Jul;148:157-166. doi: 10.1016/j.radonc.2020.04.003. Epub 2020 Apr 22. PMID: 32388150.

[10] Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, Dingemans AC, Fournier B, Hurkmans C, Lecouvet FE, Meattini I, Méndez Romero A, Ricardi U, Russell NS, Schanne DH, Scorsetti M, Tombal B, Verellen D, Verfaillie C, Ost P. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020 Jan;21(1):e18-e28. doi: 10.1016/S1470-2045(19)30718-1. PMID: 31908301.

[11] Sambi M, Qorri B, Harless W, Szewczuk MR. Therapeutic Options for Metastatic Breast Cancer. Adv Exp Med Biol. 2019;1152:131-172. doi: 10.1007/978-3-030-20301-6_8. PMID: 31456183.

[12] Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. Eur J Cancer. 2019 Mar;109:70-83. doi: 10.1016/j.ejca.2018.12.019. Epub 2019 Jan 25. PMID: 30690295.

[13] Grünewald TG, Alonso M, Avnet S, Banito A, Burdach S, Cidre-Aranaz F, Di Pompo G, Distel M, Dorado-Garcia H, Garcia-Castro J, González-González L, Grigoriadis AE, Kasan M, Koelsche C, Krumbholz M, Lecanda F, Lemma S, Longo DL, Madrigal-Esquivel C, Morales-Molina Á, Musa J, Ohmura S, Ory B, Pereira-Silva M, Perut F, Rodriguez R, Seeling C, Al Shaaili N, Shaabani S, Shiavone K, Sinha S, Tomazou EM, Trautmann M, Vela M, Versleijen-Jonkers YM, Visgauss J, Zalacain M, Schober SJ, Lissat A, English WR, Baldini N, Heymann D. Sarcoma treatment in the era of molecular medicine. EMBO Mol Med. 2020 Nov 6;12(11):e11131. doi: 10.15252/emmm.201911131. Epub 2020 Oct 13. PMID: 33047515; PMCID: PMC7645378.

[14] Knezevic CE, Clarke W. Cancer Chemotherapy: The Case for Therapeutic Drug Monitoring. Ther Drug Monit. 2020 Feb;42(1):6-19. doi: 10.1097/FTD.0000000000000701. PMID: 31568180.

[15] Livshits Z, Rao RB, Smith SW. An approach to chemotherapy-associated toxicity. Emerg Med Clin North Am. 2014 Feb;32(1):167-203. doi: 10.1016/j.emc.2013.09.002. PMID: 24275174.

[16] Lemjabbar-Alaoui H, Hassan OU, Yang YW, Buchanan P. Lung cancer: Biology and treatment options. Biochim Biophys Acta. 2015 Dec;1856(2):189-210. doi: 10.1016/j.bbcan.2015.08.002. Epub 2015 Aug 19. PMID: 26297204; PMCID: PMC4663145.

[17] Waarts MR, Stonestrom AJ, Park YC, Levine RL. Targeting mutations in cancer. J Clin Invest. 2022 Apr 15;132(8):e154943. doi: 10.1172/JCI154943. PMID: 35426374; PMCID: PMC9012285.

[18] Waarts MR, Stonestrom AJ, Park YC, Levine RL. Targeting mutations in cancer. J Clin Invest. 2022 Apr 15;132(8):e154943. doi: 10.1172/JCI154943. PMID: 35426374; PMCID: PMC9012285.

[19] Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, Rutkowski P, Blank CU, Miller WH Jr, Kaempgen E, Martín-Algarra S, Karaszewska B, Mauch C, Chiarion-Sileni V, Martin AM, Swann S, Haney P, Mirakhur B, Guckert ME, Goodman V, Chapman PB. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28;380(9839):358-65. doi: 10.1016/S0140-6736(12)60868-X. Epub 2012 Jun 25. PMID: 22735384.

[20] Popat S, Ahn MJ, Ekman S, Leighl NB, Ramalingam SS, Reungwetwattana T, Siva S, Tsuboi M, Wu YL, Yang JC. Osimertinib for EGFR-Mutant Non-Small-Cell Lung Cancer Central Nervous System Metastases: Current Evidence and Future Perspectives on Therapeutic Strategies. Target Oncol. 2023 Jan;18(1):9-24. doi: 10.1007/s11523-022-00941-7. Epub 2023 Jan 18. Erratum in: Target Oncol. 2023 Feb 8;: PMID: 36652172.

[21] Liu S, Kurzrock R. Toxicity of targeted therapy: Implications for response and impact of genetic polymorphisms. Cancer Treat Rev. 2014 Aug;40(7):883-91. doi: 10.1016/j.ctrv.2014.05.003. Epub 2014 May 17. PMID: 24867380.

[22] Martínez-Jiménez F, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, Mularoni L, Pich O, Bonet J, Kranas H, Gonzalez-Perez A, Lopez-Bigas N. A compendium of mutational cancer driver genes. Nat Rev Cancer.

2020 Oct;20(10):555-572. doi: 10.1038/s41568-020-0290-x. Epub 2020 Aug 10. PMID: 32778778.

[23] Zhang Y, Zheng J. Functions of Immune Checkpoint Molecules Beyond Immune Evasion. Adv Exp Med Biol. 2020;1248:201-226. doi: 10.1007/978-981-15-3266-5_9. PMID: 32185712.

[24] Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, Lichtor T, Decker WK, Whelan RL, Kumara HMCS, Signori E, Honoki K, Georgakilas AG, Amin A, Helferich WG, Boosani CS, Guha G, Ciriolo MR, Chen S, Mohammed SI, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Fujii H, Aquilano K, Ashraf SS, Nowsheen S, Yang X, Choi BK, Kwon BS. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol. 2015 Dec;35 Suppl:S185-S198. doi: 10.1016/j.semcancer.2015.03.004. Epub 2015 Mar 25. PMID: 25818339.

[25] Naimi A, Mohammed RN, Raji A, Chupradit S, Yumashev AV, Suksatan W, Shalaby MN, Thangavelu L, Kamrava S, Shomali N, Sohrabi AD, Adili A, Noroozi-Aghideh A, Razeghian E. Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons. Cell Commun Signal. 2022 Apr 7;20(1):44. doi: 10.1186/s12964-022-00854-y. PMID: 35392976; PMCID: PMC8991803.

[26] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252-64. doi: 10.1038/nrc3239. PMID: 22437870; PMCID: PMC4856023.

[27] Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol. 2022 Apr;19(4):254-267. doi: 10.1038/s41571-022-00600-w. Epub 2022 Jan 26. PMID: 35082367; PMCID: PMC8790946.

[28] Tang S, Qin C, Hu H, Liu T, He Y, Guo H, Yan H, Zhang J, Tang S, Zhou H. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. Cells. 2022 Jan 19;11(3):320. doi: 10.3390/cells11030320. PMID: 35159131; PMCID: PMC8834198.

[29] Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. Lancet. 2021 Sep 11;398(10304):1002-1014. doi: 10.1016/S0140-6736(21)01206-X. PMID: 34509219.

[30] Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K, Kulasinghe A. Immune Checkpoint Inhibitors in Cancer Therapy. Curr Oncol. 2022 Apr 24;29(5):3044-3060. doi: 10.3390/curroncol29050247. PMID: 35621637; PMCID: PMC9139602.

[31] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leal TA, Riess JW, Jensen E, Zhao B, Pietanza MC, Brahmer JR. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021 Jul 20;39(21):2339-2349. doi: 10.1200/JCO.21.00174. Epub 2021 Apr 19. PMID: 33872070; PMCID: PMC8280089.

[32] Zhang C, Zhang C, Wang H. Immune-checkpoint inhibitor resistance in cancer treatment: Current progress and future directions. Cancer Lett. 2023 May 28;562:216182. doi: 10.1016/j.canlet.2023.216182. Epub 2023 Apr 17. PMID: 37076040.

[33] Jenkins RW, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer. 2018 Jan;118(1):9-16. doi: 10.1038/bjc.2017.434. Epub 2018 Jan 2. PMID: 29319049; PMCID: PMC5765236.

[34] Meric-Bernstam F, Larkin J, Tabernero J, Bonini C. Enhancing anti-tumour efficacy with immunotherapy combinations. Lancet. 2021 Mar 13;397(10278):1010-1022. doi: 10.1016/S0140-6736(20)32598-8. Epub 2020 Dec 4. PMID: 33285141.

[35] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856.

[36] Chicas-Sett R, Zafra-Martin J, Morales-Orue I, Castilla-Martinez J, Berenguer-Frances MA, Gonzalez-Rodriguez E, Rodriguez-Abreu D, Couñago F. Immunoradiotherapy as An Effective Therapeutic Strategy in Lung Cancer: From

Palliative Care to Curative Intent. Cancers (Basel). 2020 Aug 5;12(8):2178. doi: 10.3390/cancers12082178. PMID: 32764371; PMCID: PMC7463603.
[37] Hynes PR, M Das J. Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT). 2023 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31194323.
[38] Laitinen LV. Personal memories of the history of stereotactic neurosurgery. Neurosurgery. 2004 Dec;55(6):1420-8; discussion 1428-9. doi: 10.1227/01.neu.0000143145.00880.f4. PMID: 15574224.
[39] Fanous AA, Prasad D, Mathieu D, Fabiano AJ. Intracranial stereotactic radiosurgery. J Neurosurg Sci. 2019 Feb;63(1):61-82. doi: 10.23736/S0390-5616.17.04210-2. Epub 2017 Sep 22. PMID: 28945054.
[40] Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, Demaria S. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009 Sep 1;15(17):5379-88. doi: 10.1158/1078-0432.CCR-09-0265. Epub 2009 Aug 25. PMID: 19706802; PMCID: PMC2746048.
[41] Chiavassa S, Bessieres I, Edouard M, Mathot M, Moignier A. Complexity metrics for IMRT and VMAT plans: a review of current literature and applications. Br J Radiol. 2019 Oct;92(1102):20190270. doi: 10.1259/bjr.20190270. Epub 2019 Jul 24. PMID: 31295002; PMCID: PMC6774599.
[42] Sultan S, Ullman K, Ester E, Melzer A, Anthony M, Kelly RF, Landsteiner A, Stampe C, Thiboutot J, Wilt TJ. Non-surgical Therapies for Early-stage Non-small Cell Lung Cancer: A Systematic Review. Washington (DC): Department of Veterans Affairs (US); 2023 Jun. PMID: 37363959.
[43] Siva S, Bressel M, Sidhom M, Sridharan S, Vanneste BGL, Davey R, Montgomery R, Ruben J, Foroudi F, Higgs B, Lin C, Raman A, Hardcastle N, Hofman MS, De Abreu Lourenco R, Shaw M, Mancuso P, Moon D, Wong LM, Lawrentschuk N, Wood S, Brook NR, Kron T, Martin J, Pryor D; FASTRACK II Investigator Group. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. Lancet Oncol. 2024 Mar;25(3):308-316. doi: 10.1016/S1470-2045(24)00020-2. PMID: 38423047.

[44] Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M, Alongi F, Ricardi U, Jereczek-Fossa BA, Westhoff P, But-Hadzic J, Widder J, Geets X, Bral S, Lambrecht M, Billiet C, Sirak I, Ramella S, Giovanni Battista I, Benavente S, Zapatero A, Romero F, Zilli T, Khanfir K, Hemmatazad H, de Bari B, Klass DN, Adnan S, Peulen H, Salinas Ramos J, Strijbos M, Popat S, Ost P, Guckenberger M. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. Lancet Oncol. 2023 Mar;24(3):e121-e132. doi: 10.1016/S1470-2045(22)00752-5. PMID: 36858728.

[45] Harrow S, Palma DA, Olson R, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Senthi S, Swaminath A, Kopek N, Liu M, Schlijper R, Bauman GS, Laba J, Qu XM, Warner A, Senan S. Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes. Int J Radiat Oncol Biol Phys. 2022 Nov 15;114(4):611-616. doi: 10.1016/j.ijrobp.2022.05.004. Epub 2022 May 26. PMID: 35643253.

[46] Palma DA, Warner A, Senan S. Points to consider regarding the SABR-COMET trial - Authors' reply. Lancet. 2020 Feb 8;395(10222):e20. doi: 10.1016/S0140-6736(19)32557-7. PMID: 32035556.

[47] Gomez DR, Tang C, Zhang J, Blumenschein GR Jr, Hernandez M, Lee JJ, Ye R, Palma DA, Louie AV, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Welsh JW, Gibbons DL, Karam JA, Kavanagh BD, Tsao AS, Sepesi B, Swisher SG, Heymach JV. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019 Jun 20;37(18):1558-1565. doi: 10.1200/JCO.19.00201. Epub 2019 May 8. PMID: 31067138; PMCID: PMC6599408.

[48] Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, Dowell JE, Cheedella N, Nedzi L, Westover KD, Pulipparacharuvil S, Choy H, Timmerman RD. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018 Jan

11;4(1):e173501. doi: 10.1001/jamaoncol.2017.3501. Epub 2018 Jan 11. PMID: 28973074; PMCID: PMC5833648.

[49] Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, Rowe SP, Ross AE, Gorin MA, Deville C, Greco SC, Wang H, Denmeade SR, Paller CJ, Dipasquale S, DeWeese TL, Song DY, Wang H, Carducci MA, Pienta KJ, Pomper MG, Dicker AP, Eisenberger MA, Alizadeh AA, Diehn M, Tran PT. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol. 2020 May 1;6(5):650-659. doi: 10.1001/jamaoncol.2020.0147. PMID: 32215577; PMCID: PMC7225913.

[50] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, Lambert B, Delrue L, Bultijnck R, Claeys T, Goetghebeur E, Villeirs G, De Man K, Ameye F, Billiet I, Joniau S, Vanhaverbeke F, De Meerleer G. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol. 2018 Feb 10;36(5):446-453. doi: 10.1200/JCO.2017.75.4853. Epub 2017 Dec 14. PMID: 29240541.

[51] Li GJ, Arifin AJ, Al-Shafa F, Cheung P, Rodrigues GB, Palma DA, Louie AV. A review of ongoing trials of stereotactic ablative radiotherapy for oligometastatic disease in the context of new consensus definitions. Ann Palliat Med. 2021 May;10(5):6045-6051. doi: 10.21037/apm-20-847. Epub 2020 Aug 7. PMID: 32787370.

[52] Turchan WT, Chmura SJ. The role of immunotherapy in combination with oligometastasis-directed therapy: a narrative review. Ann Palliat Med. 2021 May;10(5):6028-6044. doi: 10.21037/apm-20-1528. Epub 2021 Jan 4. PMID: 33440982.

[53] MOLE RH. Whole body irradiation; radiobiology or medicine? Br J Radiol. 1953 May;26(305):234-41. doi: 10.1259/0007-1285-26-305-234. PMID: 13042090.

[54] Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016 Jan-Feb;40(1):25-37. doi: 10.1016/j.currproblcancer.2015.10.001. Epub 2015 Oct 9. PMID: 26582738.

[55] Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC, Demaria S. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. Trends Immunol. 2018 Aug;39(8):644-655. doi: 10.1016/j.it.2018.06.001. Epub 2018 Jul 11. PMID: 30001871; PMCID: PMC6326574.

[56] Demaria S, Formenti SC. The abscopal effect 67 years later: from a side story to center stage. Br J Radiol. 2020 May 1;93(1109):20200042. doi: 10.1259/bjr.20200042. Epub 2020 Feb 28. PMID: 32101479; PMCID: PMC7217574.

[57] Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, Garon EB, Lee P. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol. 2017 Jul;18(7):895-903. doi: 10.1016/S1470-2045(17)30380-7. Epub 2017 May 24. Erratum in: Lancet Oncol. 2017 Jul;18(7):e371. PMID: 28551359; PMCID: PMC5538772.

[58] Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer. 2018 May;18(5):313-322. doi: 10.1038/nrc.2018.6. Epub 2018 Feb 16. PMID: 29449659; PMCID: PMC5912991.

[59] Weichselbaum RR. The role of DNA repair processes in the response of human tumors to fractionated radiotherapy. Int J Radiat Oncol Biol Phys. 1984 Jul;10(7):1127-34. doi: 10.1016/0360-3016(84)90187-1. PMID: 6378848.

[60] Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, Draganov D, Edelson RL, Formenti SC, Fucikova J, Gabriele L, Gaipl US, Gameiro SR, Garg AD, Golden E, Han J, Harrington KJ, Hemminki A, Hodge JW, Hossain DMS, Illidge T, Karin M, Kaufman HL, Kepp O, Kroemer G, Lasarte JJ, Loi S, Lotze MT, Manic G, Merghoub T, Melcher AA, Mossman KL, Prosper F, Rekdal Ø, Rescigno M, Riganti C, Sistigu A, Smyth MJ, Spisek R, Stagg J, Strauss BE, Tang D, Tatsuno K, van Gool SW, Vandenabeele P, Yamazaki T, Zamarin D, Zitvogel L, Cesano A, Marincola FM. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer. 2020 Mar;8(1):e000337. doi:

10.1136/jitc-2019-000337. Erratum in: J Immunother Cancer. 2020 May;8(1): PMID: 32209603; PMCID: PMC7064135.
[61] Zhu M, Yang M, Zhang J, Yin Y, Fan X, Zhang Y, Qin S, Zhang H, Yu F. Immunogenic Cell Death Induction by Ionizing Radiation. Front Immunol. 2021 Aug 20;12:705361. doi: 10.3389/fimmu.2021.705361. PMID: 34489957; PMCID: PMC8417736.
[62] Rückert M, Flohr AS, Hecht M, Gaipl US. Radiotherapy and the immune system: More than just immune suppression. Stem Cells. 2021 Sep;39(9):1155-1165. doi: 10.1002/stem.3391. Epub 2021 May 18. PMID: 33961721.
[63] Golden EB, Marciscano AE, Formenti SC. Radiation Therapy and the In Situ Vaccination Approach. Int J Radiat Oncol Biol Phys. 2020 Nov 15;108(4):891-898. doi: 10.1016/j.ijrobp.2020.08.023. Epub 2020 Aug 12. PMID: 32800803.
[64] Yoo GS, Ahn WG, Kim SY, Kang W, Choi C, Park HC. Radiation-induced abscopal effect and its enhancement by programmed cell death 1 blockade in the hepatocellular carcinoma: A murine model study. Clin Mol Hepatol. 2021 Jan;27(1):144-156. doi: 10.3350/cmh.2020.0095. Epub 2020 Dec 7. PMID: 33280350; PMCID: PMC7820196.
[65] Paganetti H. A review on lymphocyte radiosensitivity and its impact on radiotherapy. Front Oncol. 2023 Aug 3;13:1201500. doi: 10.3389/fonc.2023.1201500. PMID: 37601664; PMCID: PMC10435323.
[66] Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, Barcellos-Hoff MH, Demaria S. TGFß Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity. Cancer Res. 2015 Jun 1;75(11):2232-42. doi: 10.1158/0008-5472.CAN-14-3511. Epub 2015 Apr 9. PMID: 25858148; PMCID: PMC4522159.
[67] Muroyama Y, Nirschl TR, Kochel CM, Lopez-Bujanda Z, Theodros D, Mao W, Carrera-Haro MA, Ghasemzadeh A, Marciscano AE, Velarde E, Tam AJ, Thoburn CJ, Uddin M, Meeker AK, Anders RA, Pardoll DM, Drake CG. Stereotactic Radiotherapy Increases Functionally Suppressive Regulatory T Cells in the Tumor Microenvironment. Cancer Immunol Res. 2017 Nov;5(11):992-1004. doi: 10.1158/2326-6066.CIR-17-0040. Epub 2017 Oct 2. PMID: 28970196; PMCID: PMC5793220.

[68] Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. Nat Rev Clin Oncol. 2019 Feb;16(2):123-135. doi: 10.1038/s41571-018-0119-7. PMID: 30401936.

[69] Garelli E, Rittmeyer A, Putora PM, Glatzer M, Dressel R, Andreas S. Abscopal effect in lung cancer: three case reports and a concise review. Immunotherapy. 2019 Dec;11(17):1445-1461. doi: 10.2217/imt-2019-0105. PMID: 31826745.

[70] Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017 Jun 9;8:15618. doi: 10.1038/ncomms15618. PMID: 28598415; PMCID: PMC5472757.

[71] Demaria S, Guha C, Schoenfeld J, Morris Z, Monjazeb A, Sikora A, Crittenden M, Shiao S, Khleif S, Gupta S, Formenti SC, Vikram B, Coleman CN, Ahmed MM. Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? J Immunother Cancer. 2021 Apr;9(4):e002038. doi: 10.1136/jitc-2020-002038. PMID: 33827904; PMCID: PMC8031689.

[72] Bestvina CM, Pointer KB, Karrison T, Al-Hallaq H, Hoffman PC, Jelinek MJ, Juloori A, Melotek JM, Murgu S, Partouche J, Vokes EE, Weichselbaum RR, Pitroda SP, Patel JD, Chmura SJ. A Phase 1 Trial of Concurrent or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV NSCLC Study. J Thorac Oncol. 2022 Jan;17(1):130-140. doi: 10.1016/j.jtho.2021.08.019. Epub 2021 Sep 6. PMID: 34500113.

[73] Spurr LF, Martinez CA, Kang W, Chen M, Zha Y, Hseu R, Gutiontov SI, Turchan WT, Lynch CM, Pointer KB, Chang P, Murgu S, Husain AN, Cody B, Vokes EE, Bestvina CM, Patel JD, Diehn M, Gajewski TF, Weichselbaum RR, Chmura SJ, Pitroda SP. Highly aneuploid non-small cell lung cancer shows enhanced responsiveness to concurrent radiation and immune checkpoint blockade. Nat Cancer. 2022 Dec;3(12):1498-1512. doi: 10.1038/s43018-022-00467-x. Epub 2022 Nov 28. PMID: 36443406.

[74] Tozuka T, Minegishi Y, Yamaguchi O, et al. Immunotherapy with radiotherapy for brain metastases in patients with NSCLC: NEJ060. JTO Clin Res Rep. 2024;5:100655. https://doi.org/10.1016/j.jtocrr.2024.100655

[75] Suwinski R. Combination of immunotherapy and radiotherapy in the treatment of brain metastases from non-small cell lung cancer. J Thorac Dis. 2021 May;13(5):3315-3322. doi: 10.21037/jtd-2019-rbmlc-08. PMID: 34164224; PMCID: PMC8182508.

[76] Huang J, Li JJ. Multiple Dynamics in Tumor Microenvironment Under Radiotherapy. Adv Exp Med Biol. 2020;1263:175-202. doi: 10.1007/978-3-030-44518-8_10. PMID: 32588328.

[77] Theelen WSME, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts JGJV, Dumoulin DW, Bahce I, Niemeijer AN, de Langen AJ, Monkhorst K, Baas P. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019 Sep 1;5(9):1276-1282. doi: 10.1001/jamaoncol.2019.1478. PMID: 31294749; PMCID: PMC6624814.

[78] Tomaciello M, Conte M, Montinaro FR, Sabatini A, Cunicella G, Di Giammarco F, Tini P, Gravina GL, Cortesi E, Minniti G, De Vincentis G, Frantellizzi V, Marampon F. Abscopal Effect on Bone Metastases from Solid Tumors: A Systematic Review and Retrospective Analysis of Challenge within a Challenge. Biomedicines. 2023 Apr 12;11(4):1157. doi: 10.3390/biomedicines11041157. PMID: 37189775; PMCID: PMC10135682.

[79] Macki M, Fakih M, Elmenini J, Anand SK, Robin AM. Trends in the Abscopal Effect After Radiation to Spinal Metastases: A Systematic Review. Cureus. 2019 Oct 5;11(10):e5844. doi: 10.7759/cureus.5844. PMID: 31754579; PMCID: PMC6830850.

[80] McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, Zhi WI, McFarland D, Michel LS, Young R, Lefkowitz R, Spielsinger D, Zhang Z, Flynn J, Dunn L, Ho A, Riaz N, Pfister D, Lee N. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2021 Jan 1;39(1):30-37. doi:

10.1200/JCO.20.00290. Epub 2020 Aug 21. PMID: 32822275; PMCID: PMC8462641.

[81] Liu L, Shah K. The Potential of the Gut Microbiome to Reshape the Cancer Therapy Paradigm: A Review. JAMA Oncol. 2022 Jul 1;8(7):1059-1067. doi: 10.1001/jamaoncol.2022.0494. PMID: 35482355.

[82] Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, Vanpouille-Box C, Friedman K, Ferrari de Andrade L, Wucherpfennig KW, Heguy A, Imai N, Gnjatic S, Emerson RO, Zhou XK, Zhang T, Chachoua A, Demaria S. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med. 2018 Dec;24(12):1845-1851. doi: 10.1038/s41591-018-0232-2. Epub 2018 Nov 5. PMID: 30397353; PMCID: PMC6286242.

[83] Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, Hess K, de Groot P, Nguyen QN, Varghese R, Comeaux NI, Simon G, Skoulidis F, Chang JY, Papdimitrakopoulou V, Lin SH, Heymach JV. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. J Immunother Cancer. 2020 Oct;8(2):e001001. doi: 10.1136/jitc-2020-001001. PMID: 33051340; PMCID: PMC7555111.

[84] Theelen WSME, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts JGJV, Bahce I, Niemeijer ALN, Chang JY, de Groot PM, Nguyen QN, Comeaux NI, Simon GR, Skoulidis F, Lin SH, He K, Patel R, Heymach J, Baas P, Welsh JW. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021 May;9(5):467-475. doi: 10.1016/S2213-2600(20)30391-X. Epub 2020 Oct 20. Erratum in: Lancet Respir Med. 2021 Mar;9(3):e29. PMID: 33096027.

[85] Tsai CJ, Yang JT, Shaverdian N, Patel J, Shepherd AF, Eng J, Guttmann D, Yeh R, Gelblum DY, Namakydoust A, Preeshagul I, Modi S, Seidman A, Traina T, Drullinsky P, Flynn J, Zhang Z, Rimner A, Gillespie EF, Gomez DR, Lee NY, Berger M, Robson ME, Reis-Filho JS, Riaz N, Rudin CM, Powell SN; CURB Study Group. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study.

Lancet. 2024 Jan 13;403(10422):171-182. doi: 10.1016/S0140-6736(23)01857-3. Epub 2023 Dec 14. PMID: 38104577; PMCID: PMC10880046.

[86] D. Schellenberg, Z. Gabos, A. Duimering, B.J. Debenham, A. Fairchild, F. Huang, L. Rowe, D.M. Severin, M. Giuliani, A. Bezjak, B.H. Lok, S. Raman, P. Chung, Y. Zhao, C. Ho, M.I. Lock, A. Louie, S. Lefresne, H. Carolan, M.C. Liu, V. Yau, A.Y. Ye, R.A. Olson, B. Mou, I.G. Mohamed, D.W. Petrik, M. Dosani, H.H. Pai, B. Valev, S. Gaede, A. Warner, D.A. Palma. Stereotactic Ablative Radiotherapy for Oligo-Progressive Cancers: Results of the Randomized Phase II STOP Trial, International Journal of Radiation Oncology*Biology*Physics, Volume 117, Issue 2, Supplement, 2023, Page S58, https://doi.org/10.1016/j.ijrobp.2023.06.353.

[87] Mateo J, Steuten L, Aftimos P, André F, Davies M, Garralda E, Geissler J, Husereau D, Martinez-Lopez I, Normanno N, Reis-Filho JS, Stefani S, Thomas DM, Westphalen CB, Voest E. Delivering precision oncology to patients with cancer. Nat Med. 2022 Apr;28(4):658-665. doi: 10.1038/s41591-022-01717-2. Epub 2022 Apr 19. PMID: 35440717.

[88] Wahida A, Buschhorn L, Fröhling S, Jost PJ, Schneeweiss A, Lichter P, Kurzrock R. The coming decade in precision oncology: six riddles. Nat Rev Cancer. 2023 Jan;23(1):43-54. doi: 10.1038/s41568-022-00529-3. Epub 2022 Nov 24. PMID: 36434139.

[89] Edsjö A, Holmquist L, Geoerger B, Nowak F, Gomon G, Alix-Panabières C, Ploeger C, Lassen U, Le Tourneau C, Lehtiö J, Ott PA, von Deimling A, Fröhling S, Voest E, Klauschen F, Dienstmann R, Alshibany A, Siu LL, Stenzinger A. Precision cancer medicine: Concepts, current practice, and future developments. J Intern Med. 2023 Oct;294(4):455-481. doi: 10.1111/joim.13709. Epub 2023 Aug 28. PMID: 37641393.

[90] Young M, Shapiro R. Percutaneous Lung Lesion Biopsy. 2023 Jun 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. PMID: 30020662.

[91] Heerink WJ, de Bock GH, de Jonge GJ, Groen HJ, Vliegenthart R, Oudkerk M. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. Eur Radiol. 2017 Jan;27(1):138-148. doi: 10.1007/s00330-016-4357-8. Epub 2016 Apr 23. PMID: 27108299; PMCID: PMC5127875.

[92] Oliver J, Garcia-Aranda M, Chaves P, Alba E, Cobo-Dols M, Onieva JL, Barragan I. Emerging noninvasive methylation biomarkers of cancer prognosis and drug response prediction. Semin Cancer Biol. 2022 Aug;83:584-595. doi: 10.1016/j.semcancer.2021.03.012. Epub 2021 Mar 20. PMID: 33757849.

[93] Mosallaei M, Ehtesham N, Rahimirad S, Saghi M, Vatandoost N, Khosravi S. PBMCs: a new source of diagnostic and prognostic biomarkers. Arch Physiol Biochem. 2022 Aug;128(4):1081-1087. doi: 10.1080/13813455.2020.1752257. Epub 2020 Apr 15. PMID: 32293207.

[94] Kane N, Romero T, Diaz-Perez S, Rettig MB, Steinberg ML, Kishan AU, Schaue D, Reiter RE, Knudsen BS, Nickols NG. Significant changes in macrophage and CD8 T cell densities in primary prostate tumors 2 weeks after SBRT. Prostate Cancer Prostatic Dis. 2023 Mar;26(1):207-209. doi: 10.1038/s41391-022-00498-6. Epub 2022 Jan 20. PMID: 35058580; PMCID: PMC10023555.

[95] Gkika E, Firat E, Adebahr S, Graf E, Popp I, Radicioni G, Lo SS, Nestle U, Nicolay NH, Niedermann G, Duda DG, Grosu AL. Systemic immune modulation by stereotactic radiotherapy in early-stage lung cancer. NPJ Precis Oncol. 2023 Mar 2;7(1):24. doi: 10.1038/s41698-023-00358-z. PMID: 36864234; PMCID: PMC9981559.

[96] Aduquaye M, Dube S, Bashir B, Chowdhury A, Ahmed N, Leylek A, Kim J, Lambert P, Bucher O, Hunter W, Sivananthan G, Koul R, Rathod S. Impact of Pre-Treatment NLR and Other Hematologic Biomarkers on the Outcomes of Early-Stage Non-Small-Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy. Curr Oncol. 2022 Jan 4;29(1):193-208. doi: 10.3390/curroncol29010019. PMID: 35049693; PMCID: PMC8774597.

[97] De Martino M, Daviaud C, Vanpouille-Box C. Radiotherapy: An immune response modifier for immuno-oncology. Semin Immunol. 2021 Feb;52:101474. doi: 10.1016/j.smim.2021.101474. Epub 2021 Mar 23. PMID: 33741223.

[98] Stadler JC, Belloum Y, Deitert B, Sementsov M, Heidrich I, Gebhardt C, Keller L, Pantel K. Current and Future Clinical Applications of ctDNA in Immuno-Oncology. Cancer Res. 2022 Feb 1;82(3):349-358. doi: 10.1158/0008-5472.CAN-21-1718. Epub 2021 Nov 23. PMID: 34815256; PMCID: PMC9397642.

[99] Semenkovich NP, Badiyan SN, Samson PP, Stowe HB, Wang YE, Star R, Devarakonda S, Govindan R, Waqar SN, Robinson CG, Vlacich G, Pellini B,

Chaudhuri AA. Pre-radiotherapy ctDNA liquid biopsy for risk stratification of oligometastatic non-small cell lung cancer. NPJ Precis Oncol. 2023 Oct 2;7(1):100. doi: 10.1038/s41698-023-00440-6. PMID: 37783809; PMCID: PMC10545784.

[100] Wu TH, Hsiue EH, Yang JC. Opportunities of circulating tumor DNA in lung cancer. Cancer Treat Rev. 2019 Aug;78:31-41. doi: 10.1016/j.ctrv.2019.07.002. Epub 2019 Jul 15. PMID: 31326635.

[101] Oliver J, Onieva JL, Garrido-Barros M, Cobo-Dols M, Martínez-Gálvez B, García-Pelícano AI, Dubbelman J, Benítez JC, Martín JZ, Cantero A, Pérez-Ruiz E, Rueda-Domínguez A, Barragán I. Fluorometric Quantification of Total Cell-Free DNA as a Prognostic Biomarker in Non-Small-Cell Lung Cancer Patients Treated with Immune Checkpoint Blockade. Cancers (Basel). 2023 Jun 26;15(13):3357. doi: 10.3390/cancers15133357. PMID: 37444467; PMCID: PMC10341133.

[102] Marar C, Starich B, Wirtz D. Extracellular vesicles in immunomodulation and tumor progression. Nat Immunol. 2021 May;22(5):560-570. doi: 10.1038/s41590-021-00899-0. Epub 2021 Mar 22. PMID: 33753940; PMCID: PMC9389600.

[103] Zhang L, Yu D. Exosomes in cancer development, metastasis, and immunity. Biochim Biophys Acta Rev Cancer. 2019 Apr;1871(2):455-468. doi: 10.1016/j.bbcan.2019.04.004. Epub 2019 Apr 30. PMID: 31047959; PMCID: PMC6542596.

[104] Yang Z, Zhong W, Yang L, Wen P, Luo Y, Wu C. The emerging role of exosomes in radiotherapy. Cell Commun Signal. 2022 Oct 31;20(1):171. doi: 10.1186/s12964-022-00986-1. PMID: 36316715; PMCID: PMC9620591.

[105] Wan Z, Dong Y, Wei M, Gao X, Yang G, Zhang J, Liu L. Exosomes in Tumor Immunotherapy: Mediator, Drug Carrier, and Prognostic Biomarker. Adv Biosyst. 2020 Nov;4(11):e2000061. doi: 10.1002/adbi.202000061. Epub 2020 Jul 23. PMID: 32700829.

[106] Rodríguez-Ruiz ME, Rodríguez I, Mayorga L, Labiano T, Barbes B, Etxeberria I, Ponz-Sarvise M, Azpilikueta A, Bolaños E, Sanmamed MF, Berraondo P, Calvo FA, Barcelos-Hoff MH, Perez-Gracia JL, Melero I. TGFβ Blockade Enhances Radiotherapy Abscopal Efficacy Effects in Combination with

Anti-PD1 and Anti-CD137 Immunostimulatory Monoclonal Antibodies. Mol Cancer Ther. 2019 Mar;18(3):621-631. doi: 10.1158/1535-7163.MCT-18-0558. Epub 2019 Jan 25. PMID: 30683810.

[107] Benci JL, Xu B, Qiu Y, Wu TJ, Dada H, Twyman-Saint Victor C, Cucolo L, Lee DSM, Pauken KE, Huang AC, Gangadhar TC, Amaravadi RK, Schuchter LM, Feldman MD, Ishwaran H, Vonderheide RH, Maity A, Wherry EJ, Minn AJ. Tumor Interferon Signaling Regulates a Multigenic Resistance Program to Immune Checkpoint Blockade. Cell. 2016 Dec 1;167(6):1540-1554.e12. doi: 10.1016/j.cell.2016.11.022. PMID: 27912061; PMCID: PMC5385895.

[108] Nishiyama A, Nakanishi M. Navigating the DNA methylation landscape of cancer. Trends Genet. 2021 Nov;37(11):1012-1027. doi: 10.1016/j.tig.2021.05.002. Epub 2021 Jun 10. PMID: 34120771.

[109] Sasa GBK, Xuan C, Chen M, Jiang Z, Ding X. Clinicopathological implications of lncRNAs, immunotherapy and DNA methylation in lung squamous cell carcinoma: a narrative review. Transl Cancer Res. 2021 Dec;10(12):5406-5429. doi: 10.21037/tcr-21-1607. PMID: 35116387; PMCID: PMC8799054.

[110] Zhu X, Wang Y, Tan L, Fu X. The pivotal role of DNA methylation in the radio-sensitivity of tumor radiotherapy. Cancer Med. 2018 Aug;7(8):3812-3819. doi: 10.1002/cam4.1614. Epub 2018 Jun 27. PMID: 29952116; PMCID: PMC6089158.

[111] Alix-Panabières C, Pantel K. Liquid Biopsy: From Discovery to Clinical Application. Cancer Discov. 2021 Apr;11(4):858-873. doi: 10.1158/2159-8290.CD-20-1311. PMID: 33811121.

[112] Reddy AV, Sehgal S, Hill CS, Zheng L, He J, Herman JM, Meyer J, Narang AK. Upfront Chemotherapy Followed by Stereotactic Body Radiation Therapy with or without Surgery in Older Patients with Localized Pancreatic Cancer: A Single Institution Experience and Review of the Literature. Curr Oncol. 2022 Jan 11;29(1):308-320. doi: 10.3390/curroncol29010028. PMID: 35049702; PMCID: PMC8774377.

[113] Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, Dunn IF, Gaspar LE, Gatson NTN, Gondi V, Jordan JT, Lassman AB, Maues J, Mohile N, Redjal N, Stevens G, Sulman E, van den Bent M, Wallace HJ, Weinberg JS, Zadeh G, Schiff D. Treatment for Brain Metastases: ASCO-SNO-ASTRO

Guideline. J Clin Oncol. 2022 Feb 10;40(5):492-516. doi: 10.1200/JCO.21.02314. Epub 2021 Dec 21. Erratum in: J Clin Oncol. 2022 Apr 20;40(12):1392. PMID: 34932393.
[114] Basler L, Kroeze SG, Guckenberger M. SBRT for oligoprogressive oncogene addicted NSCLC. Lung Cancer. 2017 Apr;106:50-57. doi: 10.1016/j.lungcan.2017.02.007. Epub 2017 Feb 6. PMID: 28285694.
[115] Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, Dowell J, Hughes R, Abdulrahman R, Camidge DR, Gaspar LE, Doebele RC, Bunn PA, Choy H, Timmerman R. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol. 2014 Dec 1;32(34):3824-30. doi: 10.1200/JCO.2014.56.7412. Epub 2014 Oct 27. PMID: 25349291.
[116] Anscher MS, Arora S, Weinstock C, Amatya A, Bandaru P, Tang C, Girvin AT, Fiero MH, Tang S, Lubitz R, Amiri-Kordestani L, Theoret MR, Pazdur R, Beaver JA. Association of Radiation Therapy With Risk of Adverse Events in Patients Receiving Immunotherapy: A Pooled Analysis of Trials in the US Food and Drug Administration Database. JAMA Oncol. 2022 Feb 1;8(2):232-240. doi: 10.1001/jamaoncol.2021.6439. Erratum in: JAMA Oncol. 2022 Feb 1;8(2):306. PMID: 34989781; PMCID: PMC8739815.

CHAPTER VI

Abuodeh Y, Venkat P, Kim S (2016) Systematic review of case reports on the abscopal effect. Curr Probl Cancer 40:25–37

Addeo A, Passaro A, Malapelle U, Luigi Banna G, Subbiah V, Friedlaender A (2021) Immunotherapy in non-small cell lung cancer harbouring driver mutations. Cancer Treat Rev 96:102179

Alexander M, Kim SY, Cheng H (2020) Update 2020: management of non-small cell lung cancer. Lung 198:897–907

Amini A, Verma V, Simone CB 2nd, Chetty IJ, Chun SG, Donington J, Edelman MJ, Higgins KA, Kestin LL, Movsas B, Rodrigues GB, Rosenzweig KE, Rybkin II, Slotman BJ, Wolf A, Chang JY (2022) American radium society appropriate use criteria for radiation therapy in oligometastatic or oligoprogressive non-small cell lung cancer. Int J Radiat Oncol Biol Phys 112:361–375

Antoni D, Burckel H, Noel G (2021) Combining radiation therapy with ALK inhibitors in anaplastic lymphoma kinase-positive non-small cell lung cancer (NSCLC): a clinical and preclinical overview. Cancers (Basel) 13:2394

Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, Congedo MT, Gomez DR, Wright GM, Melloni G, Milano MT, Sole CV, De Pas TM, Carter DL, Warner AJ, Rodrigues GB (2014) An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer 15:346–355

Barker HE, Paget JTE, Khan AA, Harrington KJ (2015) The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer 15:409–425

Baskar R, Lee KA, Yeo R, Yeoh KW (2012) Cancer and radiation therapy: current advances and future directions. Int J Med Sci 9:193–199

Basler L, Kroeze SG, Guckenberger M (2017) SBRT for oligoprogressive oncogene addicted NSCLC. Lung Cancer 106:50–57

Baxevanos P, Mountzios G (2018) Novel chemotherapy regimens for advanced lung cancer: have we reached a plateau? Ann Transl Med 6:139

Berge EM, Doebele RC (2014) Targeted therapies in non-small cell lung cancer: emerging oncogene targets following the success of epidermal growth factor receptor. Semin Oncol 41: 110–125

Błach J, Wojas-Krawczyk K, Nicoś M, Krawczyk P (2021) Failure of immunotherapy-the molecu- lar and immunological origin of immunotherapy resistance in lung cancer. Int J Mol Sci 22:9030 Blake-Cerda M, Lozano-Ruíz F,

Maldonado-Magos F, de la Mata-Moya D, Díaz-García D, Lara- Mejía L, Zatarain-Barrón ZL, Cuevas-Góngora MF, Barron-Barron F, Corona-Cruz JF, Cabrera-Miranda L, Arroyo-Hernández M, Gerson R, Arrieta O (2021) Consolidative stereo- tactic ablative radiotherapy (SABR) to intrapulmonary lesions is associated with prolonged progression-free survival and overall survival in oligometastatic NSCLC patients: a prospective phase 2 study. Lung Cancer 152:119–12

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627–1639

Borghetti P, Bonù ML, Giubbolini R, Levra NG, Mazzola R, Perna M, Visani L, Meacci F, Taraborrelli M, Triggiani L, Franceschini D, Greco C, Bruni A, Magrini SM, Scotti V (2019) Concomitant radiotherapy and TKI in metastatic EGFR- or ALK-mutated non-small cell lung cancer: a multicentric analysis on behalf of AIRO lung cancer study group. Radiol Med 124: 662–670

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135

Brassart-Pasco S, Dalstein V, Brassart B, Dewolf M, Clavel C, Oudart JB (2020) Immunotherapy in non-small-cell lung cancer: from targeted molecules to resistance patterns. Pharmacogenomics 21:705–720

Buchbinder EI, Desai A (2016) CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol 39:98–106

Camidge DR, Pao W, Sequist LV (2014) Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol 11:473–481

Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu T-E, Badin F, Ready N, Hiltermann TJN, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR, Villaruz LC, Havel L, Krejci J, Corral Jaime J, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC, Socinski MA (2017) First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376:2415–2426

Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW (2017) The role of radiotherapy in epidermal growth factor receptor mutation-positive patients with oligoprogression: a matched-cohort analysis. Clin Oncol (R Coll Radiol) 29:568–575

Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 10:1037–1044

Chen SH, Chang JY (2019) New insights into mechanisms of cisplatin resistance: from tumor cell to microenvironment. Int J Mol Sci 20:4136

Chen H, Louie AV, Higginson DS, Palma DA, Colaco R, Sahgal A (2020) Stereotactic radiosurgery and stereotactic body radiotherapy in the management of oligometastatic disease. Clin Oncol (R Coll Radiol) 32:713–727

Chicas-Sett R, Morales-Orue I, Castilla-Martinez J, Zafra-Martin J, Kannemann A, Blanco J, Lloret M, Lara PC (2019) Stereotactic ablative radiotherapy combined with immune checkpoint inhibitors reboots the immune response assisted by immunotherapy in metastatic lung cancer: a systematic review. Int J Mol Sci 20:2173

Chicas-Sett R, Zafra-Martin J, Morales-Orue I, Castilla-Martinez J, Berenguer-Frances MA, Gonzalez-Rodriguez E, Rodriguez-Abreu D, Couñago F (2020)

Immunoradiotherapy as an effective therapeutic strategy in lung cancer: from palliative care to curative intent. Cancers (Basel) 12:2178

Chicas-Sett R, Zafra J, Rodriguez-Abreu D, Castilla-Martinez J, Benitez G, Salas B, Hernandez S, Lloret M, Onieva JL, Barragan I, Lara PC (2022) Combination of SABR with anti-PD-1 in oligoprogressive non-small cell lung cancer and melanoma: results of a prospective multicenter observational study. Int J Radiat Oncol Biol Phys 114(4):655–665. https://doi.org/10.1016/j. ijrobp.2022.05.013. Epub 2022 May 18. PMID: 35595158

Chinnaiyan P, Huang S, Vallabhaneni G, Armstrong E, Varambally S, Tomlins SA, Chinnaiyan AM, Harari PM (2005) Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). Cancer Res 65:3328–3335

Conforti F, Catania C, Toffalorio F, Duca M, Spitaleri G, Barberis M, Noberasco C, Delmonte A, Santarpia M, Lazzari C, De Pas TM (2013) EGFR tyrosine kinase inhibitors beyond focal progression obtain a prolonged disease control in patients with advanced adenocarcinoma of the lung. Lung Cancer 81:440–444

Connell PP, Hellman S (2009) Advances in radiotherapy and implications for the next century: a historical perspective. Cancer Res 69:383–392

Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, Zhou C, Shreeve SM, Selaru P, Polli A, Schnell P, Wilner KD, Wiltshire R, Camidge DR, Crinò L (2015) Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol 33:1881–1888

Dai Y, Wei Q, Schwager C, Moustafa M, Zhou C, Lipson KE, Weichert W, Debus J, Abdollahi A (2015) Synergistic effects of crizotinib and radiotherapy in experimental EML4-ALK fusion positive lung cancer. Radiother Oncol 114:173–181

Das AK, Sato M, Story MD, Peyton M, Graves R, Redpath S, Girard L, Gazdar AF, Shay JW, Minna JD, Nirodi CS (2006) Non-small-cell lung cancers with kinase

domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. Cancer Res 66:9601–9608

Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, Formenti SC (2005) Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res 11:728–734

Demaria S, Golden EB, Formenti SC (2015) Role of local radiation therapy in cancer immunother- apy. JAMA Oncol 1:1325–1332

Desideri I, Francolini G, Scotti V, Pezzulla D, Becherini C, Terziani F, Delli Paoli C, Olmetto E, Visani L, Meattini I, Greto D, Bonomo P, Loi M, Detti B, Livi L (2019) Benefit of ablative versus palliative-only radiotherapy in combination with nivolumab in patients affected by metastatic kidney and lung cancer. Clin Transl Oncol 21:933–938

Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, Stratford IJ, Poon E, Morrow M, Stewart R, Jones H, Wilkinson RW, Honeychurch J, Illidge TM (2014) Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 74:5458–5468

Elsayed M, Christopoulos P (2021) Therapeutic sequencing in ALK(+) NSCLC. Pharmaceuticals (Basel) 14:80

Facondo G, Vullo G, Valeriani M, Ascolese AM, De Sanctis V, Osti MF (2021) Stereotactic body radiation therapy (SBRT) for patients with oligometastatic/oligoprogressive adrenal metastases: outcomes and toxicities profile in a monoinstitutional study. Cancer Treat Res Commun 29: 100481

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A (2016) Atezolizumab versus docetaxel for patients with previously treated non- small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 387:1837–1846

Franceschini D, De Rose F, Cozzi S, Franzese C, Rossi S, Finocchiaro G, Toschi L, Santoro A, Scorsetti M (2020) The use of radiation therapy for oligoprogressive/oligopersistent oncogene- driven non small cell lung cancer: state of the art. Crit Rev Oncol Hematol 148:102894

Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA, Camidge DR, De Petris L, Kim DW, Chiappori A, Moro-Sibilot DL, Duruisseaux M, Crino L, De Pas T, Dansin E, Tessmer A, Yang JC, Han JY, Bordogna W, Golding S, Zeaiter A, Ou SI (2016) Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. J Clin Oncol 34:4079–4085

Gan GN, Weickhardt AJ, Scheier B, Doebele RC, Gaspar LE, Kavanagh BD, Camidge DR (2014) Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys 88:892–898

Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV (2016) Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 17: 1672–1682

Grass GD, Krishna N, Kim S (2016) The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer 40:10–24

Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, Dingemans AC, Fournier B, Hurkmans C, Lecouvet FE, Meattini I, Méndez Romero A, Ricardi U, Russell NS, Schanne DH, Scorsetti M, Tombal B, Verellen D, Verfaillie C, Ost P (2020) Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncol- ogy

and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 21:e18–e28

Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, Schwendener R, Pruschy M, Knuth A, van den Broek M (2012) Radiotherapy promotes tumor-specific effector $CD8^+$ T cells via dendritic cell activation. J Immunol 189:558–566

Habets EJ, Dirven L, Wiggenraad RG, Verbeek-de Kanter A, Lycklama À, Nijeholt GJ, Zwinkels H, Klein M, Taphoorn MJ (2016) Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospec- tive study. Neuro-Oncology 18:435–444

Harada D, Takigawa N (2021) Oligoprogression in non-small cell lung cancer. Cancers (Basel) 13: 5823

Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13:8–10 Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, Molina J, Kim J-H, Arvis CD, Ahn M-J, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387:1540–1550

Hsu ML, Naidoo J (2020) Principles of immunotherapy in non-small cell lung cancer. Thorac Surg Clin 30:187–198

Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS (2018) Safety of combining radiotherapy with immune-checkpoint inhibition. Nat Rev Clin Oncol 15:477–494
Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, Dowell J, Hughes R,

Abdulrahman R, Camidge DR, Gaspar LE, Doebele RC, Bunn PA, Choy H, Timmerman R (2014) Phase II trial of stereotactic body radiation therapy

combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32:3824–3830

Jiao Q, Bi L, Ren Y, Song S, Wang Q, Wang YS (2018) Advances in studies of tyrosine kinase inhibitors and their acquired resistance. Mol Cancer 17:36

Kagawa Y, Furuta H, Uemura T, Watanabe N, Shimizu J, Horio Y, Kuroda H, Inaba Y, Kodaira T, Masago K, Fujita S, Niimi A, Hida T (2020) Efficacy of local therapy for oligoprogressive disease after programmed cell death 1 blockade in advanced non-small cell lung cancer. Cancer Sci 111:4442–4452

Khalifa J, Amini A, Popat S, Gaspar LE, Faivre-Finn C (2016) Brain metastases from NSCLC: radiation therapy in the era of targeted therapies. J Thorac Oncol 11:1627–1643

Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B (2005) EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 352:786–792

Kogita A, Togashi Y, Hayashi H, Sogabe S, Terashima M, De Velasco MA, Sakai K, Fujita Y, Tomida S, Takeyama Y, Okuno K, Nakagawa K, Nishio K (2014) Hypoxia induces resistance to ALK inhibitors in the H3122 non-small cell lung cancer cell line with an ALK rearrangement via epithelial-mesenchymal transition. Int J Oncol 45:1430–1436

Kroeze SGC, Schaule J, Fritz C, Kaul D, Blanck O, Kahl KH, Roeder F, Siva S, Verhoeff JJC, Adebahr S, Schymalla MM, Glatzer M, Szuecs M, Geier M, Skazikis G, Sackerer I, Lohaus F, Eckert F, Guckenberger M (2021) Metastasis directed stereotactic radiotherapy in NSCLC patients progressing under targeted- or immunotherapy: efficacy and safety reporting from the 'TOaSTT' database. Radiat Oncol 16:4

Laurie SA, Banerji S, Blais N, Brule S, Cheema PK, Cheung P, Daaboul N, Hao D, Hirsh V, Juergens R, Laskin J, Leighl N, MacRae R, Nicholas G, Roberge D, Rothenstein J, Stewart DJ, Tsao MS (2019) Canadian consensus:

oligoprogressive, pseudoprogressive, and oligometastatic non-small-cell lung cancer. Curr Oncol 26:e81–e93

Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, Grewal J, Prabhu S, Loghin M, Gilbert MR, Jackson EF (2011) Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys 79:1487–1495

Li J, Wu X, Wang Z, Shen Z, Sun N, Zhu X (2015) Ionizing radiation reduces TKI resistance caused by T790M mutation in NSCLC cell lines. Zhongguo Fei Ai Za Zhi 18:475–480

Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, Mendez Romero A, Nevens D, Palma D, Park C, Ricardi U, Scorsetti M, Yu J, Woodward WA (2020) Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol 148:157–166

Liu B, Liu H, Ma Y, Ding Q, Zhang M, Liu X, Liu M (2021) EGFR-mutated stage IV non-small cell lung cancer: what is the role of radiotherapy combined with TKI? Cancer Med 10:6167–6188 Mattes MD, Eubank TD, Almubarak M, Wen S, Marano GD, Jacobson GM, Ma PC (2021) A prospective trial evaluating the safety and systemic response from the concurrent use of radiation therapy with checkpoint inhibitor immunotherapy in metastatic non-small cell lung cancer. Clin Lung Cancer 22:268–273

McRee AJ, Cowherd S, Wang AZ, Goldberg RM (2011) Chemoradiation therapy in the manage- ment of gastrointestinal malignancies. Future Oncol 7:409–426

Milano MT, Grimm J, Niemierko A, Soltys SG, Moiseenko V, Redmond KJ, Yorke E, Sahgal A, Xue J, Mahadevan A, Muacevic A, Marks LB, Kleinberg LR (2021) Single- and multifraction stereotactic radiosurgery dose/volume tolerances of the brain. Int J Radiat Oncol Biol Phys 110: 68–86

Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B,

Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M (2009) Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957

Mole RH (1953) Whole body irradiation—radiobiology or medicine? Br J Radiol 26:234–241 Nakamura M, Kageyama SI, Niho S, Okumura M, Hojo H, Motegi A, Nakamura N, Zenda S, Yoh K, Goto K, Akimoto T (2019) Impact of EGFR mutation and ALK translocation on recurrence pattern after definitive chemoradiotherapy for inoperable stage III non-squamous non-small-cell lung cancer. Clin Lung Cancer 20:e256–e264

Network NCC. (2021). Non-small cell lung cancer (Version 1.2022). Retrieved December 7, 2021, https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Senthi S, Swaminath A, Kopek N, Liu M, Moore K, Currie S, Schlijper R, Bauman GS, Laba J, Qu XM, Warner A, Senan S (2020) Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 38:2830–2838

Paz-Ares L, Horn L, Borghaei H, Spigel DR, Steins M, Ready N, Chow LQM, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaeufl M, Rodriguez O, Burgio MA, Fayette J, Gettinger SN, Harbison C, Dorange C, Finckenstein FG, Brahmer JR (2015). Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC)) J Clin Oncol 33:LBA109

Pembroke CA, Fortin B, Kopek N (2018) Comparison of survival and prognostic factors in patients treated with stereotactic body radiotherapy for oligometastases or oligoprogression. Radiother Oncol 127:493–500

Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, Mok TS, Reck M, Van Schil PE, Hellmann MD, Peters S (2018) Metastatic non-small cell lung

cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29:iv192–iv237

Postow MA, Callahan MK, Wolchok JD (2015) Immune checkpoint blockade in cancer therapy. J Clin Oncol 33:1974–1982

Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, Hamad L, Kim S, Lacouture ME, LeBoeuf NR, Lenihan D, Onofrei C, Shannon V, Sharma R, Silk AW, Skondra D, Suarez-Almazor ME, Wang Y, Wiley K, Kaufman HL, Ernstoff MS (2017) Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 5:95

Qiu B, Liang Y, Li Q, Liu G, Wang F, Chen Z, Liu M, Zhao M, Liu H (2017) Local therapy for oligoprogressive disease in patients with advanced stage non-small-cell lung cancer harboring epidermal growth factor receptor mutation. Clin Lung Cancer 18:e369–e373

Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenkov Y, Soria JC (2020) Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 382:41–50

Régina A, Demeule M, Laplante A, Jodoin J, Dagenais C, Berthelet F, Moghrabi A, Béliveau R (2001) Multidrug resistance in brain tumors: roles of the blood-brain barrier. Cancer Metastasis Rev 20:13–25

Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, Bohnet S, Zhou C, Lee KH, Nogami N, Okamoto I, Leighl N, Hodge R, McKeown A, Brown AP, Rukazenkov Y, Ramalingam SS, Vansteenkiste J (2018) CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol:Jco2018783118. https://doi.org/10.1200/JCO.2018.78.3118

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR (2017) Atezolizumab versus docetaxel in patients with previously treated non- small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265

Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez- Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239–246

Russo A, Franchina T, Ricciardi GR, Ferraro G, Scimone A, Bronte G, Russo A, Rolfo C, Adamo V (2016) Central nervous system involvement in ALK-rearranged NSCLC: promising strategies to overcome crizotinib resistance. Expert Rev Anticancer Ther 16:615–623

Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, Villaflor VM, Stadler WM, Hoffman PC, Cohen EE, Connell PP, Haraf DJ, Vokes EE, Hellman S, Weichselbaum RR (2012) Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 118:2962–2970

Schouten LJ, Rutten J, Huveneers HA, Twijnstra A (2002) Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 94: 2698–2705

Seiwert TY, Salama JK, Vokes EE (2007) The concurrent chemoradiation paradigm—general principles. Nat Clin Pract Oncol 4:86–100

Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31:3327–3334

Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, Deweese TL, Drake CG (2015) Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. Cancer Immunol Res 3:345–355

Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Jänne PA (2013) Crizotinib versus chemother- apy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394

Shukuya T, Takahashi T, Naito T, Kaira R, Ono A, Nakamura Y, Tsuya A, Kenmotsu H, Murakami H, Harada H, Mitsuya K, Endo M, Nakasu Y, Takahashi K, Yamamoto N (2011) Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. Lung Cancer 74:457–461

Singh SA, McDermott DM, Mattes MD (2020) Impact of systemic therapy type and timing on intracranial tumor control in patients with brain metastasis from non-small-cell lung cancer treated with stereotactic radiosurgery. World Neurosurg 144:e813–e823

Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371:2167–2177

Song CW, Cho LC, Yuan J, Dusenbery KE, Griffin RJ, Levitt SH (2013) Radiobiology of stereotactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. Int J Radiat Oncol Biol Phys 87:18–19

Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, Wang J, Yang JC, Lu Y, Atagi S, Ponce S, Lee DH, Liu Y, Yoh K, Zhou JY, Shi X, Webster A, Jiang H, Mok TS (2015) Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small- cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 16:990–998

Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 77:655–661

Spigel DR, Reckamp KL, Rizvi NA, Poddubskaya E, West HJ, Eberhardt WEE, Baas P, Antonia SJ, Pluzanski A, Vokes EE, Holgado E, Waterhouse DM, Ready N, Gainor JF, Aren OR, Horn L, Paz-Ares L, Baudelet C, Lestini BJ, Brahmer JR (2015) A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC). J Clin Oncol 33:8009

Spranger S, Gajewski TF (2018) Mechanisms of tumor cell–intrinsic immune evasion. Ann Rev Cancer Biol 2:213–228

Suresh K, Naidoo J, Lin CT, Danoff S (2018) Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. Chest 154:1416–1423

Takeda M, Okamoto I, Nakagawa K (2013) Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. J Thorac Oncol 8:654–657

Tanaka T, Munshi A, Brooks C, Liu J, Hobbs ML, Meyn RE (2008) Gefitinib radiosensitizes non-small cell lung cancer cells by suppressing cellular DNA repair capacity. Clin Cancer Res 14:1266–1273

Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, Dumoulin DW, Bahce I, Niemeijer AN, de Langen AJ, Monkhorst K, Baas P (2019) Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 5:1276–1282

Timmerman RD, Story M (2006) Stereotactic body radiation therapy: a treatment in need of basic biological research. Cancer J 12:19–20

Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H (2010) Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070–1076

Tsao M, Xu W, Sahgal A (2012) A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer 118:2486–2493

Tumati V, Kumar S, Yu L, Chen B, Choy H, Saha D (2013) Effect of PF-02341066 and radiation on non-small cell lung cancer cells. Oncol Rep 29:1094–1100

Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC (2014) Combinations of immunotherapy and radiation in cancer therapy. Front Oncol 4:325

Wang Z, Wei L, Li J, Zhou H, Li S, Chen D, Yu Y, Zhao L, Zhu X, Song Y (2021) Combing stereotactic body radiotherapy with checkpoint inhibitors after oligoprogression in advanced non-small cell lung cancer. Transl Lung Cancer Res 10:4368–4379

Wang XS, Bai YF, Verma V, Yu RL, Tian W, Ao R, Deng Y, Xia JL, Zhu XQ, Liu H, Pan HX, Yang L, He YK, Bai HS, Luo X, Guo Y, Zhou MX, Sun YM, Zhang ZC, Li SM, Cheng X, Tan BX, Han LF, Liu YY, Zhang K, Zeng FX, Jia L, Hao XB, Wang YY, Feng G, Xie K, Lu Y, Zeng M (2022) Randomized trial of first-line tyrosine kinase inhibitor with or without radio- therapy for synchronous oligometastatic EGFR-mutated NSCLC. J Natl Cancer Inst 115:742

Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, Aisner DL, Gaspar LE, Kavanagh BD, Doebele RC, Camidge DR (2012) Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 7:1807–1814

West H, Solomon B (2020) Brain metastassis in non-small cell lung cancer. Uptodate. Retrieved July 1, 2022, from https://www.uptodate.com/contents/brain-metastases-in-non-small-cell-lung- cancer

Williamson CW, Sherer MV, Zamarin D, Sharabi AB, Dyer BA, Mell LK, Mayadev JS (2021) Immunotherapy and radiation therapy sequencing: state of the data on timing, efficacy, and safety. Cancer 127:1553–1567

Wrona A (2019) Management of CNS disease in ALK-positive non-small cell lung cancer: is whole brain radiotherapy still needed? Cancer Radiother 23:432–438

Xu Q, Liu H, Meng S, Jiang T, Li X, Liang S, Ren S, Zhou C (2019) First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease. J Cancer 10:522–529

Xu Y, Li H, Fan Y (2021) Progression patterns, treatment, and prognosis beyond resistance of responders to immunotherapy in advanced non-small cell lung cancer. Front Oncol 11:642883 Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, Yamanaka K, Sato Y, Jokura H, Yomo S, Nagano O, Kenai H, Moriki A, Suzuki S, Kida Y, Iwai Y, Hayashi M, Onishi H, Gondo M, Sato M, Akimitsu T, Kubo K, Kikuchi Y, Shibasaki T, Goto T, Takanashi M, Mori Y,

Takakura K, Saeki N, Kunieda E, Aoyama H, Momoshima S, Tsuchiya K (2014) Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 15:387–395

Yang J, Ramalingam SS, Jänne PA, Cantarini M, Mitsudomi T (2016) LBA2_PR: osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: updated phase 1 (P1) and pooled phase 2 (P2) results. J Thorac Oncol 11:S152–S153

Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, Kris MG, Miller VA, Ladanyi M, Riely GJ (2013a) Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 19(8):2240–2247. https://doi.org/10.1158/1078-0432.CCR-12-2246. Epub 2013 Mar 7. PMID: 23470965; PMCID: PMC3630270

Yu HA, Sima CS, Huang J, Solomon SB, Rimner A, Paik P, Pietanza MC, Azzoli CG, Rizvi NA, Krug LM, Miller VA, Kris MG, Riely GJ (2013b) Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. J Thorac Oncol 8:346–351

Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, Meyerson M, Eck MJ (2008) The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A 105:2070–2075

Zafra JC-SR, Rodriguez-Abreu D et al (2021) Combination of stereotactic ablative radiotherapy with anti-PD-1 in oligoprogressive disease: final results of a prospective multicenter study. Ann Oncol 32:S949–S1039

CHAPTER VII

1. Felip Font E, Gettinger SN, Burgio MA, et al. Three-year follow-up from CheckMate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC). Ann Oncol 2017;28:v462.

2. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung can- cer (KEYNOTE-010): A randomised controlled trial. Lancet 2016;387:1540–1550.

3. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. New Engl J Med 2018;378:2288–2301.

4. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. New Engl J Med 2015;372:2521–2532.

5. Chen DS, Mellman I. Elements of cancer immunity and the cancer- immune set point. Nature 2017;541:321–330.

6. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–128.

7. Meyer C, Cagnon L, Costa-Nunes CM, et al. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. Cancer Immunol Immunother 2014;63: 247–257.

8. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non−small-cell lung cancer. New Engl J Med 2018;378:2078–2092.

9. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non−small-cell lung cancer. New Engl J Med 2018;379:2040–2051.

10. Wintner LM, Giesinger JM, Zabernigg A, et al. Quality of life during chemotherapy in lung cancer patients: Results across different treatment lines. Br J Cancer 2013;109:2301–2308.

11. Facchinetti F, Mazzaschi G, Barbieri F, et al. First-line pembrolizumab in advanced non-small cell lung cancer patients with poor performance status. Eur J Cancer 2020;130:155–167.

12. Theelen W, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: Results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 2019;5:1276–1282.

13. Welsh J, Menon H, Chen D, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: A randomized phase I/II trial. J Immunother Cancer 2020;8: e001001.

14. Bauml JM, Mick R, Ciunci C, et al. Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung cancer: A phase 2 trial. JAMA Oncol 2019;5:1283–1290.

15. Chicas-Sett R, Morales-Orue I, Castilla-Martinez J, et al. Stereotactic ablative radiotherapy combined with immune checkpoint inhibitors reboots the immune response assisted by immunotherapy in metastatic lung cancer: A systematic review. Int J Mol Sci 2019;20:2173.

16. Kissel M, Martel-Lafay I, Lequesne J, et al. Stereotactic ablative radiotherapy and systemic treatments for extracerebral oligometastases, oligorecurrence, oligopersistence and oligoprogression from lung cancer. BMC Cancer 2019;19:1237.

17. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 2014;32:3824–3830.

18. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2012;7:1807–1814.

19. Qiu B, Liang Y, Li Q, et al. Local therapy for oligoprogressive disease in patients with advanced stage non-small-cell lung cancer harboring epidermal growth factor receptor mutation. Clin Lung Cancer 2017;18:e369–e373.

20. U.S. Department of Health and Human Services FDA. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); Clinical trial endpoints for the approval of cancer drugs and biologics; 2007. https://www.fda.gov/regulatory-information/ search-fda-guidance-documents/clinical-trial-endpoints-approval-can- cer-drugs-and-biologics. Accessed April 14, 2021.

21. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310:2191– 2194.

22. McGee HM, Daly ME, Azghadi S, et al. Stereotactic ablative radiation therapy induces systemic differences in peripheral blood immunophenotype dependent on irradiated site. Int J Radiat Oncol Biol Phys 2018;101:1259–1270.

23. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. Lancet 2019;393:2051–2058.

24. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med 2018;24:1845– 1851.

25. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–e152.

26. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol 2020;148:157–166.

27. Patel JD, Bestvina CM, Karrison T, et al. Randomized phase I trial to evaluate concurrent or sequential ipilimumab, nivolumab, and stereo- tactic body radiotherapy in patients with stage IV non-small cell lung cancer (COSINR Study). J Clin Oncol 2020;38(15 suppl):9616.

28. Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys 2014;88:892–898.

29. Shukuya T, Takahashi T, Naito T, et al. Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. Lung Cancer 2011;74:457–461.

30. Torok JA, Salama JK. Combining immunotherapy and radiotherapy for the STAR treatment. Nat Rev Clin Oncol 2019;16:666–667.

31. Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypo- fractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: An open-label, multicentre, randomised, phase 2 trial. Lancet Oncol 2022;23:279–291.

32. Theelen W, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Respir Med 2021;9:467–475.

33. Chapman AM, Sun KY, Ruestow P, Cowan DM, Madl AK. Lung cancer mutation profile of EGFR, ALK, and KRAS: Meta-analysis and comparison of never and ever smokers. Lung Cancer 2016;102:122–134.

34. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. Cell 2012;150:251–263.

35. Chicas-Sett R, Zafra-Martin J, Morales-Orue I, et al. Immunoradiotherapy as an effective therapeutic strategy in lung cancer: From palliative care to curative intent. Cancers (Basel) 2020;12:2178.

36. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–135.

37. Turgeon GA, Weickhardt A, Azad AA, Solomon B, Siva S. Radiotherapy and immunotherapy: A synergistic effect in cancer care. Med J Aust 2019;210:47–53.

38. Buchwald ZS, Wynne J, Nasti TH, et al. Radiation, immune checkpoint blockade and the abscopal effect: A critical review on timing, dose and fractionation. Front Oncol 2018;8:612.

39. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.

40. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti−CTLA-4 antibody. Clin Cancer Res 2009;15:5379–5388.

41. Marciscano AE, Ghasemzadeh A, Nirschl TR, et al. Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy. Clin Cancer Res 2018;24:5058–5071.

42. Tang C, Welsh JW, de Groot P, et al. Ipilimumab with stereotactic ablative radiation therapy: Phase I results and immunologic correlates from peripheral T cells. Clin Cancer Res 2017;23:1388–1396.

43. Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. Nat Rev Clin Oncol 2019;16:123–135.

44. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. OncoImmunology 2014;3:e28780.

45. Theurich S, Rothschild SI, Hoffmann M, et al. Local tumor treatment in combination with systemic ipilimumab immunotherapy prolongs overall survival in patients with advanced malignant melanoma. Cancer Immunol Res 2016;4:744–754.

46. Chicas-Sett R, Morales-Orue I, Rodriguez-Abreu D, Lara-Jimenez P. Combining radiotherapy and ipilimumab induces clinically relevant radiation-induced abscopal effects in metastatic melanoma patients: A systematic review. Clin Transl Radiat Oncol 2018;9:5–11.

47. Vanpouille-Box C, Diamond JM, Pilones KA, et al. TGFb Is a master regulator of radiation therapy-induced antitumor immunity. Cancer Res 2015;75:2232–2242.

48. Benci JL, Xu B, Qiu Y, et al. Tumor interferon signaling regulates a multigenic resistance program to immune checkpoint blockade. Cell 2016;167:1540–1554 e12.

49. Chen D, Verma V, Patel RR, Barsoumian HB, Cortez MA, Welsh JW. Absolute lymphocyte count predicts abscopal responses and outcomes in patients receiving combined immunotherapy and radiation therapy: Analysis of 3 phase 1/2 trials. Int J Radiat Oncol Biol Phys 2020;108:196–203.

CHAPTER VIII

1. Bagchi S, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. Annu Rev Pathol. 2021;16:223-49.

2. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017;168(4):707-23.

3. Liu YT, Sun ZJ. Turning cold tumors into hot tumors by improving T-cell infiltration. Theranostics. 2021;11(11):5365-86.

4. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016;40(1):25-37.

5. Chicas-Sett R, Morales-Orue I, Castilla-Martinez J, Zafra-Martin J, Kannemann A, Blanco J, et al. Stereotactic Ablative Radiotherapy Combined with Immune Checkpoint Inhibitors Reboots the Immune Response Assisted by Immunotherapy in Metastatic Lung Cancer: A Systematic Review. Int J Mol Sci. 2019;20(9).

6. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157-66.

7. Popp I, Vaes RDW, Wieten L, Adebahr S, Hendriks L, Bavafaye Haghighi E, et al. Radiotherapy to reinvigorate immunotherapy activity after acquired resistance in metastatic non-small-cell lung cancer: A pooled analysis of two institutions prospective phase II single arm trials. Radiother Oncol. 2023;190:110048.

8. Franceschini D, De Rose F, Cozzi S, Franzese C, Rossi S, Finocchiaro G, et al. The use of radiation therapy for oligoprogressive/oligopersistent oncogene-driven non small cell lung cancer: State of the art. Crit Rev Oncol Hematol. 2020;148:102894.

9. Zhao X, Shao C. Radiotherapy-Mediated Immunomodulation and Anti-Tumor Abscopal Effect Combining Immune Checkpoint Blockade. Cancers (Basel). 2020;12(10).

10. Chicas-Sett R, Zafra J, Rodriguez-Abreu D, Castilla-Martinez J, Benitez G, Salas B, et al. Combination of SABR With Anti-PD-1 in Oligoprogressive Non-

Small Cell Lung Cancer and Melanoma: Results of a Prospective Multicenter Observational Study. Int J Radiat Oncol Biol Phys. 2022;114(4):655-65.
11. McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2021;39(1):30-7.
12. Schellenberg D, Gabos Z, Duimering A, Debenham BJ, Fairchild A, Huang F, et al. Stereotactic Ablative Radiotherapy for Oligo-Progressive Cancers: Results of the Randomized Phase II STOP Trial. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):S58.
13. Nelson BE, Adashek JJ, Sheth AA, Subbiah V. Predicting the Abscopal Effect: Associated Tumor Histologic Subtypes and Biomarkers. Mol Cancer Ther. 2023;22(6):706-16.
14. Alix-Panabières C, Pantel K. Liquid Biopsy: From Discovery to Clinical Application. Cancer Discov. 2021;11(4):858-73.
15. Semenkovich NP, Samson P, Badiyan SN, Vlacich GR, Stowe HB, Pellini B, et al. Circulating Tumor DNA for Early Risk Stratification of Oligometastatic Lung Cancer. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):S29-S30.
16. Sánchez-Herrero E, Serna-Blasco R, Robado de Lope L, González-Rumayor V, Romero A, Provencio M. Circulating Tumor DNA as a Cancer Biomarker: An Overview of Biological Features and Factors That may Impact on ctDNA Analysis. Front Oncol. 2022;12:943253.
17. Krebs MG, Malapelle U, André F, Paz-Ares L, Schuler M, Thomas DM, et al. Practical Considerations for the Use of Circulating Tumor DNA in the Treatment of Patients With Cancer: A Narrative Review. JAMA Oncol. 2022;8(12):1830-9.
18. Oliver J, Onieva JL, Garrido-Barros M, Cobo-Dols M, Martínez-Gálvez B, García-Pelícano AI, et al. Fluorometric Quantification of Total Cell-Free DNA as a Prognostic Biomarker in Non-Small-Cell Lung Cancer Patients Treated with Immune Checkpoint Blockade. Cancers (Basel). 2023;15(13).

19. Jeon SH, Song C, Eom KY, Kim IA, Kim JS. Modulation of CD8(+) T Cell Responses by Radiotherapy-Current Evidence and Rationale for Combination with Immune Checkpoint Inhibitors. Int J Mol Sci. 2023;24(23).
20. Urabe F, Kosaka N, Ito K, Kimura T, Egawa S, Ochiya T. Extracellular vesicles as biomarkers and therapeutic targets for cancer. Am J Physiol Cell Physiol. 2020;318(1):C29-c39.
21. Yang Z, Zhong W, Yang L, Wen P, Luo Y, Wu C. The emerging role of exosomes in radiotherapy. Cell Commun Signal. 2022;20(1):171.
22. Wan Z, Dong Y, Wei M, Gao X, Yang G, Zhang J, et al. Exosomes in Tumor Immunotherapy: Mediator, Drug Carrier, and Prognostic Biomarker. Adv Biosyst. 2020;4(11):e2000061.
23. Tsai CJ, Yang JT, Shaverdian N, Patel J, Shepherd AF, Eng J, et al. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. The Lancet. 2024;403(10422):171-82.
24. Theelen W, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts J, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021;9(5):467-75.
25. Eberst G, Vernerey D, Laheurte C, Meurisse A, Kaulek V, Cuche L, et al. Prognostic value of CD4+ T lymphopenia in non-small cell lung Cancer. BMC Cancer. 2022;22(1):529.
26. Gkika E, Firat E, Adebahr S, Graf E, Popp I, Radicioni G, et al. Systemic immune modulation by stereotactic radiotherapy in early-stage lung cancer. NPJ Precis Oncol. 2023;7(1):24.
27. Kim CG, Hong MH, Kim KH, Seo IH, Ahn BC, Pyo KH, et al. Dynamic changes in circulating PD-1(+)CD8(+) T lymphocytes for predicting treatment response to PD-1 blockade in patients with non-small-cell lung cancer. Eur J Cancer. 2021;143:113-26.

28. Zhang J, Gao J, Li Y, Nie J, Dai L, Hu W, et al. Circulating PD-L1 in NSCLC patients and the correlation between the level of PD-L1 expression and the clinical characteristics. Thorac Cancer. 2015;6(4):534-8.
29. Padinharayil H, Varghese J, John MC, Rajanikant GK, Wilson CM, Al-Yozbaki M, et al. Non-small cell lung carcinoma (NSCLC): Implications on molecular pathology and advances in early diagnostics and therapeutics. Genes Dis. 2023;10(3):960-89.
30. Bousquets-Muñoz P, Díaz-Navarro A, Nadeu F, Sánchez-Pitiot A, López-Tamargo S, Shuai S, et al. PanCancer analysis of somatic mutations in repetitive regions reveals recurrent mutations in snRNA U2. NPJ Genom Med. 2022;7(1):19.
31. Uhlen M, Karlsson MJ, Zhong W, Tebani A, Pou C, Mikes J, et al. A genome-wide transcriptomic analysis of protein-coding genes in human blood cells. Science. 2019;366(6472):eaax9198.
32. Zimta AA, Sigurjonsson OE, Gulei D, Tomuleasa C. The Malignant Role of Exosomes as Nanocarriers of Rare RNA Species. Int J Mol Sci. 2020;21(16).
33. Lv Z, Wang T, Cao X, Sun M, Qu Y. The role of receptor-type protein tyrosine phosphatases in cancer. Precision Medical Sciences. 2023;12(1):48-57.
34. Song Y, Wang Z, He L, Sun F, Zhang B, Wang F. Dysregulation of Pseudogenes/lncRNA-Hsa-miR-1-3p-PAICS Pathway Promotes the Development of NSCLC. J Oncol. 2022;2022:4714931.
35. Hua YT, Xu WX, Li H, Xia M. Emerging roles of MiR-133a in human cancers. J Cancer. 2021;12(1):198-206.
36. Braghini MR, Lo Re O, Romito I, Fernandez-Barrena MG, Barbaro B, Pomella S, et al. Epigenetic remodelling in human hepatocellular carcinoma. J Exp Clin Cancer Res. 2022;41(1):107.
37. Yu Z, Wang G, Zhang C, Liu Y, Chen W, Wang H, et al. LncRNA SBF2-AS1 affects the radiosensitivity of non-small cell lung cancer via modulating microRNA-302a/MBNL3 axis. Cell Cycle. 2020;19(3):300-16.
38. Zhou Y, Yan J, Chen H, Zhou W, Yang J. MicroRNA-133a-3p Inhibits Lung Adenocarcinoma Development and Cisplatin Resistance through Targeting GINS4. Cells Tissues Organs. 2022:1-12.

39. Yan H, Tang S, Tang S, Zhang J, Guo H, Qin C, et al. miRNAs in anti-cancer drug resistance of non-small cell lung cancer: Recent advances and future potential. Front Pharmacol. 2022;13:949566.
40. de Miguel-Perez D, Ortega FG, Tejada RG, Martínez-Única A, Peterson CB, Russo A, et al. Baseline extracellular vesicle miRNA-30c and autophagic CTCs predict chemoradiotherapy resistance and outcomes in patients with lung cancer. Biomarker Research. 2023;11(1):98.
41. Zafra Martin J, Onieva JL, Roman A, Garrido M, Oliver J, Martinez-Galvez B, et al. Dynamic Exosome Analysis to Predict Response to the Combination of SABR and Immunotherapy in Oligoprogressive Disease. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):e274-e5.
42. Spurr LF, Martinez C, Kang W, Chen M, Zha Y, Hseu R, et al. Concurrent Radiation and Immunotherapy Augments Local Immunity and Improves Survival in Aneuploid NSCLC. International Journal of Radiation Oncology, Biology, Physics. 2023;117(2):S23.
43. U.S. Department of Health and Human Services FaDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007.
44. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.
45. McGee HM, Daly ME, Azghadi S, Stewart SL, Oesterich L, Schlom J, et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. Int J Radiat Oncol Biol Phys. 2018;101(5):1259-70.
46. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e52.
47. Onieva JL, Cháves P, Oliver J, Garrido-Barros M, Zafra J, Sojo B, et al. Abstract 1910: flowTOTAL: A comprehensive bioinformatics workflow for flow cytometry automatic analysis. Cancer Research. 2022;82(12_Supplement):1910-.

48. Li J, Kho AT, Chase RP, Pantano L, Farnam L, Amr SS, et al. COMPSRA: a COMprehensive Platform for Small RNA-Seq data Analysis. Scientific Reports. 2020;10(1):4552.
49. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biology. 2014;15(12):550.
50. Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med. 2018;24(12):1845-
51. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol*. 2020;38(25):2830-2838.