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Señor

**DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E.

S.

D.

REF: Expediente No. 12 -049620- solicitud de patente de invención a favor de **ABRAXIS BIOSCIENCE, LLC.** Título: **COMBINACIÓN DE COMPOSICIONES DE NANOPARTÍCULAS DE TAXANO E INHIBIDORES DE HEDGEHOG.**

RECURSO DE REPOSICIÓN

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante, manifiesto a usted que debidamente notificado de la Resolución No. 48173 del 5 de Agosto de 2014, interpongo contra ella en debido término, **RECURSO DE REPOSICIÓN**, para que sea revocada en su totalidad, y en su lugar se conceda el Privilegio de Patente, para el objeto de la solicitud en referencia.

Respaldo el RECURSO en los siguientes

HECHOS

1. La resolución No. 48173 arriba citada niega el Privilegio exclusivo de Patente de Invención para el objeto de la solicitud de la referencia, considerando que el capítulo reivindicatorio carece de nivel inventivo. Lo anterior, de acuerdo con las siguientes consideraciones.
 - i. Determinación del Estado de la Técnica

Consultadas las fuentes de información con que se cuenta se encontraron los siguientes documentos, que anticipan el objeto de esta solicitud.

No	Documento	Título	Fecha de publicación
D1	US2007281040	<i>"Combination therapy of hedgehog inhibitors, radiation and chemotherapeutic agents"</i>	06/Diciembre/2008
D2	US2007116761	<i>"Novel formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof"</i>	24/Mayo/2007
D3	US2009123932	<i>"Quantitative test to detect disease progression markers of epithelial ovarian cancer patients"</i>	14/Mayo/2009

Considera el examinador que la presente invención no cumple con el requisito de nivel inventivo en vista de D1 y D2 y D2 y D3.

RESUELVE

ARTÍCULO PRIMERO: Denegar la patente de invención a la creación titulada **"COMBINACIÓN DE COMPOSICIONES DE NANOPARTÍCULAS DE TAXANO E INHIBIDORES DE HEDGEHOG"**.

FUNDAMENTOS

Nos permitimos mostrar nuestro total desacuerdo frente a las todas y cada una de las objeciones de la Resolución No. 48173 toda vez que en dicho análisis no se demostró de manera concluyente que la invención carecía de nivel inventivo. A continuación, me permito desvirtuar todas y cada una de las afirmaciones de su Despacho en contra del nivel inventivo de la invención y expuestas en la Resolución No. 48173.

En primera instancia, ponemos a su consideración un nuevo pliego reivindicatorio conformado por siete (7) reivindicaciones, las cuales mantienen total sustento en el capítulo descriptivo de la presente solicitud, y no exceden en ningún momento el alcance de la invención previamente divulgada.

El capítulo descriptivo de la actual solicitud se modificó con el objetivo de corregir la terminología para que quedara en concordancia con la solicitud prioritaria.

Dentro de las modificaciones realizadas a dicho pliego reivindicatorio, es preciso resaltar que las reivindicaciones fueron significativamente restringidas incluyendo en la reivindicación 1 paclitaxel e inhibidores de Hedgehog específicos.

Por otro lado, frente al comentario del señor Examinador según el cual *la expresión "una combinación" utilizada en el preámbulo de las reivindicaciones carece de claridad ya que no se puede establecer a partir de dicha expresión cual es el objeto real de las reivindicaciones*. Comunicamos que las reivindicaciones se corrigieron para divulgar un kit de piezas en lugar de una combinación, el cual es materia patentable y permite establecer con precisión el objeto real de la solicitud.

De esta manera, encontramos que mediante la actual modificación se superan las objeciones de claridad, ya que el término *kit de partes* no abarca la administración de los agentes mediante formas farmacéuticas y por lo tanto no está orientado a un método de tratamiento, a la vez que restringe el alcance de la invención a una sola configuración.

Ahora bien, el señor Examinador manifiesta que *si se entendiera que el objeto de la solicitud está orientado al kit, entonces este carece de sustento real en la descripción ya que no existe ejemplificación del kit y de igual forma la solicitud carece de estudios o resultados que permitan establecer el efecto técnico de dichos productos toda vez que la descripción únicamente divulga el efecto de la combinación de las nano partículas que comprenden paclitaxel y los inhibidores de Hedgehog identificados con...*

Frente a este comentario nos permitimos manifestar nuestro desacuerdo y señalar que en el párrafo [0208] del capítulo descriptivo de la actual solicitud se encuentra sustento a este kit de partes,

La invención también proporciona kits para uso en los actuales métodos y/o kits que comprenden una composición descrita aquí. Los kits de la invención incluyen uno o más contenedores que comprenden composiciones que contienen nanopartículas de taxano (o forma de dosificación unitarias y/o artículos de fabricación) y/o un agente que inhibe la ruta de señalización de hedgehog y en algunas modalidades, comprenden adicionalmente instrucciones para uso de acuerdo con cualquiera de los métodos descritos aquí.

Por consiguiente, los kits presentes en el nuevo pliego reivindicatorio encuentran suficiente sustento en el capítulo descriptivo.

Por otro lado, el señor Examinador expone que "la solicitud carece de estudios o resultados que permitan establecer el efecto técnico de dichos productos toda vez que la descripción únicamente divulga el efecto de la combinación de las nano partículas que comprenden paclitaxel y los inhibidores de Hedgehog identificados con los códigos: IPI926 (Fórmula I) ABI2012 o GDC449 (fórmula II), ABI914, ABI2086, ABI2099, ABI1C4, ABI1C5, ABI1C6 y ABI1C7, por lo que el efecto técnico de la invención, es decir, el efecto sorprendente en el control del tumor primario no se encuentra sustentado para las combinaciones de paclitaxel y los inhibidores de Hedgehog identificados con los códigos: XL139, IPI609 y LDE225"

Con el objetivo de superar esta objeción, la reivindicación 1 se modificó para divulgar,

Un kit de partes que comprende,

- a) nanopartículas que comprenden un paclitaxel y una albúmina, y
- b) un inhibidor de hedgehog, e instrucciones para un régimen de dosificación, donde el inhibidor de hedgehog se selecciona del grupo que consiste de:

2-cloro-N-(4-cloro-3-piridin-2-ilfenil)-4-metilsulfonilbenzamida; N-
[(3R,3'R,3'aS,4aR,6'S,6aR,6bS,7'aR,9S,12aS,12bS)-3',6',11,12b-
tetrametilspiro[1,2,3,4,4a,5,6,6a,6b,7,8,10,12,12a-tetradecahidronafto[2,1-a]azulen-
9,2'-3a,4,5,6,7,7a-hexahidro-3H-furo[3,2-b]piridina]-3-il]metanesulfonamida; 2-
cloro-N-(4-cloro-3-(isoquinolin-1-il)fenil)-4-(metilsulfonil)benzamida; 4-acetamido-
N-(4-cloro-3-(isoquinolin-1-il)fenil)benzamida; N-(4-cloro-3-(isoquinolin-1-il)fenil)-
2-metil-6-(trifluorometil)nicotinamida; 1-(4-cloro-3-(isoquinolin-1-il)fenil)-3-
fenilurea; (3S,3'R,3'aS,6'S,6aS,6bS,7'aR,9R,11aS,11bR)-3',6',10,11b-
tetrametilspiro[2,3,4,6,6a,6b,7,8,11,11a-decahidro-1H-benzo[a]fluoreno-9,2'-
3a,4,5,6,7,7a-hexahidro-3H-furo[3,2-b]piridina]-3-ol; y un derivado de la misma.

Donde, 2-cloro-N-(4-cloro-3-piridin-2-ilfenil)-4-metilsulfonilbenzamida es la nomenclatura IUPAC de ABI1914; 4-acetamido-N-(4-cloro-3-(isoquinolin-1-il)fenil)benzamidac es la nomenclatura IUPAC para ABI2088; N-(4-cloro-3-(isoquinolin-1-il)fenil)-2-metil-6-(trifluorometil)nicotinamida es la nomenclatura IUPAC para ABI2099; 1-(4-cloro-3-(isoquinolin-1-il)fenil)-3-fenilurea es la nomenclatura IUPAC para ABI1C5, N-(4-cloro-3-(isoquinolin-1-il)phenil)picolinamida es la nomenclatura IUPAC para ABI1C6; y 4-chloro-N-(4-chloro-3-(isoquinolin-1-yl)phenyl)-3-nitrobenzenesulfonamide es la nomenclatura IUPAC para ABI1C7.

De acuerdo a lo anterior, mediante esta modificación la reivindicación 1 se restringe de tal modo que ya no se reivindican los inhibidores de Hedgehog de forma general, si no específicamente aquellos identificados con los códigos: ABI1914, ABI2088, ABI2099, ABI1C5, ABI1C6 y ABI1C7, los cuales, como expuso el señor Examinador, encuentran total sustento en el capítulo descriptivo. Por lo tanto, se considera superada tal objeción.

Adicionalmente, el señor Examinador considera que "la reivindicación 1 carece de concisión y claridad, debido a que abarca un número ilimitado de combinaciones posibles, ya que incluye todos los derivados de taxano e inhibidores de hedgehog conocidos y que puedan desarrollarse en el futuro".

Como se expuso en párrafos anteriores, la reivindicación 1 se limitó significativamente para incluir paclitaxel en lugar de taxano e inhibidores de hedgehog específicos. Como consecuencia de estas modificaciones, la reivindicación 1 ya no abarca un número ilimitado de combinaciones posibles. La materia reivindicada se encuentra lo suficientemente restringida para que esta se pueda considerar clara y concisa. Del mismo modo, la reivindicación 1 encuentra total soporte en el capítulo descriptivo, de forma que ya que no es necesario extrapolar los resultados de actividad biológica, sino que estos se encuentran debidamente sustentados para la totalidad de las combinaciones de paclitaxel con los inhibidores de hedgehog divulgados en la reivindicación 1.

En cuanto al requerimiento realizado por la falta de invención, el señor Examinador había propuesto los siguientes grupos inventivos:

- 1er grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel y los inhibidores de Hedgehog ciclopamina e IPI926.
- 2do grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel y los inhibidores de Hedgehog ABI2012, ABI1914, ABI2086, ABI2099, ABI1C4, ABI1C5, ABI1C6 y ABI1C7.
- 3er grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel y el inhibidor de Hedgehog LDE225.
- 4to grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel, los inhibidores de Hedgehog ciclopamina e IPI926 y gemcitabina.
- 5to grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel, los inhibidores de Hedgehog ABI2012, ABI1914, ABI2086, ABI2099, ABI1C4, ABI1C5, ABI1C6 y ABI1C7 y gemcitabina.
- 6to grupo inventivo: Combinación farmacéutica que comprende nanopartículas de paclitaxel, el inhibidor de Hedgehog LDE225 y gemcitabina.

De nuevo, como resultado de las modificaciones realizadas sobre la reivindicación 1, el alcance de la invención se restringe a unos inhibidores de hedgehog específicos, los cuales se encuentran en su totalidad dentro del mismo grupo inventivo. Así, tal y como comentó el señor examinador, debido a que estos comparten una estructura común, involucran un único concepto inventivo y cumplen con el requerimiento de unidad de invención.

Ahora, frente a la Gemcitabina, el señor Examinador no presenta ningún argumento para sustentar que los kits de partes que comprenden Gemcitabina tienen un concepto inventivo diferente a los kits de partes que no comprenden Gemcitabina. Más aún, la Gemcitabina, la cual se divulga en la reivindicación dependiente 3, constituye una realización de la invención divulgada en la reivindicación independiente 1. Adicionalmente, un kit de partes que comprende Gemcitabina encuentra su debido soporte en el capítulo descriptivo en los párrafos [0209] y [0210].

*En algunas modalidades, el kit comprende adicionalmente una cantidad efectiva de un agente adicional terapéutico, tal como **gemcitabina**...*

Por lo tanto, ya que se restringe el alcance de la invención de modo que todos los inhibidores de Hedgehog reivindicados comparten una estructura común, y la Gemcitabina constituye una realización de la materia divulgada en la reivindicación 1, consideramos que se supera la objeción del señor Examinador.

En cuanto al nivel inventivo de la invención, el señor Examinador rechaza el pliego reivindicatorio ya que considera que el nivel inventivo de la invención se ve afectado por las enseñanzas de los documentos D1 "Combination therapy of hedgehog inhibitors, radiation and chemotherapeutic agents", D2 "Novel formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof" y D3 "Quantitative test to detect disease progression markers of epithelial ovarian cancer patients". Frente a lo cual nos permitimos manifestar nuestro total desacuerdo y los respectivos argumentos a favor de la no obviedad de la misma.

Según los comentarios del señor examinador, la invención no cumple con el requisito de nivel inventivo debido que la materia divulgada representa simplemente una sustitución obvia de las composiciones de nanopartículas de *paclitaxel* y albúmina de D2, para usarse en combinación con las composiciones de D1 o D3.

Frente a esto, nos permitimos señalar que ninguna de las referencias citada menciona en absoluto un **kit de partes** que comprende nanopartículas que comprenden un paclitaxel y una albúmina, y un inhibidor de hedgehog, e instrucciones para un régimen de dosificación, donde el inhibidor de hedgehog se selecciona del grupo que consiste de: 2-cloro-N-(4-cloro-3-piridin-2-ilfenil)-4-metilsulfonilbenzamida; N-[(3R,3'R,3'aS,4aR,6'S,6aR,6bS,7'aR,9S,12aS,12bS)-3',6',11,12b-tetrametilspiro[1,2,3,4,4a,5,6,6a,6b,7,8,10,12,12a-tetradecahidronafto[2,1-a]azulen-9,2'-3a,4,5,6,7,7a-hexahidro-3H-furo[3,2-b]piridina]-3-il]metanesulfonamida; 2-cloro-N-(4-cloro-3-(isoquinolin-1-il)fenil)-4-(metilsulfonil)benzamida; 4-acetamido-N-(4-cloro-3-(isoquinolin-1-il)fenil)benzamida; N-(4-cloro-3-(isoquinolin-1-il)fenil)-2-metil-6-(trifluorometil)nicotinamida; 1-(4-cloro-3-(isoquinolin-1-il)fenil)-3-fenilurea; (3S,3'R,3'aS,6'S,6aS,6bS,7'aR,9R,11aS,11bR)-3',6',10,11b-tetrametilspiro[2,3,4,6,6a,6b,7,8,11,11a-decahidro-1H-benzo[a]fluoreno-9,2'-3a,4,5,6,7,7a-hexahidro-3H-furo[3,2-b]piridina]-3-ol; y un derivado de la misma, como lo requiere la reivindicación 1.

En primer lugar, los documentos referenciados no proporcionan instrucciones concretas que motiven a su combinación o a modificar en algún aspecto la materia que reivindican, por lo tanto su combinación resulta improbable. Por su lado, los documentos D1 y D3, no presentan indicio alguno de que pueda haber un efecto secundario asociado al uso de tensoactivos como vehículo de *Taxol*, así, un versado en la materia no estaría motivado a buscar mecanismos de entrega alternativos a los divulgados en estos documentos. De la misma forma, D2 no menciona que las nanopartículas de Taxol se puedan llegar a combinar con inhibidores de hedgehog, así como tampoco mencionan algún efecto asociado a estos. Por lo tanto cada documento citado se centra en sus propios conceptos inventivos y su combinación resulta improbable.

Por su lado, el documento D1 divulga *Taxol*, que es una formulación líquida de paclitaxel disuelta en Cremophor, lo cual es significativamente diferente de la composición de nanopartícula de paclitaxel/albumina que se reivindica en la presente solicitud. Más aún D1, reporta simplemente ensayos *in vitro*, enfocándose en la mejora de las actividades citotóxicas y apoptóticas de un inhibidor de hedgehog mediante el *Taxol*.

Nos permitimos enfatizar en el hecho que el *Taxol* divulgado en el documento D1 y la composición de nanopartículas de paclitaxel/albúmina reivindicada en la presente solicitud, **son productos farmacéuticos fundamentalmente diferentes.**

La diferencia **estructural** entre *Taxol* y la composición de nanopartículas de paclitaxel/albúmina implica que los dos medicamentos tienen farmacologías distintas, con patrones de biodistribución y farmacocinéticas muy diferentes. En consecuencia, los dos fármacos no pueden considerarse como sustitutos equivalentes cuando se utilizan como agentes únicos, y mucho menos cuando se emplean en terapias de combinación.

Por otro lado, nos permitimos reiterar que la composición divulgada en D1, no podría funcionar sin la presencia de Cremophor, más aún, si se omitiera el Cremophor de la composición descrita en D1, este ya no podría llamarse *Taxol* y por lo tanto, se estaría describiendo materia totalmente diferente a la divulgada por la anterioridad.

Frente a este argumento, el señor examinador emite el comentario "*la reivindicación 1 utiliza el conector "comprende" que la convierte en una reivindicación abierta por lo cual puede contener cualquier tipo de excipiente e incluso otros agentes activos*". Como respuesta, nos permitimos señalar que el Cremophor no es ni un excipiente, ni otro agente activo. El Cremophor tiene una función muy definida en la composición divulgada en D1, la cual es disolver el paclitaxel.

Procedemos a poner el uso de Cremophor en contexto con el objetivo de hacer más evidente la diferencia sustancial que existe entre la composición líquida de D1 y las nanopartículas de la presente invención.

En primer lugar, el paclitaxel, y en general los taxanos, son fármacos con una solubilidad acuosa muy deficiente. Lo anterior constituye un problema en el campo técnico de la solicitud, ya que el medio por el cual se transportan estos medicamentos a las células es mediante el plasma sanguíneo, el cual está compuesto de aproximadamente 90% de agua. Así, la pobre solubilidad acuosa para los taxanos, presenta retos significativos para el desarrollo de terapéuticos para el cáncer con base en taxano (Párr. [0005]). El documento D1, enfrenta este problema mediante el uso de Cremophor, el cual consigue solubilizar los taxanos. Es decir, el Cremophor en el documento D1, es el vehículo mediante el cual se hace llegar el paclitaxel a las células cancerígenas. Sin embargo, se ha comprobado que este tipo de agentes que permiten solubilizar el *Taxol* presentan números efectos secundarios que comprometen la seguridad del fármaco.

Frente a esto, la presente invención propone un **mecanismo de entrega mejorado** mediante nanopartículas que comprenden albúmina, las cuales se incorporan fácilmente en los procesos de transporte propios del cuerpo y son capaces de explotar la atracción de los tumores a la albúmina, permitiendo el suministro de mayores concentraciones del fármaco activo encapsulado en las nanopartículas al sitio objetivo (Párr. [0006]).

Así, teniendo en cuenta que la presente solicitud proporciona un mecanismo de entrega con capacidad de mejorar la solubilidad del fármaco **al evitar la necesidad de químicos tóxicos, tales como disolventes**, no encontramos sentido alguno en el argumento del señor Examinador que indica que, como la reivindicación emplea el conector "*comprende*", no se está excluyendo que la materia reivindicada también pueda contener Cremophor.

Si bien las reivindicaciones se deben leer en su sentido más amplio, a estas también se les debe dar una **interpretación razonable**. Por lo tanto, no tendría sentido alguno el desarrollar un fármaco para que incorpore un mecanismo de entrega que evita el uso de disolventes, para luego, incorporar un disolvente, que en este punto, no cumpliría ninguna función ni aportaría ventaja alguna. Más aún, en el capítulo descriptivo se indica que la composición reivindicada es sustancialmente libre de estos disolventes,

*Así, en algunas modalidades, la composición descrita aquí es **sustancialmente libre (tal como libre)** de tensoactivos, tales como Cremophor (que incluye Cremophor EL® (BASF)). En algunas modalidades, la composición de nanopartículas es sustancialmente libre (tal como libre) de tensoactivos (Párr. [0167]).*

Mediante lo anterior, enfatizamos que la presente invención no comprende el uso de Cremophor, sino que por el contrario, divulga **un mecanismo de entrega mejorado** que permite eliminar los efectos secundarios asociados al uso de tensoactivos.

Por lo tanto, la presente solicitud logra resolver un problema técnico que no se había resuelto en el estado de la técnica, ya que ninguno de los documentos citados comprende materia que motive o sugiera al versado en la materia, que mediante una combinación de nanopartículas de paclitaxel/albúmina e inhibidores de hedgehog específicos, se puede lograr un resultado sorprendente en el tratamiento de enfermedades proliferación.

Adicionalmente, es necesario mencionar que en el campo técnico de la solicitud se conoce que el Cremophor presente en el Taxol de D1, tiene efectos sobre el paclitaxel y por lo tanto también los puede tener sobre otro fármaco o fármacos administrados en combinación con el Taxol. En consecuencia, se desconoce el tipo de efecto que pueda tener el Taxol que comprende Cremophor divulgado por D1, sobre otros fármacos en una terapia de combinación.

Más aún, no es razonable concluir que un versado en la materia podría deducir de forma obvia y directamente de las enseñanzas de los documentos citados, que las ventajas que una composición de nanopartículas de paclitaxel/albúmina tiene sobre una formulación de *Taxol* que comprende Cremophor, podrían extrapolarse a una terapia de combinación que comprende el uso de paclitaxel unido a la albúmina.

Para ilustrar esto, nos permitimos presentar el siguiente ejemplo. El poli(ácido L-glutámico) -paclitaxel ("PG-TXL" o "PPX"), el cual es un conjugado de polímero de paclitaxel libre de Cremophor, ha demostrado una eficacia antitumoral significativamente superior a la del *Taxol*¹. A pesar de que el PG-TXL aislado demostró una eficacia mejorada respecto al *Taxol*, no se observó ninguna mejora en la eficacia cuando se combina con otros medicamentos en una terapia de combinación. Por lo tanto, a pesar de que una formulación de paclitaxel libre de Cremophor, mostró una eficacia mejorada cuando se utiliza de forma aislada, esto no se tradujo en una eficacia mejorada a una terapia de combinación. Así, se demuestra que las ventajas que pueden resultar de una composición de nanopartículas de paclitaxel/albúmina **no se pueden predecir de una manera obvia a partir de las enseñanzas del estado de la técnica.**

Adicionalmente, las reivindicaciones de la presente solicitud se basan en el hallazgo sorprendente de que un inhibidor hedgehog la reivindicación 1, cuando se utiliza en **combinación** con una composición de nanopartículas de paclitaxel/albúmina, mejora la entrega de taxano a los tumores y mejora aún más la eficacia terapéutica de la composición de nanopartículas de taxano/albúmina. Así, la presente invención se basa en el hallazgo del **efecto sinérgico** que tienen las nanopartículas de taxano/albúmina con los inhibidores de hedgehog de la reivindicación 1. Como es del conocimiento de la persona normalmente versada en la materia, un efecto sinérgico es la interacción que da como resultado efectos combinados o aditivos con la administración de dos o más fármacos, que resultan ser **mayores** que aquellos que podrían haberse alcanzado si alguno de los medicamentos se hubiera administrado solo.

¹ C. Li y S. Wallace, «Polymer-Drug Conjugates: Recent Development in Clinical,» *Adv Drug Deliv Rev*, pp. 886-898, Mayo 22 2008

Por lo tanto, la entrega mejorada de taxano a los tumores y la eficacia terapéutica de la composición de nanopartículas de taxano/albúmina es resultado específico de tal combinación, y por lo tanto, no se hubiera podido obtener ni deducir a partir de los efectos de la composición de nanopartículas de taxano/albúmina y de los inhibidores de hedgehog específicos por separado. Este efecto sorprendente se obtiene **después de realizar tal combinación**, por lo tanto, el versado en la materia no habría podido deducir dicho efecto de forma obvia.

Por otro lado, es del conocimiento de la persona normalmente versada en la materia, que el desarrollo de una nueva composición farmacéutica, no es tan simple como tomar un compuesto presente en un fármaco e incluirlo en una composición de otro fármaco y esperar que mediante esta combinación, el fármaco resultante vaya a tener las ventajas y los efectos combinados de los dos fármacos.

Por el contrario y como es parte del conocimiento del campo técnico de la solicitud, los mecanismos biológicos son proceso extremadamente complejos, donde cualquier cambio, sustitución o eliminación, puede tener consecuencias inesperadas, tanto positivas como negativas. Por lo tanto, en el desarrollo de un nuevo fármaco, como es el caso de la presente invención, es necesario llevar a cabo rigurosos estudios para poder concluir los efectos que tienen las combinaciones, sustituciones o eliminaciones de ciertos componentes.

De esta manera, no es posible anticipar mediante las enseñanzas del estado de la técnica la materia reivindicada en la presente invención, ya que se tendrían que considerar aspectos fundamentales de la actividad farmacológica de la nueva combinación, como son por ejemplo, la estabilidad de la combinación, la seguridad, la farmacocinética, la efectividad, etc. El diseño de toda composición farmacéutica implica rigurosos procesos de investigación, ya que el efecto de una nueva composición, **nunca es predecible**.

Dicho lo anterior, nos permitimos indicar que un versado en la materia no estaría motivado a incluir inhibidores de hedgehog en la composición de nanopartículas de D2, ya que tendría que entrar a considerar todos los aspectos que se mencionaron en el párrafo anterior. Por el contrario, estaría fuertemente motivado por las enseñanzas

de D2 a mantener la composición de nanopartículas tal y como divulga la anterioridad, en lugar de buscar comprometer la estabilidad de la composición mediante los inhibidores de hedgehog.

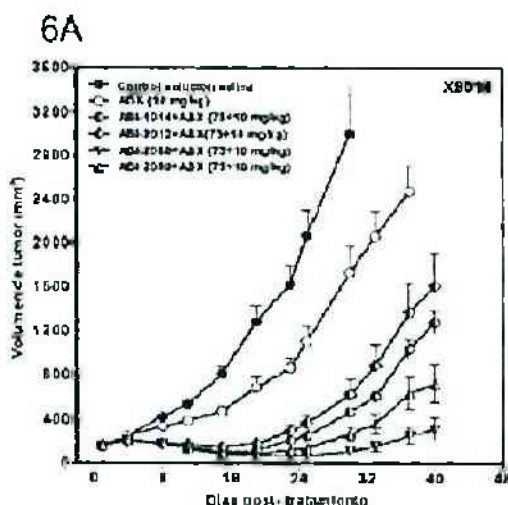
En conclusión, dado que es imposible predecir las ventajas o efectos secundarios que pueda tener una nueva composición, la presente solicitud no se pudo haber derivado de manera obvia de la mera lectura del estado de la técnica. Ya que el éxito de probar una nueva combinación, no se puede anticipar, si no que se revela después de la realización de múltiples ensayos considerando un gran número de variables. De esta forma, **las probabilidades de éxito** como resultado de la combinación de las sugerencias de D1 y D2 y D2 y D3 sugiere la presencia de nivel inventivo en la materia actualmente reivindicada.

Por último, como se mencionó, la reivindicación 1 se limitó de tal forma se reivindican unos inhibidores de hedgehog específicos. Por su lado, D1 divulga que los inhibidores de hedgehog que logran tener un efecto en las actividades citotóxicas y apoptóticas son la ciclopamina y la jervina. Entre los inhibidores de hedgehog divulgados en la reivindicación 1, no hay ninguno que haga referencia, o que al menos tenga una estructura similar a los inhibidores de hedgehog de D1. Lo mismo aplica a D3, el cual divulga específicamente el inhibidor de hedgehog GDC0449, el cual no se encuentra dentro del grupo de inhibidores de hedgehog presentes en el pliego reivindicatorio.

En concordancia con el comentario del señor Examinador, y bajo el cual se realizó la modificación a la reivindicación 1 *"La descripción únicamente divulga el efecto de la combinación de las nanopartículas que comprenden paclitaxel y los inhibidores de hedgehog identificados con los códigos: IPI926 (Fórmula I) ABI2012 o GDC449 (fórmula II), ABI914, ABI2086, ABI2099, ABI1C4, ABI1C5, ABI1C6 y ABI1C7"*

Así, frente al comentario del señor Examinador según el cual *"no encuentra en la solicitud información técnica que permita evidenciar las ventajas o efectos sorprendentes que atribuye la solicitante a las combinaciones reivindicadas en comparación con las disponibles en el estado de la técnica"*

Nos permitimos manifestar nuestro desacuerdo ya que en el capítulo descriptivo cuenta con los resultados de los ensayos realizados sobre todas las combinaciones de las composiciones de nanopartículas de paclitaxel/albúmina con los inhibidores de Hedgehog del pliego reivindicatorio. Para evidenciar lo anterior, nos referimos a la Figura 6A,



Como se evidencia, la composición de nanopartículas de paclitaxel/albúmina con los inhibidores de Hedgehog específicos, muestra una disminución en la velocidad con que aumenta el volumen del tumor en comparación con el fármaco control. Específicamente, el ABI2088 muestra aproximadamente 100% de inhibición de crecimiento de tumor. Por lo tanto, la solicitud sí incluye información técnica que permita evidenciar las ventajas o efectos sorprendentes que se atribuye a las combinaciones reivindicadas.

Por lo tanto, los documentos D1 y D3 no divulgan información que hubiera llevado al versado en la materia a seleccionar los inhibidores de hedgehog reivindicados en el pliego reivindicatorio, por el contrario, el versado en la materia se hubiera visto motivado por las enseñanzas de D2 y D3 a escoger los inhibidores de hedgehog divulgados en el estado de la técnica, lo cual es un indicio de nivel inventivo.

En vista de los argumentos presentados, no existen herramientas técnicas que permitan al normalmente versado en la materia a llegar a al objeto de la actual solicitud. Por lo tanto, la invención cumple con los requisitos de nivel inventivo.

PETICIÓN

Por las razones anteriormente expuestas, solicito a ese despacho **REVOCAR** la decisión tomada mediante la Resolución No. 48173 del 05 de Agosto de 2014 y tendiente a obtener la concesión del Privilegio de Patente de conformidad con los artículos 14 y 48 de la Decisión 486 de la comunidad Andina.

NOTIFICACIONES

Recibiré notificaciones en la Secretaría General de la Superintendencia de Industria y Comercio, o en su defecto, en mi oficina de Abogado, situada en la Calle 70ª No. 4-41 de esta ciudad de Bogotá.

Del Señor Director



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.S.J.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

EXHIBIT 1

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Polymer-Drug Conjugates: Recent Development in Clinical Oncology

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Abstract

Targeted drug delivery aims to increase the therapeutic index by making more drug molecules available at the diseased sites while reducing systemic drug exposure. In this update, we provide an overview of polymer-drug conjugates that have advanced into the clinical trials. These systems use synthetic water-soluble polymers as the drug carriers. The preclinical pharmacology and recent data in clinical trials with poly(L-glutamic acid)-paclitaxel (PG-TXL) are discussed first. This is followed by a summary of conjugates of a variety of polymeric conjugates with chemotherapeutic agents. Results from early clinical trials of these polymer-drug conjugates have demonstrated several advantages over the corresponding parent drugs, including fewer side effects, enhanced therapeutic efficacy, ease of drug administration, and improved patient compliance. Collectively, these data warrant further clinical development of polymer-drug conjugates as a new class of anticancer agents.

Keywords

Polymer-Drug Conjugates; Anticancer Drugs; Nanocarriers; Paclitaxel; PG-TXL

1. Introduction

Most chemotherapeutic drugs used clinically are limited by a relatively low therapeutic index, owing to toxic side effects. In the field of anticancer therapy, two strategies for improving the therapeutic efficacy of anticancer agents have emerged over the past several decades. The first approach is the design and development of agents that modulate the molecular processes and pathways specifically associated with tumor progression. The success of this approach is shown by the successful introduction of a new breed of molecularly targeted anticancer agents such as imatinib mesylate (Gleevec), gefitinib (Iressa), trastuzumab (Herceptin), and cetuximab (C225, Erbitux). Alternatively, existing anticancer agents can be made more effective by using nanocarriers that bring more drug molecules to the tumor site, compared with the conventional formulation, while reducing exposure of normal tissues to the drug.

The idea of covalently attaching chemotherapeutic agents to a water-soluble polymer was first proposed by Ringsdorf [1] in the mid-1970s. In this model, it was envisioned that not only could the pharmacokinetics of the drug attached to the polymeric carrier be modulated but also

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that active targeting could be achieved if a homing moiety was introduced to the same polymeric carrier (Fig. 1). Since then, polymer-drug conjugates have become a fast-growing field, with nearly a dozen polymeric conjugates advancing to the clinical trial stage (Table 1). Results from early clinical trials of these polymer-drug conjugates have demonstrated several advantages over the corresponding parent drugs, including fewer side effects, enhanced therapeutic efficacy, ease of drug administration, and improved patient compliance. Increased therapeutic efficacy is achieved primarily through an enhanced permeability and retention (EPR) effect of long-circulating polymers [2]. Among synthetic polymer-drug conjugates, poly(L-glutamic acid) (PG)-paclitaxel (PG-TXL) (CT-2103, Xyotax®) has advanced to Phase III clinical trials and is positioned to be the first of its class to reach the market. We previously reviewed the chemistry and applications of PG conjugates with various chemotherapeutic agents [3]. In this article, we will update the current clinical development of polymer-drug conjugates as novel anticancer agents, with particular emphasis on PG-TXL. Many excellent reviews with different focuses have been published, including those based on polymer-protein conjugates [4–7], most of which use polyethylene glycol (PEG) as the drug carrier [5–9]. These materials will not be covered here.

2. PG-TXL (CT-2103)

2.1. Antitumor Activity

Paclitaxel (Taxol®, TXL) is a mitotic spindle poison that promotes microtubular aggregation and interferes with essential cellular functions such as mitosis, cell transport, and cell motility [10]. Taxol® has shown a remarkable anti-neoplastic effect in a wide range of human cancers. Initially approved for the treatment of refractory ovarian cancer in 1992, it is now the first-line therapy for metastatic breast cancer and advanced ovarian cancer. In women with metastatic breast cancer, Taxol® produced an objective response rate of 32–62% [11]. Its effectiveness has also been demonstrated against non-small cell lung cancer (NSCLC), head and neck cancer, melanoma, and Kaposi's sarcoma. Because of its poor aqueous solubility, use of Taxol® requires a mixture of polyethoxylated castor oil (Cremophor) and ethanol as a vehicle, and it must be infused over 3 to 24 h.

PG-TXL was initially developed to overcome the poor aqueous solubility of Taxol® and hypersensitivity reaction associated with the use of Taxol® formulated with Cremophor/ alcohol. In PG-TXL, paclitaxel is conjugated to a synthetic polyamino acid, poly(L-glutamic acid) (PG) through its 2'-hydroxyl group via an ester linkage (Fig. 2). The resulting conjugate is highly water soluble (>20 mg/kg) and has demonstrated significantly enhanced antitumor efficacy and improved safety compared with paclitaxel in preclinical studies [12]. In a well-established syngeneic murine ovarian OCa-1 carcinoma model, a single dose of PG-TXL in saline (10 mg equiv. paclitaxel/ml) at a dose of 80 mg equiv. paclitaxel/kg caused significant tumor growth delay compared with the same dose of Taxol® in Cremophor/alcohol. Furthermore, a complete tumor cure was observed in all mice injected (n = 26) with PG-TXL at its maximal tolerated dose (MTD) of 160 mg equivalent paclitaxel/kg, which is two-fold higher than that of free paclitaxel. Similarly, treatment with PG-TXL caused complete tumor eradication at the MTD of PG-TXL (60 mg equiv. paclitaxel/kg) and at a lower dose of 40 mg/kg in Fischer rats with well-established rat breast 13762F adenocarcinoma. In contrast, paclitaxel at the dose of 40 mg/kg (its MTD) caused only a transient growth delay of approximately 15 days (Fig. 3).

The antitumor activity of PG-TXL was further evaluated in a panel of syngeneic murine tumors (MCA-4 and MCA-35 breast cancer, HCa-1 hepatocellular carcinoma, and FSA-II sarcoma; intramuscular inoculation), a human SKOV3ip1 ovarian tumor injected intraperitoneally, and an orthotopic human MDA-MB-435Lung2 breast tumor grown in the mammary fat pad of nude mice [13,14]. All treatments were given intravenously as a single bolus injection. All

murine tumors, whether sensitive or resistant to paclitaxel treatment, showed significant growth delay with PG-TXL at its maximum tolerated dose (160 mg equivalent paclitaxel/kg) or even at lower doses. In SKOV3ip1 tumor, PG-TXL significantly extended the survival of the mice. The median survival time for PG-TXL at 120 mg equivalent paclitaxel/kg was 75 days. In contrast, no difference in median survival time was found between paclitaxel-treated mice (56 days) and Cremophor vehicle-treated mice (59 days). In an orthotopic, metastatic MDA-MB-435Lung2 tumor model, PG-TXL at 120 mg equivalent paclitaxel/kg produced regression of the tumor in 50% of the cases. In the remaining mice with progressively growing tumors, micrometastases in the lung were found in only 25% of the animals. In comparison, treatment with paclitaxel at 60 mg/kg did not result in tumor regression, and metastases were found in 42% of the mice. In nude mice bearing i.p. implanted NMP-1 and HEY ovarian tumors, which were paclitaxel-resistant, significant improvement in survival and even some cures were observed after a single i.p. treatment with PG-TXL [14]. These studies demonstrated that PG-TXL has significant therapeutic activity against a broad range of solid tumors and metastatic disease.

2.2. Preclinical Pharmacology and Mechanism of Action

The observation that PG-TXL had antitumor activity superior to that of free paclitaxel and that PG-TXL was active against paclitaxel-resistant tumors in preclinical studies suggests that PG-TXL might possess favorable pharmacokinetic properties and/or have a mechanism of action different from that of paclitaxel. *In vitro*, both paclitaxel and PG-TXL induced extensive telomere erosion and telomeric associations, which are the early manifestations of programmed cell death [15]. Morphological analysis and biochemical characterizations in a panel of breast cancer cell lines confirmed that both PG-TXL and paclitaxel had similar abilities to induce apoptosis, independent of p53 status. Flow cytometric analysis further revealed that both PG-TXL and the free drug induced a characteristic G2/M arrest in the cell cycle [16]. However, compared with paclitaxel, PG-TXL appears to have reduced potency *in vitro*. For example, PG-TXL is >20 times less potent in supporting the growth of a paclitaxel-dependent CHO mutant cell line [12]. These data are consistent with the disturbance of microtubule polymerization as the major mechanism of action for PG-TXL and suggest that the release of paclitaxel or active species from PG-TXL is required for PG-TXL to exert its action.

In vivo, PG-TXL showed a biodistribution pattern different from that of free paclitaxel [17]. On the basis of area under the tissue concentration-time curve (AUC) values, tumor exposure to paclitaxel was five times greater when administered as PG-TXL than as paclitaxel formulated in Cremophor EL/alcohol vehicle. PG-TXL was retained much longer than free paclitaxel in the tumor due to a slower elimination of the drug conjugate. Furthermore, concentrations of free paclitaxel released from PG-TXL remained relatively constant in tumor tissue over a period of 144 h, whereas the concentration of free paclitaxel in the tumor of mice injected with paclitaxel in Cremophor EL/alcohol was reduced more than 6-fold by 144 h after injection. Singer et al. [18] showed that PG-TXL had a prolonged blood half-life and negligible release of the activity agent, paclitaxel (<1% of the total taxane). Thus, enhanced permeability and retention effect of PG-TXL are likely important contributing factors responsible for the superior therapeutic index of PG-TXL observed in preclinical studies.

Results comparing cellular uptake of tritium-labeled [^3H]PG-TXL ([^3H] labeled on PG polymer) and PG-[^3H]TXL ([^3H] labeled on paclitaxel) in tumor cells are intriguing. Whereas an insignificant amount of radioactivity was found taken up by MDA-MB-453 breast cancer cells when [^3H]PG-TXL was used, there was a time-dependent increase of cell-associated radioactivity when PG-[^3H]TXL was incubated with MDA-MB-453 cells. Moreover, cellular uptake of PG-[^3H]TXL was more than 100 times higher than that of [^3H]PG-TXL [16]. These results suggest that it was the free paclitaxel released into the culture media that had been taken

up by the cells. Intact PG-TXL was probably taken up by cancer cells through less efficient pinocytosis. PG-TXL, however, can be taken up efficiently by phagocytosis. Using HPLC/mass spectral analysis, Shaffer et al. [19] recently compared the profiles of PG-TXL metabolites in murine RAW 264.7 cells with monocyte/macrophage-like activity and in cancer cells (NCI-H460 lung cancer cells and HT-29 colon cancer cells). They showed that the major intracellular metabolites of PG-TXL resulting from the degradation of polymer backbone were monoglutamyl-2'-paclitaxel (Glu-2'-TXL) and diglutamyl-2'-paclitaxel (H₂N-Glu-Glu-2'-TXL). Significantly, the intracellular concentrations of Glu-2'-TXL and H₂N-Glu-Glu-2'-TXL were 100–1000 times higher in RAW 264.7 cells than in the cancer cells [19].

If PG-TXL could be efficiently taken up by macrophages, what is the role of macrophages residing in the tumors in intratumoral dispersion of PG-TXL? An *in vivo* imaging study using PG-DTPA-Gd, a magnetic resonance imaging (MRI)-visible PG surrogate, showed that PG-DTPA-Gd was initially localized to the perivascular space after its intravenous injection but was distributed to the necrotic zone of the tumors at later times (2–4 days). Interestingly, immunohistochemical analysis revealed that biotinylated PG-DTPA-Gd co-localized with macrophages in the necrotic areas (Fig. 4) [20]. These results suggest that PG-DTPA-Gd, and possibly other PG-drug conjugates, may be captured by resident macrophages in the necrotic areas or by migrating macrophages that eventually infiltrate into the necrotic tissues. Consistent with this hypothesis, recent studies using a monoclonal antibody that specifically recognizes PG-TXL showed that PG-TXL was taken up by macrophages *in vitro* through endocytosis [21] and that PG-TXL preferentially localized to perinecrotic areas in tumors *in vivo* [22]. Further study showed that enhancement of the necrotic tissue of the tumors was observed only with polymeric contrast agents and not with low-molecular-weight contrast agents, including oligo(L-glutamic acid)-DTPA-Gd [20], suggesting that prolonged blood circulation is required for the polymer to interact with macrophages.

Consistent with the MRI findings obtained with PG-DTPA-Gd, autoradiographic studies in mice injected with PG-[³H]TXL found that radioactivity was primarily located in the periphery of the tumor initially and was heterogeneously distributed throughout the tumor at a later time (i.e., by day 6) (Fig. 5) [17]. Three possible routes may account for the dispersion of radioactive species towards the center of the tumor: 1) diffusion of intact PG-[³H]TXL; 2) diffusion of small-molecular-weight metabolites of PG-[³H]TXL such as free [³H]paclitaxel, Glu-2'-TXL, and H₂N-Glu-Glu-2'-TXL; and 3) uptake of PG-[³H]TXL by macrophages and subsequent migration of macrophages within the tumor mass. Intact PG-TXL, as has been found with other macromolecules and nanoparticles, is more likely to localize in the perivascular space after extravasation from tumor microvessels with minimal penetration into the tumor matrix [23, 24]. Therefore, in addition to the possible role of macrophages in the dispersion of PG-TXL within the tumor interstitium, the role of PG-TXL degradation in perivascular fluid space on the dispersion of active species (i.e., radioactivity associated with PG-[³H]TXL and its metabolites) throughout the tumor mass should be further examined.

Recent studies suggest that selective proteolysis of the PG backbone through the action of cellular proteases in tumors, particularly cathepsin B, may be responsible for the increased site-specific delivery and enhanced antitumor activity of PG-TXL [19,25]. Cathepsin B is a lysosomal cysteine protease in normal cells and tissues. In premalignant and malignant lesions, the expression of cathepsin B is highly upregulated, and the enzyme is secreted and becomes associated with the cell surface [26]. Cathepsin B has been implicated in the degradation of the extracellular matrix, a crucial step in tumor dissemination and angiogenesis. Using a noninvasive near-infrared fluorescence optical imaging technique, we recently demonstrated selective degradation of L-PG polymer but not D-PG polymer in an orthotopic U87 glioma tumor model (Fig. 6) [25]. Such a technique can be very useful in investigating the spatial and

temporal distribution of the degradation products of PG-based polymeric drugs and the effect of polymer degradation on the antitumor activity of polymer-drug conjugates.

2.3. Clinical Findings

Results of clinical trials of CT-2103 (Xyotax®, PG-TXL) from data available in the literature are summarized in Table 1.

Phase I Studies—In the CT-2103 formulation used in clinical studies, the median molecular weight of PG-TXL is 48,000 Da, and the content of paclitaxel is about 37% by weight, equivalent to approximately one paclitaxel molecule for every 11 glutamic acid units in each PG polymer chain [18]. This formulation eliminated the use of Cremophor and alcohol and allows infusion of paclitaxel as PG-TXL over 30 minutes. In the initial clinical trials in the United Kingdom, the investigators gave PG-TXL (CT-2103) to cancer patients in a 30-minute infusion every 3 weeks at doses ranging from 30 to 720 mg/m² [27]. They detected CT-2103 in the plasma of all of the patients and observed a long plasma half-life of up to 185 h. CT-2103 could be detected in plasma 3 weeks after administration at a dose of 200 mg/m². Importantly, the AUC of free paclitaxel was about 1% to 2% of the AUC of CT-2103, which supported the *in vivo* stability of CT-2103 in the plasma and the slow, prolonged release of the active moiety [28]. The steady-state volume of distribution range was low ($V_{ss} = 2.7\text{--}13.2\text{ L}$), which suggests that the distribution of CT-2103 was restricted mainly to the plasma and other extracellular body fluids [29]. The MTD was 233 mg/m² with a 3-weekly schedule and 177 mg/m² with a more intense 2-weekly schedule. The dose-limiting toxicity (DLT) was primarily neuropathy. Notably, alopecia was almost absent in patients treated with CT-2103 compared with an incidence of over 50% following Taxol® as a 3- or 24-h infusion.

A second Phase I study evaluated the MTD of CT-2103 in combination with carboplatin in patients with a variety of solid tumors refractory to conventional treatment [30]. The MTD was determined to be 250 mg/m², and DLTs observed at 250 mg/m² were neutropenia and thrombocytopenia. Interestingly, the three patients who had partial responses in this series were all patients with ovarian cancer who had previously undergone unsuccessful Taxol® therapy.

Another Phase I study determined the MTD and DLTs of PG-TXL and concurrent radiation (50.4 Gy) in patients with esophageal and gastric cancer [31]. The MTD was found to be 70 mg/m²/week, with gastritis, esophagitis, neutropenia, and dehydration being the DLTs. Strong antitumor activity was observed in this Phase I study, with four (33%) of 12 patients with locoregional disease undergoing a complete clinical response. An additional seven patients (58%) had partial response (>50% tumor reduction by post-treatment endoscopy). These promising preliminary results with combined PG-TXL and radiation indicate that PG-TXL warrants further evaluation as a radiosensitizer in other solid tumors.

Phase II Studies—A multicenter Phase II trial of PG-TXL to determine the efficacy and toxicity in heavily pretreated patients with advanced ovarian cancer has been completed [18, 32]. Ninety-nine patients registered in this trial received PG-TXL at a dose of 175 mg/m² every 3 weeks. The toxic effects were mild and consisted of grade 3 neuropathy (15%), grade 3 neutropenia (15%), and grade 4 neutropenia (9%). The observed response rates (28% in platinum-sensitive patients and 10% in platinum-resistant patients with one or two prior regimens) are in line with results seen in studies of other agents.

A recent report on a Phase II study in patients with metastatic breast cancer showed an unexpected incidence (22%) of hypersensitivity reactions [33]. This reaction is puzzling, considering that the approximate incidence of grade 3 or 4 hypersensitivity reaction in over 1,400 patients who have received CT-2103 in clinical trials was only 2%. Because the majority of women were postmenopausal at the study entry, one possible explanation is the differing

pharmacokinetics of CT-2103 in this population of patients. Further studies are needed to determine the possible roles of sex, hormonal status, and the duration of treatment in hypersensitivity reactions to CT-2103. Of the 18 patients treated with CT-2103, four (22%) had responses. In comparison, a study with Taxol® in a similar population of patients with largely HER2-negative metastatic breast cancer showed a 14% objective response rate in the first-line setting [33]. Unfortunately, because of the unexpected high incidence of hypersensitivity reaction, this Phase II study was terminated early, and the authors were unable to evaluate the clinical benefit rate or time to progression.

In an ongoing Phase II trial in patients with androgen independent prostate cancer, CT-2103 was found well tolerated and demonstrates activity measured by PSA response and PSA velocity changes [34]. Of the 21 patients enrolled to date (16 previously treated/5 untreated), 2 previously treated patients and 1 previously untreated responded based on a 50% PSA reduction that were maintained for at least 8 wks. In addition, 4 previously treated and 2 untreated patients demonstrated a delay in their PSA velocity. Adverse events included hypersensitivity reaction (1 patient), grade 2/3 neuropathy (7 patients), grade 3/4 neutropenia (8 patients) and grade 3 thrombocytopenia (1 patient). Currently, this trial continues to enroll patients.

Phase II studies in patients with resistant colorectal cancer and in previously untreated high-risk patients with NSCLC have been completed [18].

Phase III Studies—More than 1,700 patients with NSCLC have participated in Phase III trials of PG-TXL (CT-2103), which included two Phase III trials of CT-2103 as first-line treatment in performance status-2 (PS2) patients (STELLAR 3 and STELLAR 4) and one Phase III trial of CT-2103 as second-line treatment in PS0-2 patients (STELLAR 2) [18,35]. In the STELLAR 3 trial, CT-2103 plus carboplatin AUC 6 was compared with Taxol® plus carboplatin; in the STELLAR 4 trial, CT-2103 used as a single agent was compared with gemcitabine or vinorelbine; in STELLAR 2, CT-2103 used as a single agent was compared with docetaxel. In all studies, the primary efficacy end point was the duration of overall survival. The total numbers of patients in the STELLAR 2, STELLAR 3, and STELLAR 4 trials were 850, 400, and 477, respectively. As the results of the Phase III study completed in 2005, there was no significant overall improvement in survival of the patients evaluated. However, these studies did demonstrate similar efficacy, reduced side effects, and more convenient administration of CT-2103 compared with the control treatment arms [18,35].

Interestingly, in a subset evaluation of women with NSCLC, the premenopausal women fared significantly better as long as their estrogen levels were normal. Clinical data from a pooled analysis of CTI's STELLAR 3 and 4 trials showed that in the 198 women treated on those trials, superior survival was observed in those who received CT-2103 ($p = 0.03$). The most notable effect was among women less than 55 years old and presumably pre-menopausal who were treated with CT-2103 compared with standard chemotherapy (median survival 10.0 vs. 5.3 months, hazard ratio = 0.51, log rank $p = 0.038$), while a survival trend ($p = 0.134$) was observed in women 55 years of age and older (post-menopausal) [36]. The favorable antitumor activity among women less than 55 years stimulated the initiation of the PIONEER 1 clinical Phase III trial to evaluate prospectively CT-2103 given at a dose of 175 mg/m² once every 3 weeks in women with advanced NSCLC and PS2 status [37].

In general, CT-2103-related nonhematological toxicities were similar to those for other agents, with dose-related neurotoxicity as the most important clinical issue [35]. Neuropathy was a common toxicity associated with exposure to taxanes. In STELLAR 3, the frequency of neuropathy (all grades) was similar between treatment arms; grade 3 neuropathy occurred in 17% of patients receiving CT-2103 (210 mg/m²) versus 10% of patients receiving Taxol®.

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CT-2103-induced neuropathy seemed to be dose dependent. Grade 3 neuropathy was limited to 4% of patients receiving single-agent CT-2103 175 mg/m² in STELLAR 4. Neurotoxicity occurred significantly later with CT-2103 (210 mg/m²) compared with Taxol® in STELLAR 3, suggesting that there might be slow accumulation of CT-2103 in peripheral nerves at doses greater than (175 mg/m²). Alternatively, the longer terminal half-life of CT-2103 might be related to increased neurotoxicity at higher CT-2103 doses. These observations suggest that significant neurotoxicity can be minimized by administering CT-2103 at 175 mg/m². Consequently, this dose will be used in subsequent trials.

A randomized Phase III trial of maintenance chemotherapy comparing 12 monthly cycles of single agent paclitaxel or Xyotax™ versus no treatment in women with stage III/IV ovarian epithelial or peritoneal cancer is currently recruiting participants (www.cancer.gov). This trial, sponsored by the National Cancer Institute and the Gynecologic Oncology Group (GOG), is projected to recruit 1550 eligible participants. The primary objective of this study is to determine whether Xyotax™ or paclitaxel, administered to women with advance ovarian cancer who have attained a clinically-defined complete response to primary platinum/taxane chemotherapy, will reduce the death rate, compared to retreatment at the time of documented disease progression. The secondary objective is to determine if, in this clinical setting, Xyotax™ produces a more favorable toxicity profile and superior quality of life compared to paclitaxel.

Summary—Compared with conventional paclitaxel-based treatment, PG-TXL showed three safety-related advantages. First, alopecia was rare, and complete hair loss was not observed. Second, nausea and vomiting were uncommon. Third, hypersensitivity reactions were rarely observed, and those that did occur were usually mild to moderate; thus, routinely used prophylactic premedications were not required. CT-2103 is active against a variety of cancers. Further studies to define toxicity and efficacy in patients with less prior therapy are needed to determine the role of CT-2103 in these cancers as first-line and second-line therapy. Of note is the observed improvement in overall survival for women receiving CT-2103 vs. control in combined log-rank analysis of STELLAR 3 and 4 Phase III trials. Consequently, a request for approval of CT-2103 for the treatment of NSCLC in women with normal estrogen levels (premenopausal) based on non-inferiority will be submitted to the EMEA, the European equivalent of the FDA, in 2008. In the United States, a confirmatory Phase III trial was initiated in 2007 on 450 women (normal premenopausal estrogen levels) for the treatment of NSCLC, comparing CT-2103 and carboplatin with paclitaxel and carboplatin. If results are favorable, CT-2103 will be submitted to the FDA for approval in 2009.

2.4. Modulation of Antitumor Therapy with External Radiation

Combining chemotherapy and radiotherapy has significantly improved response and survival rates in patients with many solid tumors. Many chemotherapeutic agents can increase the radiosensitivity of tumors, thus potentiating the tumor response to radiation-caused damage. We hypothesized that combining radiotherapy and chemotherapy using a polymer-drug conjugate could lead to a stronger radiosensitizing effect than using the parent drug owing to sustained release of the free drug from polymer-bound drug in the tumor. Irradiation can in turn potentiate the tumor response to polymer-drug conjugates by increasing tumor vascular permeability and thus the uptake of these conjugates into solid tumors. To test this hypothesis, PG-TXL was used as a model polymer-drug conjugate. Administration of PG-TXL delayed the growth of OCa-1 syngeneic murine ovarian tumors in C3H/Kam mice. However, when PG-TXL was given in combination with tumor irradiation, antitumor activity was significantly enhanced. Using tumor growth delay as an end point, enhancement factors ranging from 1.36 to 4.4 were observed; these values depended on the doses of PG-TXL and radiation delivered. Complete tumor regression was found with the use of increased radiation doses (>10 Gy) and

PG-TXL doses (>80 mg/kg equivalent paclitaxel) [38,39]. Similar results were observed in a mammary MCA-4 carcinoma model [40]. In contrast, combined radiotherapy and paclitaxel treatment yielded an enhancement factor of less than 1.0 in MCA-4 tumors, indicating that conjugation of paclitaxel with PG is necessary to improve the radiosensitization effect of paclitaxel. When the treatment end point was tumor cure, the enhancement factors were as high as 8.4 and 7.2 after fractionated and single-dose radiotherapy, respectively [41,42].

To determine whether prior irradiation affects tumor uptake of PG-TXL, [^3H]PG-TXL was injected into mice with OCa-1 ovarian tumors 24 h after local irradiation at 15 Gy [39]. The uptake of [^3H]PG-TXL in irradiated tumors was 28% to 38% higher than that in nonirradiated tumors at different times after injection of [^3H]PG-TXL, suggesting that irradiation increased the accumulation of PG-TXL in the tumors. Thus, the super-synergistic effect of combined radiotherapy and PG-TXL-based chemotherapy is partly ascribed to the enhanced permeability and retention effect of macromolecules caused by irradiation.

These promising preclinical studies have prompted the initiation of clinical trials combining PG-TXL with concurrent radiation in patients with esophageal and gastric cancer [31]. Data from this Phase I trial demonstrated major tumor responses in 91% of patients.

3. Other Polymer-Drug Conjugates in the Clinic

Over the last decade, nearly a dozen polymer-drug conjugates have entered clinical studies (Table 2). Early results have generally been promising, and antitumor activity has been seen in chemotherapy-refractory patients. On the basis of the current status in clinical studies, these conjugates can be categorized into three groups: 1) Conjugates that have progressed further to Phase II/III trials or conjugates for which further studies are planned. Polymer-drug conjugates belonging to this category include PK1, PK2, HMPA copolymer-platinum, polymeric micelle NK911, carboxymethyl-dextran-bound CPT DE-310, and poly(L-glutamic acid)-paclitaxel XyotaxTM. 2) Conjugates that further clinical development has been either discontinued or suspended because of unacceptable toxicity, inadequate linker chemistry, or pharmacoeconomic considerations. HMPA copolymer-camptothecin, HMPA copolymer-paclitaxel, PEG-camptothecin, PEG-paclitaxel, and PG-CPT (CT-2106) belong to this group. 3) Conjugates just entered into clinical trial studies, such as PEG-SN38 (EZN-2208) and a linear, cyclodextrin-bound CPT (IT101).

3.1. HMPA Copolymer-Doxorubicin (PK1)

Doxorubicin is an anthracycline cytotoxic agent widely used in the treatment of solid tumors, lymphoma, and leukemia. The DLTs of doxorubicin include bone marrow suppression, mucositis, and cardiotoxicity. In an attempt to reduce its toxicity, doxorubicin was conjugated to a water-soluble synthetic polymer, *N*-(2-hydroxypropyl) methacrylamide (HMPA)/methacrylic acid copolymers through a tetrapeptide linker (Gly-Phe-Leu-Gly) [43,44]. The tetrapeptide linker allowed selective release of the active drug in the tumors through the action of lysosomal enzymes. The conjugate, known as PK1, was found to be more potent than free doxorubicin in antitumor activity in preclinical animal studies [45,46]. PK1 was the first synthetic polymer-anticancer drug conjugate that entered clinical trials (in 1994) [47]. Data from Phase II trials for the treatment of breast, NSCLC, and colon cancers were presented in 2002 and showed positive responses in six of 63 patients, with manageable side effects [48]. The subject of development history, mechanism of action, and pharmacology for PK1 has been reviewed extensively [48–51].

3.2. HMPA Copolymer-Doxorubicin-Galactosamine (PK2)

PK2 is a 27-kDa HMPA copolymer derivatized with 6.5% mol/wt, <2% free doxorubicin, and 2 % mol/wt galactose, with efficient targeting of the asialoglycoprotein receptor selectively expressed on hepatocytes and in hepatomas. In preclinical murine models, 80% of an administered dose targeted the liver, associated with high anticancer activity. PK2 remained the only targeted polymeric conjugate to be tested clinically to date [52]. In Phase I/II trial, the maximum tolerated dose of PK2 was 160 mg/m², with neutropenia being the DLT. Hepatic targeting was confirmed by planar imaging and single photon emission computed tomography (SPECT) with ¹²³I-labeled PK2 co-injected with unlabeled PK2. The majority of conjugate was present in normal liver (16.9% after 24 h), with lower accumulations within the hepatic tumors (3.2%).

3.3. HMPA Copolymer-Camptothecin (MAG-CPT, PNU166148) and HMPA Copolymer-Paclitaxel (PNU166945)

The camptothecins (CPTs) are a family of synthetic and semisynthetic analogues of 20(S)-camptothecin that exhibit a broad range of anticancer activity by inhibiting topoisomerase-1 activity. Two properties of CPT compounds limit their therapeutic efficacy in humans: instability of the lactone form because of preferential binding of the carboxylate to serum albumin, and a lack of aqueous solubility. Conjugation of CPT to water-soluble polymeric carriers has in general resulted in improved stability of the lactone ring and increased aqueous solubility.

In HMPA-CPT (MAG-CPT, PNU166148), CPT is attached to the copolymer at the C-20 hydroxyl group of CPT through an ester linkage. A Phase I study in a total of 23 patients showed DLTs of myelosuppression, neutropaenic sepsis, and diarrhoea. The maximum tolerated dose and dose recommended for further clinical study was 200 mg equivalent CPT/m². The plasma half-life of both MAG-CPT and released CPT was extended to > 6 days, indicating that the kinetics of free CPT was release rate dependent [53]. Results presented in an earlier clinical study showed serious bladder toxicity which became dose limiting. Patients with higher plasma AUC values had the more severe symptoms of renal toxicity [54].

In HMPA copolymer-paclitaxel (PNU166945), paclitaxel was linked to the same tetrapeptide linker used to create PK1 and PK2. In a Phase I clinical study in a small patient cohort (12 patients), one patient with advanced breast cancer had a partial response. PNU166945 showed toxicity consistent with commonly observed toxicities associated with paclitaxel [55]. One patient developed grade 3 neurotoxicity. Dose escalation was discontinued prematurely due to concerns about potential clinical neurotoxicity.

3.4. HMPA Copolymer-Platinate (AP5346)

The platinum-based compounds, cisplatin and carboplatin, are standard treatment regimens for a wide range of cancers. The DLTs of these drugs include nephrotoxicity, neurotoxicity, and myelosuppression. 1,2-Diaminocyclohexane (DACH) has received increasing attention in recent years because of its activity against cisplatin-resistant cancer cells. In AP5346, DACH-platinum was bound to HMPA via a pH-sensitive chelate. A methacrylamide monomer substituted with a triglycine aminomalonate group provided the primary binding site for the DACH-platinum moiety [56]. The conjugate contained approximately 10% platinum by weight and had a molecular weight of 25 kDa, which was designed to allow glomerular filtration while also being large enough to benefit from an EPR effect. While negligible in neutral solutions, release of the DACH-platinum moiety was increased at low pH so that platinum release was favored in environments such as the extracellular space of hypoxic tumors and the intracellular lysosomal compartment. In a clinical Phase I study, AP5346 was administered as a 1-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle. Twenty-six patients received 41

cycles. Antitumor activity included two partial responses in metastatic melanoma and ovarian cancer and an additional CA-125 normalization in a suspected ovarian cancer. AP5346 administered weekly for 3 weeks out of every 4 weeks was tolerated up to a dose of 640 mg P/m^2 on the first cycle. The pharmacokinetics of AP5346 indicated a prolonged half-life (mean terminal half-life $t_{1/2} = 72$ h) and evidence of antitumor activity. Additional human clinical trials are planned for this agent.

3.5. PEG-Camptothecin (Pegamotecan) and PEG-SN38 (EZN-2208)

Pegamotecan was developed by Enzon Pharmaceuticals, Inc. The conjugate consists of two CPT molecules conjugated to a 40-kDa PEG using an alaninate ester linkage. Free CPT must be cleaved from the PEG to be pharmacologically active. The hydroxyl group (-OH) at the 20-position of CPT is the active portion of the molecule responsible for the conformational changes between the active lactone and relatively inactive carboxylate forms. The 20-OH of CPT in Pegamotecan, is blocked by the alaninate linker, which stabilizes the CPT molecule into its active lactone conformation [57]. The MTD of Pegamotecan when administered weekly for 3 of 4 weeks was 3,240 mg/m^2 , with neutropenia being its DLT [58]. Other grade 3 and 4 toxic effects were anemia, thrombocytopenia, fatigue, prolonged partial thromboplastin time, hemorrhagic cystitis, dysuria, and urinary frequency. Of the 27 patients enrolled, two patients had unconfirmed partial responses. Further development of Pegamotecan appears to be discontinued; the drug is no longer listed in the company's drug portfolio/pipeline (www.enzon.com).

The main limitation of PEG as drug carrier is the presence of only two reactive groups per polymer chain, which leads to an intrinsically low drug payload. To overcome this limitation, the construction of a dendron structure at the PEG's end chain has been proposed. Enzon is currently developing a conjugate of SN38, an active metabolite of CPT, with a 40-kDa PEG containing four arms. EZN-2208 has shown activity in a panel of human tumor xenografts [59]. A Phase I study of EZN-2208 to evaluate the safety and tolerability of intravenous EZN-2208 in patients with advanced solid tumors or lymphoma is currently enrolling participants (<http://clinicaltrials.gov>).

3.6. PEG-poly(Aspartic Acid)-Doxorubicin Micelles (NK911)

The polymeric micelle consists of a PEG-poly(aspartic acid) block copolymer conjugated with doxorubicin (NK911) [60]. PEG is believed to form the outer shell of the micelle, producing a 'stealth' effect that prevents NK911 from being captured by the liver and spleen. The doxorubicin-conjugated poly(aspartic acid) chain is hydrophobic and is believed to form the hydrophobic inner core of the micelles in aqueous media. The hydrophobic inner core enables NK911 to entrap a sufficient amount of doxorubicin. NK911 has a diameter of about 40 nm. The plasma AUC and the tumor AUC of NK911 were lower than those of liposomal doxorubicin because NK911 was less stable in the bloodstream than doxorubicin [60]. Twenty-three patients participated in a Phase I study performed at the National Cancer Center Hospital, Tokyo, Japan. Neutropenia was the predominant hematological toxicity, and grade 3 or 4 neutropenia was observed at doses of 50 and 67 mg/m^2 . The DLT occurred at a dose of 67 mg/m^2 (grade 4 neutropenia lasting more than 5 days). A partial response was obtained in one patient with metastatic pancreatic cancer among the 23 patients. A Phase II trial of NK911 for the treatment of metastatic pancreatic cancer is ongoing.

3.7. Cyclodextrin-Based Polymer-CPT (IT-101)

IT101 is a conjugate of CPT and a linear, cyclodextrin-based polymer (CDP) [61,62]. The components of CDP are beta-cyclodextrin and polyethylene-glycol (PEG). Camptothecin is covalently attached to CDP through a glycine linker, which preserves CPT in its active form and increases its water solubility. Preclinical efficacy of i.v. IT-101 (molecular weight ~90

kDa) demonstrated a significant antitumor effect with IT-101 in a range of mouse xenografts, including several tumors that were resistant to CPT [62]. Pharmacokinetic and biodistribution studies indicated that CDP-CPT conjugate gave prolonged plasma half-life, which led to enhanced distribution to tumor when compared to CPT alone [61]. These favorable results prompted the initiation of a Phase I trial designed to determine the safety, MTD, and the pharmacokinetics of IT-101 when administered intravenously to patients with relapsed or refractory cancer. A total enrollment of 36 patients is expected to complete by first quarter of 2008.

3.8. Carboxymethyldextran-Exatecan (DE-310)

In DE-310, DX-8951 (exatecan mesylate, a CPT analogue) is linked to carboxymethyldextran (Mw = 340 kDa) via a glycyl-glycyl-phenylalanyl-glycyl-peptidyl spacer. This peptide spacer is intended to provide sustained release of the active moiety DX-8951 within the tumor as a result of enzymatic cleavage of the peptide by cathepsin B and cathepsin L [63]. In Phase I trial, patients received DE-310 as a 3-hour infusion once every 2 weeks (dose, 1.0–2.0 mg/m²) or once every 6 weeks (dose, 6.0–9.0 mg/m²) [64]. Neutropenia and grade 3 thrombocytopenia, and grade 3 hepatotoxicity with veno-occlusive disease, were dose-limiting toxicities. Other hematologic and nonhematologic toxicities were mild to moderate and reversible. The apparent half-life of conjugated DX-8951, glycyl-DX-8951, and DX-8951 was 13 days. The observed long blood half-lives are no surprising considering that DE-310 had the highest molecular weight among all polymer-drug conjugates tested so far. Of the 27 patients enrolled into the study, 1 patient achieved a histologically proven complete remission, 1 patient confirmed partial remission, and 14 additional patients showed disease stabilization.

3.9. PG-Gly-CPT (CT-2106)

PG was an effective solubilizing carrier of CPT and stabilized the E-ring lactone structure in CPT. PG-CPT conjugate was obtained by directly coupling the hydroxy group at the C20(S)-position of CPT with the carboxylic acid of PG [65]. When given intravenously in four doses every 4 days at an equivalent CPT of 40 mg/kg, PG-CPT delayed the growth of established H322 human lung tumors grown subcutaneously in nude mice. In mice that received intratracheal inoculation of H322 cells, the same treatment prolonged the median survival duration in mice by four-fold when compared with that in untreated control mice. These results showed that PG was as efficient carrier of CPT [65].

Studies have systematically investigated the structural effects of the antitumor efficacy of PG-bound CPT, including linkers between PG and CPT, the point of attachment of PG on the CPT molecule, the polymer molecular weight, and drug loading [66–68]. Coupling through the 20 (S)-hydroxy group of CPT with or without a glycine linker yielded the most active conjugates, because this site is located in close proximity to the lactone ring; thus, the E-ring lactone is better protected by the linked PG chains. However, the linkers affected the maximum drug payload; for example, only 15% (by weight) of CPT loading could be achieved for direct conjugation of PG-CPT by the ester linkage because of steric hindrance, whereas up to 50% CPT loading could be achieved for the case with a glycine as linker [67]. Increasing the molecular weight of PG from 33 to 50 kDa improved the antitumor efficacy of PG-Gly-CPT, probably because of an increased plasma half-life and reduced renal clearance [66]. Considering its ease of synthesis, superior aqueous solubility and stability, and marked efficacy in various *in vivo* tumor models, PG-Gly-CPT with 30–35% CPT was selected for further study.

CT-2106 (PG-Gly-CPT) entered clinical Phase I trials in April 2004. Preliminary results on pharmacokinetics in 19 patients with CT-2106 administered as a 10 minute intravenous infusion every 3 weeks were recently presented [69,70]. The apparent termination t_{1/2} of unconjugated CPT is quite long—approximately 40 h. Five days after the first administration

(cycle 1), the excretion in urine of CT-2106 and unconjugated CPT accounted for 27.9% and 5.1% of the administered dose, respectively. Thus, CT-2106 generates prolonged systemic exposures to unconjugated CPT in plasma, and the urine excretion levels of conjugated camptothecin are substantial. A major CPT conjugated species found in urine was glu-gly-CPT. DLs included grade 3/4 neutropenia with concomitant grade 3 thrombocytopenia (3 patients, 105 mg/m²) and grade 2 hematuria (1 patient, 25 mg/m²). Most adverse events have been mild or moderate. Four patients had stable disease (SD) for >9 weeks; 2 lung cancer patients (25 mg/m²) had SD for >27 weeks. In a second Phase I trial in 26 patients, the MTD, toxicity, pharmacokinetics, and response rate of CT-2106 when administered weekly for 3 consecutive weeks of every 4-week cycle were determined [71]. With this schedule, the MTD was 75 mg/m². DLTs observed were grade 3 or 4 neutropenia and concomitant grade 3 or 4 thrombocytopenia in the three patients treated at 105 mg/m² and grade 2 hematuria in a patient treated at 25 mg/m². Of the 25 patients assessable for response, no objective responses (complete or partial) were noted. Three patients had stable disease. The absence of objective responses (complete or partial) was not surprising in this heavily treated population.

Presently, Cell Therapeutics has no clinical trial material for additional trials. Further development of CT-2106 is delayed so that the company can focus resources on the development of XyotaxTM and other agents in the pipeline.

4. Conclusions

Results from early clinical trials of about a dozen polymer-drug conjugates have demonstrated several advantages over the corresponding parent drugs, including fewer side effects, enhanced therapeutic efficacy, ease of drug administration, and improved patient compliance. Owing to its favorable physicochemical properties, PG has been shown to be an excellent polymeric carrier of therapeutic agents. XyotaxTM (PG-TXL) has become the first polymer-drug conjugate for the delivery of cytotoxic chemotherapeutic agents to advance to clinical Phase III trials. Clinical data collected over the last decade warrant further development of polymer-drug conjugates as a new class of anticancer agents. Future generation of polymer-drug conjugates will have to meet a number of challenges, including the development of novel polymers with modulated rates of degradation, versatile conjugation chemistry allowing site-specific attachment of targeting moieties, and polymerization methods that allow accurate control of polymer molecular weights and molecular weight distributions. The incorporation of novel imaging techniques into the clinical trial design of new polymer-drug conjugates is also expected to facilitate noninvasive monitoring of drug delivery efficiency in the era of individualized therapy.

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Fig. 1.

Model for targetable polymer-drug conjugates according to Ringsdorf [1], in which a solubility enhancer, a pharmacokinetic modifier, a homing device, and specific drugs or imaging probes could be attached to the same polymeric chain.

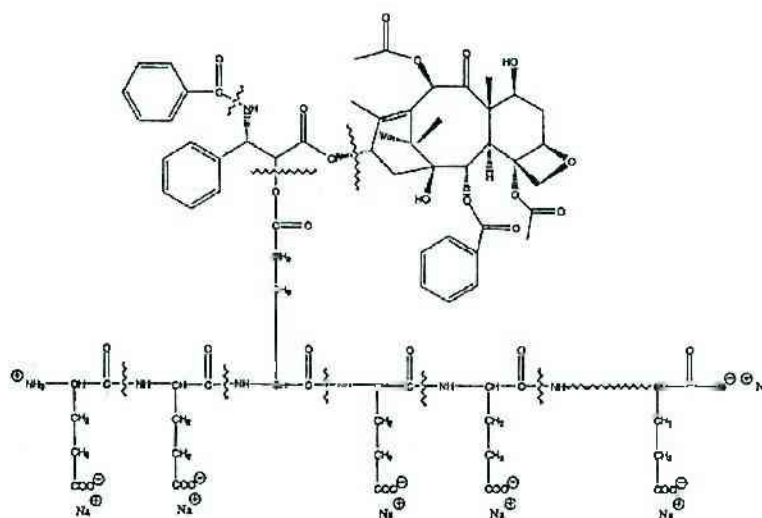


Fig. 2.
Structure of PG-TXL.

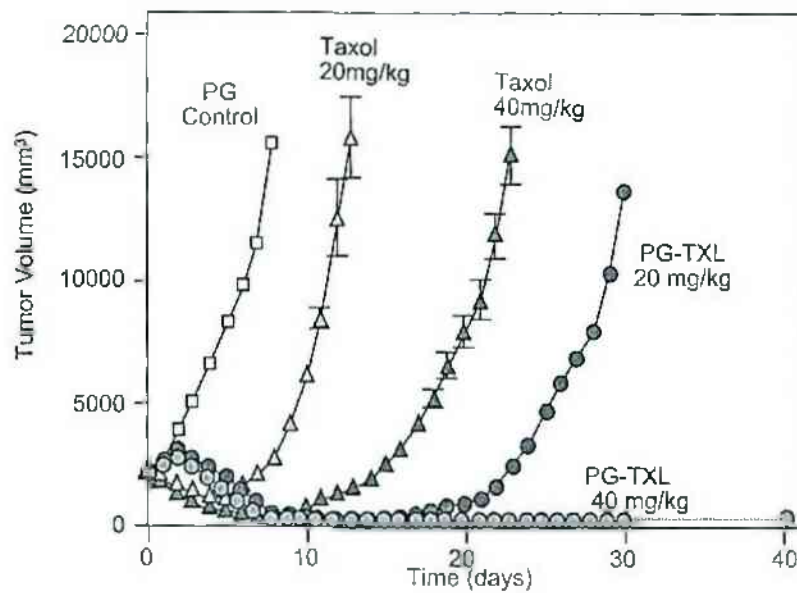


Fig. 3.

Antitumor activity of PG-TXL in rats bearing rat breast tumor 13762F. Each drug was injected i.v. in a single dose at the indicated equivalent paclitaxel concentration. Data are presented as means $\pm$ SD of tumor volume (adapted from reference [12]).

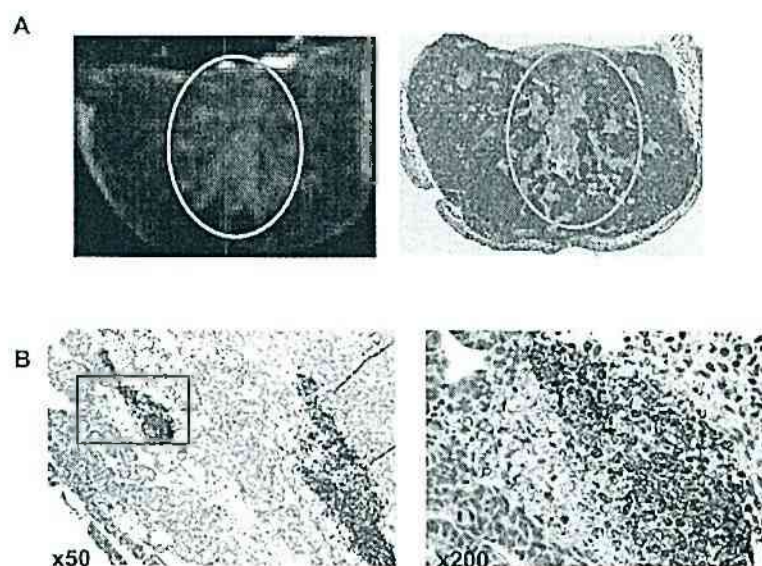


Fig. 4.

A: Representative T₁-weighted MRI image from a mouse bearing a subcutaneously inoculated Colo-205 tumor (left) and a photograph of the corresponding H&E-stained section of the tumor (right). The mouse received intravenous injections of L-PG-DTPA-Gd (0.04 mmol Gd/kg). L-PG-DTPA-Gd was distributed within the necrotic area (circle). B: Co-localization of macrophages and biotinylated L-PG-DTPA-Gd in the necrotic area in OCA-1 tumors. Staining with antibody directed against macrophage antigen F4/80 (reddish-pink) and with streptavidin-horseradish peroxidase and DAB for biotinylated L-PG-DTPA-Gd showed widespread macrophage infiltration in necrotic areas as well as distribution of the polymer and its degradation products to the necrotic area (brown). The sections were counterstained with hematoxylin (blue) to label the nuclei of viable tumor cells. Examples of biotin-L-PG-DTPA-Gd staining and dual F4/80 and biotin staining are indicated with arrows and arrowheads, respectively (from reference [20]).

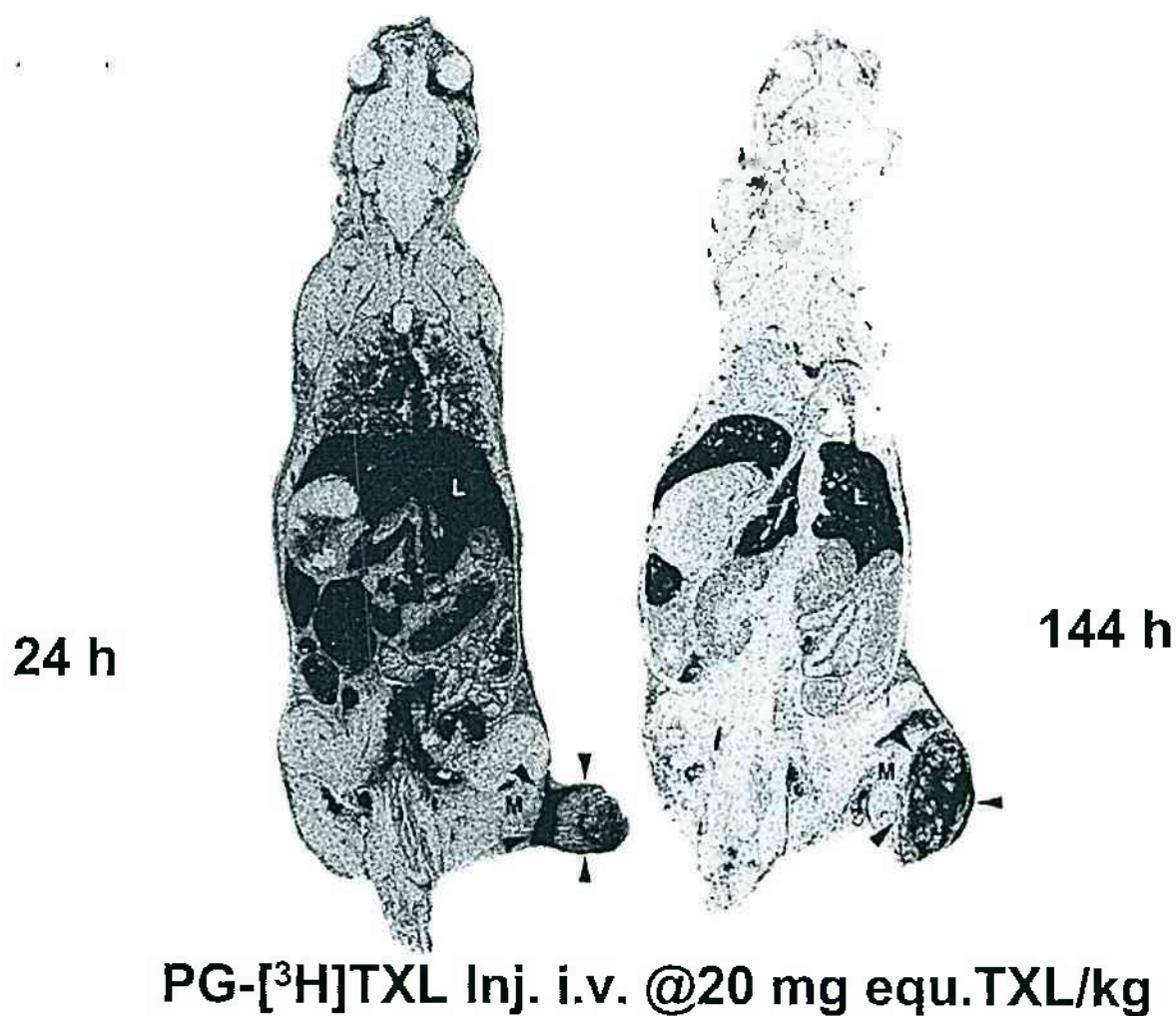


Fig. 5.

Whole-body autoradiographs of mice killed 1 day (A) and 6 days (B) after tail vein injection of PG-[³H]TXL. Most radioactivity was localized to tumor periphery at 1 day after injection, but by day 6, radioactivity had diffused into the center of the tumor. L: liver; M: muscle; Arrow head: tumor (from reference [17]).

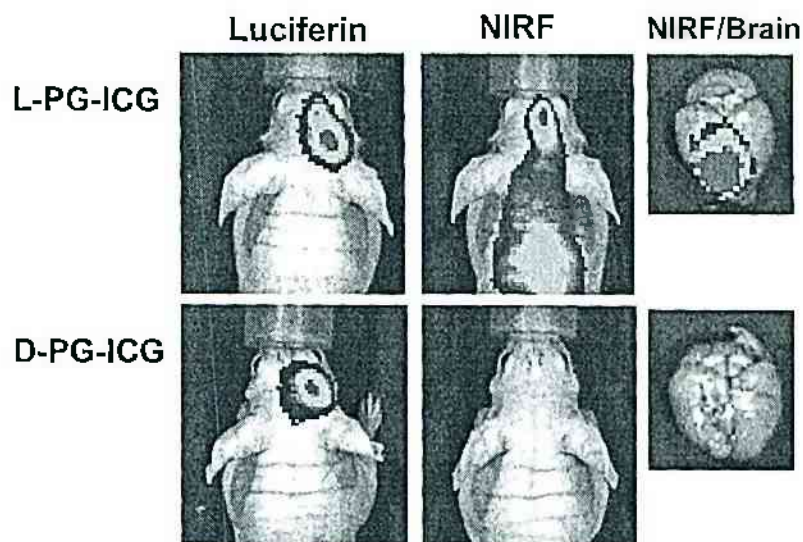


Fig. 6.

Representative *in vivo* near-infrared fluorescence (NIRF) images of cathepsin B activity in intracranially inoculated U87/TGL tumors. The mice used in the study had the same tumor burden, as indicated by the bioluminescence signal generated after intravenous injection of luciferin. NIRF Images were acquired 24 h after intravenous injection of L-PG-NIR813 (50 nmol/mouse) or D-PG-NIR813 (50 nmol/mouse) with the same NIR dye loading (10%) and the same molecular weight (17,500). The NIRF signal was visualized in the mouse injected with L-PG-NIR813 but not the mouse injected with D-PG-NIR813 (from reference [25]).

Table 1
Summary of clinical studies of PG-TXL (CT-2103)

Effect Studied	Status
Safety and Pharmacokinetics	Phase Ia (n = 19 on 3- weekly schedule); Phase Ib (n = 11 on 2-weekly schedule)
Safety	Phase I (n = 22) PG-TXL used in combination with carboplatin; solid tumors
Safety	Phase I (n = 21) PG-TXL plus concurrent radiation; esophageal and gastric cancer
Safety and Efficacy	Phase II (n = 99) patients with heavily pretreated ovarian cancer
Safety and Efficacy	Phase II (n = 18) patients with metastatic breast cancer
Safety and Efficacy	Phase II (n = 21) patients with androgen independent prostate cancer
Efficacy	Phase III (n = 400) CT-2103 plus carboplatin compared to Taxol® plus carboplatin; STELLAR 3 trial in PS2 pts with NSCLC
Efficacy	Phase III (n = 477) CT-2103 as a single agent compared to gemcitabine or vinorelbine; STELLAR4 trial in PS2 patients with NSCLC
Efficacy	Phase III (n = 850) CT-2103 as a single agent compared to docetaxel; STELLAR 2 trial in PS0-2 patients with NSCLC

Table 2

Polymer-drug conjugates in clinical trials

Conjugates	Indication	Status	Con
HPMA-Doxorubicin(PK1; FCE28068)	Lung and breast cancers	Phase II as of 2002	Pf12
HPMA-doxorubicin- galactosamine (PK2, FCE28069)	Hepatocellular carcinoma	Phase I/II	Pf12
HPMA-camptothecin (PNU166148)	Solid tumors	Phase I; discontinued	Pf12
HPMA-paclitaxel (PNU166945)	Solid tumors	Phase I; discontinued	Pf12
HPMA-platinite (AP5346, ProLindac)	Ovarian, melanoma, and colorectal cancers	Phase I	Aec
PEG-Camptothecin(Pegamotecan)	Solid tumors	Phase I; discontinued	Enz
PEG-SN38 (EZN-2208)	Solid tumors	Phase I; initiated as of October 2007	Enz
Polymeric Micelles(NK911)	Pancreatic cancer	Phase II	Nip
Cyclodextrin-Based Polymer-CPT (IT-101)	Solid tumors	Phase I	Insc
Carboxymethyl dextran-Exatecan (DE-310)	Solid tumors	Phase I	Dai
PG-IXL (CT-2103, Xyotax)	Lung, ovarian, colorectal, breast, and esophageal cancers	Phase III	Cel
PG-camptothecin(CT2106)	Colorectal, lung, and ovarian cancers	Phase I	Cel

EXHIBIT 2

Phase III Trial Comparing Paclitaxel Poliglumex (CT-2103, PPX) in Combination with Carboplatin Versus Standard Paclitaxel and Carboplatin in the Treatment of PS 2 Patients with Chemotherapy-Naïve Advanced Non-small Cell Lung Cancer

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Introduction: Performance status (PS) 2 patients with non-small cell lung cancer (NSCLC) experience more toxicity, lower response rates, and shorter survival times than healthier patients treated with standard chemotherapy. Paclitaxel poliglumex (PPX), a macromolecule drug conjugate of paclitaxel and polyglutamic acid, reduces systemic exposure to peak concentrations of free paclitaxel and may lead to increased concentrations in tumors due to enhanced vascular permeability.

Methods: Chemotherapy-naïve PS 2 patients with advanced NSCLC were randomized to receive carboplatin (area under the curve = 6) and either PPX (210 mg/m²/10 min without routine steroid premedication) or paclitaxel (225 mg/m²/3 h with standard premedication) every 3 weeks. The primary end point was overall survival.

Results: A total of 400 patients were enrolled. Alopecia, arthralgias/myalgias, and cardiac events were significantly less frequent with PPX/carboplatin, whereas grade ≥3 neutropenia and grade 3 neuropathy showed a trend of worsening. There was no significant difference in the incidence of hypersensitivity reactions despite the

absence of routine premedication in the PPX arm. Overall survival was similar between treatment arms (hazard ratio, 0.97; log rank $p = 0.769$). Median and 1-year survival rates were 7.9 months and 31% for PPX versus 8 months and 31% for paclitaxel. Disease control rates were 64% and 69% for PPX and paclitaxel, respectively. Time to progression was similar: 3.9 months for PPX/carboplatin versus 4.6 months for paclitaxel/carboplatin ($p = 0.210$).

Conclusion: PPX/carboplatin failed to provide superior survival compared with paclitaxel/carboplatin in the first-line treatment of PS 2 patients with NSCLC, but the results with respect to progression-free survival and overall survival were comparable and the PPX regimen was more convenient.

Key Words: Non-small cell lung cancer, Paclitaxel poliglumex, PPX, CT-2103, PS 2, Toxicity.

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Patients with non-small cell lung cancer (NSCLC) usually present with inoperable, advanced disease. Untreated, these patients have a 1-year survival rate of approximately 10%.¹ Combination chemotherapy regimens provide a statistically significant survival benefit, with 1-year survival rates of 30% to 40% in performance status (PS) 0 to 1 individuals and 2-year survival rates exceeding 10%.^{2–5} Retrospective reviews and meta-analyses of phase III trials have shown that patients with compromised PS (e.g., PS 2) have significantly impaired survival compared with PS 0 to 1 patients.^{6–8} This may be due to highly aggressive disease or comorbid conditions and impaired organ function, which can exacerbate chemotherapy toxicity. Consequently, PS 2 patients are often excluded from chemotherapy trials. Toxicity may deter clinicians from using standard platinum-based combination regimens for PS 2 patients, who often receive palliative care or single-agent, non-platinum therapy instead.

A recent, prospectively planned subanalysis of Cancer and Leukemia Group B (CALGB) 9730, however, demonstrated that PS 2 patients benefited from platinum-based combination therapy compared with a single agent.⁹ Of the nearly 600 patients enrolled in CALGB 9730, 99 were PS 2. Within this cohort, overall response rate, median survival, and 1- and 2-year survival rates were 24%, 4.7 months, 18%, and 9% for the paclitaxel/carboplatin regimen versus 10%, 2.4 months, 10%, and 0% for single-agent paclitaxel.

Paclitaxel polyglumex (PPX) is an anionic, polymeric macromolecule consisting of paclitaxel conjugated to glutamic acid residues.¹⁰ The large number of anionic charges renders this molecule water soluble. The ester bond between paclitaxel and the polyglutamate backbone is stable and resistant to spontaneous hydrolysis; therefore, PPX is not broken down by plasma esterases. Consequently, the circulating polymer is relatively less toxic to normal tissue and theoretically better at delivering paclitaxel to the target cells.¹¹ Aqueous solubility also permits rapid intravenous administration and obviates the need for toxic solubilizing agents such as Cremophor. Finally, this molecule capitalizes on enhanced tumor permeability and retention of macromolecules to maximize tumor paclitaxel exposure.

Preclinical models demonstrated activity in NSCLC lines and synergy with platinating agents, including carboplatin.^{12,13} In a phase II trial of 28 patients with treatment-naïve advanced NSCLC, PPX at a dose of 175 mg/m² every 3 weeks yielded a median survival of 8.1 months in a PS 0 to 1 population and 5.4 months in a PS 2 cohort. In phase I trials, PPX has been combined at doses as high as 225 mg/m² every 3 weeks with carboplatin (area under the curve [AUC] = 6) without untoward short-term toxicity.¹⁴ Based on cumulative neurotoxicity, the recommended phase II dose in this setting was 210 mg/m².

The observations from the phase II single-agent trial, the ability to combine PPX at full dose with standard doses of carboplatin, its convenient administration, and the potential of decreased toxicity compared with standard paclitaxel laid the groundwork for a phase III trial, PGT303. This trial, also known as Selected Targeted Efficacy in Lung Cancer to Lower Adverse Reactions 3 (STELLAR 3), compared standard paclitaxel/carboplatin with PPX/carboplatin in PS 2 patients.

MATERIALS AND METHODS

Study Design

This open-label, phase III study compared paclitaxel 225 mg/m² with PPX at 210 mg/m² each in combination with carboplatin (AUC = 6) given every 3 weeks for up to 6 cycles. Patients were excluded from the study for disease progression (PD), intolerable toxicity, withdrawal of consent, or investigator discretion.

Randomization was stratified based on disease stage (IV versus other), gender, history of brain metastases, and geographic location (US versus Western Europe/Canada versus Eastern Europe).

Antiemetic prophylaxis was permitted for carboplatin including dexamethasone to prevent delayed nausea and

vomiting. The paclitaxel arm required routine hypersensitivity prophylaxis; however, the use of routine antihistamines or hypersensitivity prophylaxis was prohibited on the PPX arm. Hematopoietic growth factor support was permitted according to American Society of Clinical Oncology guidelines.¹⁵

End Points

The primary study end point was survival. Secondary objectives included response rate, time to progression (TTP), safety, and quality of life. Radiographic response was assessed every 2 cycles. For patients who completed therapy without evidence of PD, indicator lesions were re-evaluated every 8 weeks until documentation of PD or start of second-line therapy.

Safety data were collected on all patients. Disease-related symptoms were measured by the Functional Assessment of Cancer Therapy Lung Cancer Subscale (FACT-LCS) at baseline and within 3 days of each treatment.

Eligibility Criteria

All enrollees had histologically or cytologically confirmed NSCLC, an Eastern Cooperative Oncology Group (ECOG) PS 2 and stage IV, stage IIb (but not candidates for combined modality therapy with curative intent), or locally advanced or recurrent disease previously treated with radiation and/or surgery. Eligibility stipulated age ≥ 18 years; adequate organ function, including baseline absolute neutrophil count $\geq 1500/\mu\text{L}$; platelet count $\geq 100,000/\mu\text{L}$; creatinine ≤ 1.5 times the upper limit of normal (ULN); bilirubin $\leq$ ULN; transaminases ≤ 2.5 times ULN (≤ 5 times ULN in patients with hepatic metastases); and alkaline phosphatase ≤ 2.5 times ULN, unless bone metastases were present. Patients with stable, treated brain metastases were eligible. Adequate contraception was required for female patients of reproductive potential.

Exclusion criteria included any small cell or carcinoid histology; prior systemic therapy for NSCLC; active, untreated brain metastases; other active primary invasive malignancies requiring treatment; grade ≥ 2 neuropathy; clinically significant infection; exposure to other investigational agents within 4 weeks of study entry; and unstable concomitant medical conditions. The protocol was approved by the institutional review board at each participating institution. All patients gave informed consent.

Representative case report forms were carefully reviewed to make certain that patient characteristics supported PS 2 designations.

Efficacy Parameters and Statistical Considerations

Overall survival was defined as the interval between randomization and death from any cause. Patients remaining alive, including those lost to follow-up, were censored at the date of last contact. Nonstratified log-rank testing was used for the formal primary comparison of survival. This study targeted accrual of 370 evaluable patients with 80% power and 0.05 type I error to show a 1.5-month improvement in median survival from a projected baseline of 4 to 5.5 months. In addition, secondary analyses were conducted using Cox

regression models of prognostic factors associated with survival in patients with NSCLC.

Response was assessed by response evaluation criteria in solid tumors.¹⁶ Disease control was determined by the percentage of patients alive without PD for at least 12 weeks. A two-sided Fisher exact test with an α level of 0.05 for statistical significance was used. TTP was defined as the interval between randomization and PD and was analyzed using an unstratified log-rank test. Toxicities were compared between the treatment arms using the Fisher's exact test.

Quality of Life

Disease-related symptoms were measured by the FACT-LCS, a validated, five-point Likert-type scale ranging from 0 (not at all) to 4 (very much). The total LCS score ranged from 0 to 28, with higher scores indicative of fewer symptoms. The percentage of patients with at least two-point improvements in their LCS scores at the beginning of cycle 2 was compared by treatment arm.

RESULTS

Disposition of Patients

Four hundred patients were enrolled between December 2002 and December 2003; 199 patients were assigned to the PPX arm and 201 to the paclitaxel arm. Three patients, all in the paclitaxel treatment arm, did not receive study treatment: one developed PD before starting therapy, a second had an elevated baseline bilirubin and did not meet eligibility criteria, and a third was withdrawn from the study due to rapid PD and intercurrent pneumonitis.

The arms were well balanced with regard to baseline characteristics (Table 1). Seventy-seven percent of patients were male, 94% white, and 63% from Eastern Europe. Median age was 61 years on the PPX arm and 63 years on the paclitaxel arm. Seventy-three percent of patients had stage IV disease, and 7% had brain metastases at baseline. Russia contributed the largest proportion of patients (35%), followed by the United States (23%). The differences between Eastern European enrollees and their Western European, US, and Canadian counterparts are delineated in Table 2.

Treatment Completion Rates

The median number of cycles was four in each arm. In the PPX arm, 27% of patients completed six cycles of therapy compared with 36% in the paclitaxel arm ($p = 0.0411$; Fisher's exact test). The most frequent reasons for stopping treatment were PD (36% versus 34%, respectively) and adverse effects (27% versus 20%, respectively). Nine percent of patients withdrew consent in the PPX arm compared with 6% in the paclitaxel arm.

Efficacy

Median overall survival was 7.8 months in the PPX arm and 7.9 months in the paclitaxel arm (Fig. 1A). One-year survival was identical at 31%. The 18- and 24-month survival rates were numerically higher in the PPX arm (20 and 13%, respectively) compared with the paclitaxel arm (11 and 11%, respectively), but these differences were not statistically significant.

TABLE 1. Demographic and Baseline Characteristics

	PPX/Carboplatin (n = 199)	Paclitaxel/Carboplatin (n = 201)
Gender		
Male	151 (76%)	156 (78%)
Female	48 (24%)	45 (22%)
Race		
White	189 (95%)	188 (94%)
Black	8 (4%)	9 (5%)
Asian	2 (1%)	1 (<1%)
Hispanic	0 (0%)	2 (1%)
Other	0 (0%)	1 (<1%)
Age at randomization, (yr)		
Mean (SD)	61.1 (10.6)	61.5 (10.1)
Median (range)	61.0 (35–86)	63.0 (36–89)
Geographic site		
United States	46 (23%)	45 (22%)
Western Europe and Canada	30 (15%)	27 (13%)
Eastern Europe	123 (62%)	129 (64%)
Stage at randomization		
IIa	2 (1%)	0 (0%)
IIb	51 (26%)	55 (27%)
IV	146 (73%)	146 (73%)
History of brain metastases		
Yes	14 (7%)	15 (7%)
No	185 (93%)	186 (93%)
Smoking history		
Yes	170 (85%)	171 (85%)
No	29 (15%)	30 (15%)

PPX, paclitaxel poliglumex; SD, standard deviation.

TABLE 2. Demographic and Baseline Characteristics at Entry Based on Region

Region	US/Western Europe/Canada (n = 148)	Eastern Europe (n = 252)
≥5% weight loss within 6 mo of randomization	58 (39%)	104 (41%)
Histologic diagnosis		
Squamous cell carcinoma	43 (29%)	134 (53%)
Adenocarcinoma	78 (53%)	72 (29%)
Other	27 (18%)	46 (18%)
Stage at enrollment		
Stage IV/recurrent	122 (82%)	170 (67%)
Stage IIb	26 (18%)	80 (32%)
History of brain metastases	21 (14%)	8 (3%)
Prior radiation	47 (32%)	40 (16%)
Median FACT-LCS score	18.7	17.0
Current use of tobacco	46 (31%)	113 (45%)
Baseline opioid use	19 (13%)	12 (5%)
Baseline hemoglobin ≥11 g/dL	110 (74%)	220 (87%)

FACT-LCS, functional assessment of cancer therapy lung cancer subscale.

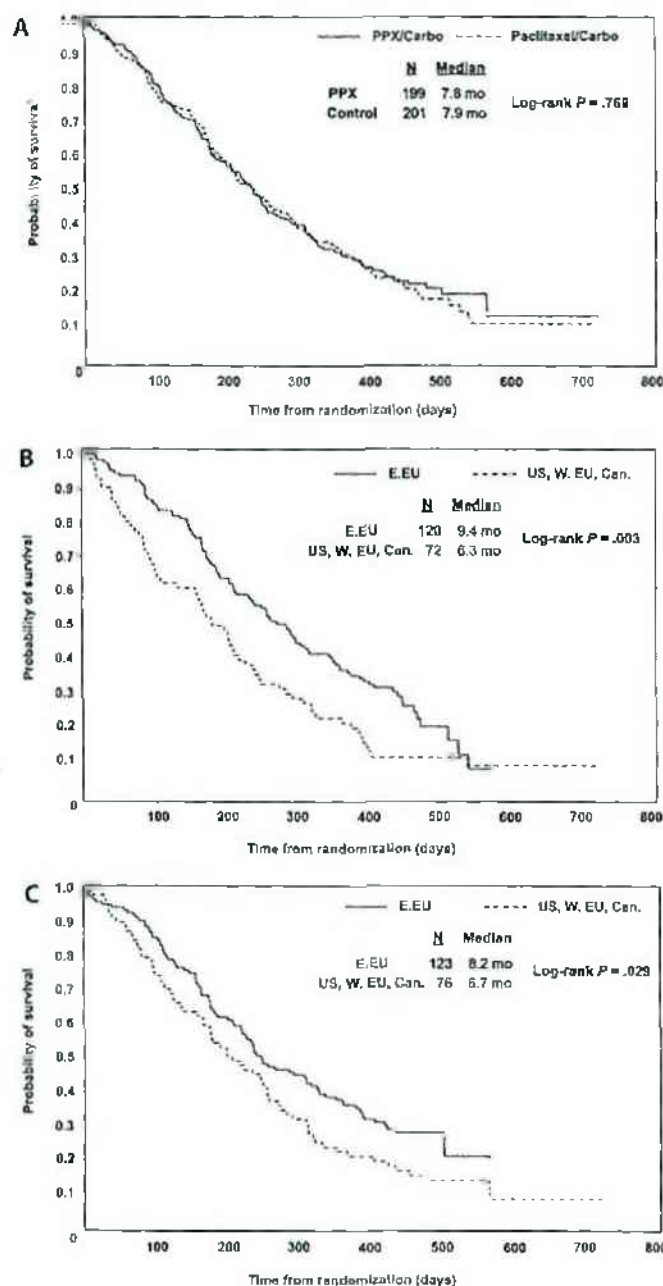


FIGURE 1. Overall survival using Kaplan-Meier estimation. (A) Paclitaxel poliglumex/carboplatin versus paclitaxel/carboplatin. (B) Paclitaxel/carboplatin—United States/Western Europe/Canada versus Eastern Europe. (C) PPX/carboplatin—United States/Western Europe/Canada versus Eastern Europe.

Prespecified analyses by stratification factors (Table 3) demonstrated that median survival in the paclitaxel arm was significantly better in Eastern Europe and Russia than in the United States and Western Europe (9.4 versus 6.3 months; $p = 0.003$; Fig. 1B). There was less difference in median survival on the PPX arm (8.2 versus 6.7 months; $p = 0.029$; Fig. 1C). Women on the paclitaxel arm had a median survival similar to those in the experimental arm (8.3 versus 7.9 months). However, at 12, 18, and 24 months, survival rates

were better on PPX compared with paclitaxel (37 versus 25%, 26 versus 5%, and 13 versus 5%, respectively). Survival for men was similar in both arms with virtually identical median survival (7.9 versus 7.9 months) and 1- (29 versus 33%) and 2-year (13 versus 13%) survival rates.

Cox multivariate stepwise modeling, with all other factors constant, demonstrated that weight loss before study entry, tobacco use, elevated lactate dehydrogenase levels, and elevated calcium levels significantly increased the probability of death.

Response and TTP

The overall response rate was 20% for the PPX arm with 1% complete responses and 37% for the paclitaxel arm with 2% complete responses; these results significantly favored the paclitaxel arm (Table 4). Blended response rates differed by geographic region: 35% for Eastern Europe, 23% for Western Europe and Canada, and 14% for the United States. Disease control rate was 64% in the PPX arm, compared with 69% in the paclitaxel arm.

Median TTP was 3.9 months in the PPX arm and 4.6 months on the paclitaxel arm ($p = 0.210$). The proportion of patients receiving subsequent therapy and the type of therapy administered were not different in the 2 arms. Eighteen percent of those enrolled in the PPX arm went on to radiation therapy, compared with 13% in the paclitaxel arm. Nearly 50% in each arm received additional chemotherapy; no specific agents predominated. Roughly 7% of patients received epidermal growth factor receptor tyrosine-kinase inhibitors as second-line or subsequent therapy.

Quality of Life

FACT-LCS evaluations were completed by 180 patients on the PPX/carboplatin arm and 172 patients on the paclitaxel/carboplatin arm. No significant difference in the FACT-LCS scores was seen.

Toxicity

Drug Delivery

Patients received nearly 90% of planned doses during the second and subsequent cycles. The mean delivered dose intensity per cycle was comparable in both arms. In Eastern Europe, 75% of patients received 4 to 6 cycles, compared with 44 and 49% in the United States and Western Europe/Canada, respectively. The mean normalized carboplatin dose per cycle per patient was the same for both arms (AUC = 5.6).

Relative Toxicities

Patients enrolled in the paclitaxel arm were significantly more likely to experience cardiac toxicity, alopecia, and musculoskeletal toxicity (Table 5). However, those in the PPX arm experienced significantly more nausea and vomiting. More grade 3/4 neuropathy was seen on the PPX arm (17 versus 10%), but this difference was not statistically significant. Time to first manifestation of neuropathy was generally later in the PPX arm—a median of 89 days compared with 54 days for the paclitaxel arm (log-rank $p < 0.001$). By day 100, the incidence was equal. Fatigue was higher in the PPX arm than the paclitaxel arm: 15 versus 8% ($p = 0.05$); however,

TABLE 3. Subgroup Analysis of Overall Survival

Subgroup	PPX/Carboplatin		Paclitaxel/Carboplatin		Hazard Ratio ^a	Log-Rank Test; <i>p</i>
	<i>n</i>	Median Survival, d (95% CI)	<i>n</i>	Median Survival, d (95% CI)		
Overall	199	237 (205–271)	201	239 (206–287)	0.97 (0.78–1.21)	0.769
Gender						
Male	151	237 (199–275)	156	239 (204–288)	1.04 (0.80–1.34)	0.780
Female	48	236 (174–380)	45	248 (167–323)	0.76 (0.48–1.20)	0.239
Geographic location						
United States	46	217 (164–291)	45	173 (100–248)	0.79 (0.50–1.23)	0.298
Western Europe/Canada	30	188 (118–275)	27	206 (103–322)	1.08 (0.63–1.86)	0.773
Eastern Europe	123	249 (219–326)	129	287 (233–347)	1.00 (0.75–1.33)	0.992
Disease stage at randomization						
IV	146	237 (189–283)	146	236 (205–277)	0.92 (0.71–1.19)	0.528
Other	53	246 (182–311)	55	274 (181–404)	1.09 (0.70–1.70)	0.715
History of brain metastases						
Yes	14	207 (145–320)	15	229 (87–328)	1.13 (0.51–2.50)	0.770
No	185	237 (206–275)	186	239 (206–292)	0.97 (0.77–1.22)	0.778

^a Hazard ratio (CI-2103 to paclitaxel) was estimated by Cox regression with treatment arm as a single covariate.

PPX, paclitaxel poliglumex; CI, confidence intervals.

TABLE 4. Efficacy Results in the Intent-to-Treat Population

	PPX/Carboplatin	Paclitaxel/Carboplatin
No. patients	199	201
Survival		
Median (d)	237	239
95% CI	205–271	206–287
Hazard ratio (95% CI); log-rank <i>p</i> value	0.97 (0.78–1.21); 0.769	
1-yr survival rate (%)	31	31
95% CI	24–37	25–38
2-yr survival rate (%)	13	11
95% CI	5–22	4–18
Time to progression		
Median (d)	118	139
95% CI	100–129	118–156
Hazard ratio (95% CI); log-rank <i>p</i> value	1.14 (0.93–1.40); 0.210	
Disease control, % (95% CI)	64 (57–70)	69 (62–75)
Response rate (patients with measurable disease only)		
No. patients	191	192
PR + CR, % (95% CI)	20 (15–27)	37 (30–44)
Confirmed PR + CR, % (95% CI)	13 (9–19)	28 (22–35)

PPX, paclitaxel poliglumex; CI, confidence intervals; PR, partial response; CR, complete response.

grade 3/4 fatigue was similar between arms: 2 versus 3% ($p = 0.66$).

The incidence of grade 3/4 thrombocytopenia was significantly higher in the PPX arm ($p < 0.001$) but was not associated with more thrombocytopenic bleeding or higher transfusion requirements. Five percent of patients on the PPX

arm required platelet transfusions, compared with 3% on the paclitaxel arm ($p = 0.42$). The incidence of febrile neutropenia was 6% in the PPX arm versus 3% in the paclitaxel arm ($p = 0.32$). The reported incidence of neutropenia in Eastern Europe was 24%, compared with 47% in the United States and 42% in Western Europe/Canada. The use of supportive care, including transfusions, erythropoietin, and granulocyte colony-stimulating factor, was similar between treatment arms but different based on geographic regions. The use of red blood cell growth factor support in the United States/Western Europe/Canada was 38% compared with less than 1% in Eastern Europe ($p < 0.001$); the use of white blood cell growth factor support in the United States/Western Europe/Canada was 31% compared with 7% in Eastern Europe ($p < 0.001$). Seven percent of those in Eastern Europe required red blood cell transfusions compared with 16% in the United States/Western Europe/Canada ($p = 0.006$).

Twelve percent of patients in each arm died within 30 days of treatment, but only 1% of all deaths were attributable to study drugs. There were 7.5% disease-related deaths, and 3.5% were due to comorbidities.

Total infusion time for the PPX combination was 48 minutes, compared with 224 minutes for the paclitaxel combination. The incidence of hypersensitivity reactions was 2% for the paclitaxel/carboplatin arm with standard premedications of steroids and H1 and H2 blockers, compared with 1% for the PPX/carboplatin arm without routine hypersensitivity reaction prophylaxis. However, 28% of PPX patients, mostly in the United States and Canada, received steroid prophylaxis and/or antihistamines beginning in cycle 1 as antiemetic prophylaxis for carboplatin.

DISCUSSION

STELLAR 3 is the first dedicated phase III trial ever conducted and reported in treatment-naïve PS 2 patients with

TABLE 5. No. (%) Patients with Treatment-Related Adverse Effects by Maximum NCI Common Toxicity Grade

Adverse Effects	PPX/Carboplatin (n = 199)			Paclitaxel/Carboplatin (n = 198)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Nonhematologic						
Infection and infestation	5 (3%)	1 (<1%)	1 (<1%)	4 (2%)	1 (<1%)	0
Neuropathy	99 (50%)	30 (15%)	3 (2%)	117 (59%)	18 (9%)	1 (<1%)
Cardiac	0	0	0	6 (3%)	1 (<1%)	0
Alopecia	27 (14%)	0	0	83 (42%)	0	0
Arthralgia	13 (7%)	2 (1%)	0	33 (17%)	2 (1%)	0
Myalgia	17 (9%)	2 (1%)	0	29 (15%)	5 (3%)	0
Fatigue	29 (15%)	4 (2%)	0	16 (8%)	5 (3%)	0
Nausea	97 (49%)	9 (5%)	0	70 (35%)	10 (5%)	0
Vomiting NOS	59 (30%)	8 (4%)	0	39 (20%)	3 (2%)	1 (<1%)
Hematologic						
Neutropenia	72 (36%)	18 (9%)	35 (18%)	53 (27%)	14 (7%)	17 (9%)
Febrile neutropenia	11 (6%)	4 (2%)	5 (3%)	5 (3%)	2 (1%)	2 (1%)
Thrombocytopenia	72 (36%)	38 (19%)	5 (3%)	25 (13%)	14 (7%)	0

NCI, National Cancer Institute; PPX, paclitaxel poliglumex; NOS, not otherwise specified.

NSCLC. Based on the preplanned statistical analysis, PPX failed to yield superior survival compared with paclitaxel in this setting, the primary end point, but disease control rates, TTP, and overall survival rates were comparable, as was dose delivery. Hence, potential utility for PPX in the PS 2 population still exists.

An unplanned subanalysis of women enrolled in this study by baseline estradiol levels, reported at the American Society of Clinical Oncology annual meeting in 2006, demonstrated a significant survival advantage for PPX in women with premenopausal estradiol levels (> 30 pg/mL).¹⁷ This observation will be prospectively evaluated in a phase III study.

The overall survival for PS 2 patients enrolled in this trial was substantially longer than expected based on previously reported data. In the Lilenbaum et al. study (CALGB 9730),⁹ the median survival for PS 2 patients receiving paclitaxel and carboplatin was 4.7 months, compared with nearly 8 months for both arms in this trial. A previous phase II study of PPX alone at a lower dose of 175 mg/m² showed survival of 5.4 months in the PS 2 cohort. Whereas survival in North America and Western Europe mirrored recent experience with carboplatin and paclitaxel in PS 2 patients (Table 6), Eastern Europe differed substantially with far better sur-

vival observed in both arms. This may be due to a younger population with fewer comorbidities, less prior radiation, less advanced disease, less baseline anemia, and possibly lower incidence of readily recognizable central nervous system metastases. It may also be due to "contamination" by PS 0 to 1 patients, although auditing of case report forms does not support this theory, and there are no known geographic differences in the nature of PS evaluation. Still, PS designation remains highly subjective and open to debate.

PPX/carboplatin produced fewer myalgias and arthralgias, less alopecia, and delayed time to neuropathy, but more nausea, vomiting, and fatigue and overall worse neuropathy than paclitaxel/carboplatin. The increased incidence of nausea and vomiting in the PPX arm may have been due to lack of routine premedication for hypersensitivity reaction. Febrile neutropenia rates were comparable in each arm. Although the incidence of grade ≥ 3 thrombocytopenia was significantly higher for the PPX arm, it was readily manageable and did not result in more platelet transfusions. PPX administration was also more convenient than paclitaxel with a significantly shorter administration time (48 versus 224 minutes) and no significant increase in hypersensitivity reactions despite the absence of routine premedication.

TABLE 6. Comparative Analysis of Taxane-Based Regimens in Treatment-naïve PS 2 NSCLC in North America

Study	Regimen	No. Patients	Median Survival (mo)	1-yr Survival (%)
CALGB 9730 ^a	Paclitaxel	50	2.4	10
CALGB 9730 ^b	Paclitaxel/carboplatin	49	4.7	19
ECOG 1594 ^c	Paclitaxel/carboplatin	15	4.6	13
ECOG 1599 ^b	Paclitaxel/carboplatin	38	6.1	19
PGT303	Paclitaxel/carboplatin	201	8.0	31
PGT303	PPX/carboplatin	199	7.9	31

PS, performance status; NSCLC, non-small cell lung cancer; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; PPX, paclitaxel poliglumex.

The toxic death rates in this study were comparable with those observed in recent trials including ECOG 1594, ECOG 1599, and CALGB 9730.^{4,9,18} The reduction in toxic deaths compared with trials completed in the 1990s and earlier is likely due to better ancillary and supportive care management. The optimal approach to patients with NSCLC remains unknown, particularly in patients with compromised PS. STELLAR 3 showed that two platinum-based doublets are relatively well-tolerated with better than expected survival rates in PS 2 patients. The results of STELLAR 4, in which PPX at a dose of 175 mg/m² was compared with investigators' choice of single-agent gemcitabine or vinorelbine as front-line therapy for PS 2 patients and overall median survival exceeded 7 months, suggested that the addition of a platinating agent may not necessarily confer a survival benefit.¹⁹ Safety analysis of STELLAR 4 suggested a similar outcome and less neuropathy and neutropenia for the 175 mg/m² PPX dose compared with the 210 mg/m² dose used in STELLAR 3. No published PS 2-specific phase III trial to date has compared a platinum combination with a nonplatinum single agent. In the absence of a proven dose response for taxanes in NSCLC, and given the similar survival rates in STELLAR 3 and 4, future studies of PPX in NSCLC will be conducted at a dose of ≤ 175 mg/m².

In a Cox multivariate analysis of prognostic factors, the most significant negative prognostic factors included extrathoracic metastasis ($p = 0.006$), antecedent weight loss $\geq 5\%$ ($p = 0.006$), and LCS score < 18 ($p = 0.019$). Geographic site (Eastern Europe versus Western Europe/United States/Canada) had a clear-cut bearing on outcome ($p \leq 0.001$). These factors should be considered as stratifications in future trials.

Several other strategies are under investigation in the PS 2 population. The Southwest Oncology Group recently reported the results of a phase II trial investigating the role of erlotinib in PS 2 patients²⁰; and the CALGB has completed a PS 2-specific, randomized phase II trial evaluating docetaxel in combination with either bortezomib or cetuximab.²¹

Other chemotherapy "only" studies are also in progress. Gridelli et al.²² are completing a randomized phase II trial of pemetrexed either alone or followed after two cycles by gemcitabine in advanced NSCLC patients unsuitable for platinum-based treatment. To date, the sequential arm has not shown superiority to the single-agent arm.²² US Oncology, in a phase III trial, is comparing gemcitabine alone to combination gemcitabine/carboplatin. Single-agent versus doublet chemotherapy has been tested in several European trials in "elderly" NSCLC patients with somewhat conflicting results, but has never been tested exclusively in PS 2 patients.

CONCLUSIONS

PS 2 patients constitute a sizable percentage of new NSCLC patients; yet they have been largely excluded from or underrepresented in clinical trials in the last 10 to 15 years based on a general perception of overall poor outcome. Single-agent therapy is considered by many to be the standard approach despite data showing a benefit of combination therapy. The results of STELLAR 3 confirmed the tolerability

and efficacy of doublet treatment with carboplatin plus either PPX or paclitaxel. Future studies in PS 2 patients should focus on the nature of comorbidities, pretreatment disease characteristics, treatment-related quality of life, and toxicity management. Patients with poor PS require special attention to ensure clinically meaningful therapeutic benefits. In this vein, newer chemotherapeutics such as PPX have a potential role.

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Industria y Comercio SUPERINTENDENCIA		PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA RELACIÓN DE ANEXOS	
Dependencia: 2020		Fecha: <u>20/4</u> , <u>09</u> , <u>19</u> AAAA MM DD	
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		Recorrido:	
Radicador:		Planilla:	

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Item	Unidad de Conservación
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2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	Soporte Documental
X	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

El cd contiene:
 1 archivo en formato Word no procesado.