

LY900003: A novel compound for the treatment of non-small cell lung cancer

Review Article

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Summary

Non-small cell lung cancer (NSCLC) accounts for 75-80% of all lung cancers and has a five-year disease free survival rate of 8-14%. The disease free survival for advanced patients (ie, Stage IIIC and IV) has plateaued at eight months. These bitter statistics create a need for additional research into the treatment of NSCLC. The future of lung cancer therapy relies on the combination of standard chemotherapy agents (eg, platinum therapy plus paclitaxel, docetaxel, vinorelbine, or gemcitabine) with 'novel agents'. These novel therapies must target growth mechanisms unique to tumor cells. The protein kinase C (PKC) isoenzyme has been associated with tumor development and progression in several types of cancer. LY900003 (Affinitac), an antisense oligonucleotide, targets this isoenzyme and is an example of a novel agent. All clinical studies exploring the efficacy, safety, pharmacokinetics, and tolerability of LY900003 in the treatment of any type of cancer-related malignancy are presented. LY900003 offers modest to little efficacy as monotherapy for most tumor types. However, Phase II trials of LY900003 in combination with traditional chemotherapeutic agents, such as docetaxel, cisplatin, paclitaxel, and gemcitabine, have demonstrated promising prolongation of survival endpoints in advanced NSCLC. The future of this antisense compound lies in its absolute efficacy with other chemotherapeutic agents in ongoing Phase III trials. To optimize the benefits of novel agents that target tumor-specific factors, such as LY900003, the selection of patients with specific prognostic factors may become essential.

I. Introduction

Although not as widely publicized, more Americans die each year from lung cancer than breast, prostate, and colorectal cancers combined (Cancer Facts and Figures 2002). Lung cancer is comprised of two types; non-small cell (NSCLC) and small cell (SCLC). Non-small cell cancer (NSCLC) accounts for 75-80% of all lung cancers and has a five-year survival rate of 8-14% (Hansen 2002). It grows and spreads more slowly than SCLC. However, even with relatively slow tumor growth, approximately 75% of all NSCLC patients present with advanced cancers (ie, defined by the American Joint Committee on Cancer as Stage IIIB or IV) (Hansen, 2002; Patel et al, 1993). This group has a very low five-year disease free survival rate. Specifically, 20% of all NSCLC patients are at Stage IIIB cancer (ie, tumors that have invaded tissue outside the lungs, including mediastinal, scalene, supraclavicular, and hilar lymph nodes or contain malignant pleural effusions) and have a five-year disease free survival rate of 5%. Twenty-seven percent present with Stage IV cancer (ie, tumors that have metastatic involvement) and have a five-year disease free survival rate of less than 2% (Ginsberg et

al, 2001). Therefore, approximately half of NSCLC cancer patients are diagnosed with a poor prognosis.

Treatment goals for this group of patients are no longer curative, as complete resection is not possible. Instead, the palliation of symptoms and prolongation of survival time are the primary objectives. This can be achieved through palliative chemotherapy or best supportive care (ie, palliative radiotherapy, analgesics, and psychological support, Ginsberg et al, 2001).

Chemotherapy is considered the standard of care, as several meta-analyses have demonstrated acceptable treatment costs and quality of life improvements by reducing disease-related symptoms in patients with a performance status between 0-2 (Marino et al, 1994, Grilli et al, 1993; Stewart, 1995).

However, even with chemotherapy, the median survival of a patient with advanced or metastatic NSCLC is approximately six to eight months (Ginsberg et al, 2001 and Kim; Murren 2002). The American Society of Clinical Oncologists (ASCO) recently reported that the benefits of treatment have plateaued for advanced NSCLC (Evans and Lynch, 2001). The future of lung cancer therapy relies on the combination of standard chemotherapy agents (eg, platinum therapy plus paclitaxel, docetaxel, vinorelbine, or

gemcitabine) with 'target agents.' These novel therapies must be aimed at growth mechanisms unique to tumor cells, distinguishing them from standard chemotherapy, which are often toxic to human cells.

A number of novel pipeline products are currently being investigated. These include LY900003 (Affinitac, Eli Lilly & ISIS Pharmaceuticals), OSI-774 (Tarceva, Roche), and trastuzumab (Herceptin, Genentech), along with the recent approval of ZD-1839 (Iressa, Astra-Zeneca). This article reviews data on LY900003, focusing on the efficacy and safety profiles that have been displayed in published clinical trials and meeting abstracts. LY900003 was developed by ISIS Pharmaceuticals (Carlsbad, CA) and received fast track status for the indication of NSCLC in November 2000 (Peterson and Moore, 2003). Eli Lilly and Company licensed this compound in August 2001 and is responsible for commercialization and future clinical studies. LY900003 is considered to be a novel therapy due to its targeted effect on the protein kinase C (PKC). This isoenzyme has been implicated with the cancer growth pathway of numerous tumor lines.

II. Antisense technology

LY900003 is an antisense oligonucleotide, a new class of molecules known to modify gene expression by interacting with messenger RNA (mRNA) (Tamm et al, 2001). In general, most diseases are caused by the inappropriate production of proteins (Jansen and Zangemeister-Wittke, 2002). Conventional drugs are directed to interact with these proteins. In contrast, antisense agents, such as LY900003, inhibit the production of these specific proteins.

Antisense oligonucleotides are developed to act as complements to mRNA involved in the production of disease-specific proteins. These antisense agents bind to mRNA, which allows an enzyme, RNase H, present in the cytoplasm to degrade mRNA (Tamm et al, 2001; Jansen and Zangemeister-Wittke 2002). The end result is the inhibition of disease-promoting protein production. Currently, only one antisense agent is available on the market (Kim and Murren, 2002). Fomivirsen (Vitravene) was approved in 1998 by the Food and Drug Administration (FDA) for the treatment of retinitis induced by the cytomegalovirus in acquired immunodeficiency (AIDs) patients. In oncology, the identification of cancer-related molecular sites allows antisense technology to target tumor-associated DNA products without affecting normal gene expression. As a class, antisense oligonucleotides demonstrate minor toxicities with a unique mechanism of action, making them desirable add-on treatments to standard chemotherapy.

III. Pharmacokinetics / Pharmacodynamics

The identification of specific molecular targets has allowed for the design of rationally targeted drug therapies for specific tumor types. LY900003 is specifically aimed

at inhibiting the production of protein kinase C-alpha (PKC- α) and does not affect other protein kinase C molecules (Yuen et al, 1999). The class of PKC isoenzymes is involved in numerous physiological processes, specifically the signal transduction of numerous growth factors, neurotransmitters, and hormones (Mani et al, 2002). However, the PKC- α isoenzyme has been implicated in malignant transformation and proliferation and has demonstrated anti-apoptotic activity. An association has been demonstrated between certain cancers and a high expression of PKC- α . Specifically, high expression of this isoenzyme has been identified in human lung, bladder, breast, prostate, hepatoma, colon, glioblastoma, and medulloblastoma cancers (Yuen et al, 1999; Nemunaitis et al, 1999; Mani et al, 2002). By inhibiting PKC- α , LY900003 is hypothesized to have a therapeutic effect in cancers over-expressing this protein. The targeted selection of PKC- α by LY900003 prevents a myriad of side effects that would occur if the entire PKC class was selected. LY900003 has shown initial efficacy in several tumor types, however, the most promising results have occurred in NSCLC.

LY900003 is a phosphorothioate oligodeoxy nucleotide, 20 oligonucleotides in length. The phosphorothioate component forms the backbone of the molecule, and is thought to increase stability in the serum and provide resistance to metabolizing exonucleases. The drug has a bi-phasic half-life, with the first phase of elimination occurring in 40 minutes with a 1.0 mg/kg/day dose and 60 minutes with a 3.0 mg/kg/day dose. This rapid initial clearance is due to tissue distribution. However, once the drug reaches the tissue, it is cleared much slower from these compartments. The later phase half-life is estimated to be five days in the renal cortex, and one to three days in other tissues. LY900003 displays non-linear kinetics, achieving a steady state plasma concentration at 24 hours with a continuous infusion. Drug clearance from the plasma occurs through tissue distribution and metabolism via an oligonucleotide-shortening exonuclease. In a Phase I two-hour infusion trial, less than 1% of the drug was recovered in urine samples 24 hours after administration (Yuen et al, 1999; Nemunaitis et al, 1999).

The drug has been tested as monotherapy in Phase I trials in three different dosing regimens: a 2-hour infusion three times a week (Nemunaitis et al, 1999), a 24-hour infusion once a week (Advani et al, 1999), and a 21-day continuous infusion (Yuen et al, 1999; Sikic et al, 1997). Pharmacokinetic analyses of the different dosing schedules have indicated that a continuous infusion is the optimum dosing regimen. This appears to minimize side effects, specifically fever, chills, and myalgias. Additionally, animal studies have indicated that complement activation and prolongation of activated partial thromboplastin time (aPTT) occur in primates when the plasma concentration is greater than 40 $\mu\text{g/mL}$ (Yuen et al, 1999) A continuous infusion provides lower plasma levels compared to intermittent dosing, which avoids this toxic effect (Advani et al, 2000).

IV. Clinical trials

A. Phase I

LY900003 was tested initially in several tumor types in Phase I trials (Yuen et al, 1999; Nemunaitis et al, 1999; Mani et al, 2002; Sikic et al, 1999; Yuen et al, 2000, 2001). The drug regimen, type of tumors treated, and results of the published trials are summarized in **Table I**. Three different dosing schedules were used in the seven Phase I trials listed, due to changing knowledge about optimizing the safety and efficacy profiles of the drug, as discussed previously. A dose escalation scheme of 0.5, 1.0, 1.5, 2.0, and 3.0 mg/kg/day as a 21-day continuous infusion was conducted (Yuen et al, 1999). The continuous infusion regimen was selected based on the short half-life of the drug. Four of six patients that received 3.0 mg/kg/day developed dose-limiting toxicities of thrombocytopenia and fatigue. Based on this, a 21-day continuous infusion of 2.0 mg/kg/day was chosen for

phase II trials to minimize adverse events. This was later changed to a 14-day infusion in combination with other chemotherapeutic agents for patient convenience.

The majority of severe adverse events seen in Phase I trials were thrombocytopenia (TCP), nausea, fatigue, fever, and diarrhea. Grade 3 (ie, severe) and 4 (ie, life threatening or disabling) toxicities were limited. Some level of efficacy was demonstrated in ovarian, lymphoma, colon, lung, and renal cancers.

Because the objectives of Phase I trials in oncology are to determine the safety and tolerability of investigational agents along with identifying a dose for phase II trials, any evidence of efficacy is very exciting. Favorable results were seen in a phase I trial of advanced cancer (N=18), with the majority of patients having advanced NSCLC (N=12).

Table 1: Phase I trials

LY900003 Regimen	Type of cancer (number)	Efficacy (number)	Grade 3 & 4 Toxicities (number)	Comments
2 hour infusion three times weekly x 3 weeks Q 28 days; Doses 0.15-6.0 mg/kg/day (Nemunaitis et al, 1999)	Colon (9); Melanoma (6); Renal (4); Lymphoma (3); Small cell lung (2); NSCLC (4); Sarcoma (1); Other (1)	-Complete response (2, lymphoma); stabilization of disease (10)	G3 TCP (1) G3 nausea (1)	-Elimination half-life of 1-1.5 hours -Decision to investigate longer infusions
CIV* x 21 days Q 28 days; Doses of 0.5, 1.0, and 1.5 mg/kg/day (Sikic et al, 1997)	Pancreatic (3); Colon (2); Stomach (1); Lung (1); Breast (1); Ovarian (1)	-Stable disease x 4 months (Colon (1) & Ovarian (1))	None	-Ongoing at time of abstract
CIV* x 21 days Q 28 days; Doses of 0.5, 1.0, and 1.5, 2.0, 3.0 mg/kg/day (Yuen et al, 1999)	Ovarian (4); Colon (3); Pancreatic (3); Sarcoma (3); Lung (2); Gastric (2); Esophageal (1); Breast (1); Melanoma (1); Lymphoma (1)	-60% reduction in abdominal mass x 11 months (Ovarian (1)) -Decreased CA-125 levels x 5 & 7 months (Ovarian (2))	G3 fatigue (4) G4 TCP (1) G2 TCP with G4 bleeding (1) G3 TCP: 3	-Phase II trial initiated in ovarian patients in progress -Majority of adverse events occurred in 3.0 mg/kg/day
24 hour continuous infusion Q week; Doses 6, 12, 18, 24, 30 mg/kg/week (Advani et al, 1999)	Refractory solid tumors (11)	-Stable disease x 3+ months (Colon (1))	G3 fever/chills (1)	-Ongoing at time of presentation
Cycle 1: Carboplatin AUC 6, Paclitaxel (175 mg/m); Cycle 2: LY900003 CIV* x 14 days + (carboplatin & paclitaxel day 4) Q 28 days (Sikic et al, 1999)	NSCLC (9); Unknown (2); Cervical (2); Esophageal (1); Sarcoma (1)	-Not presented	G3 diarrhea (1) G3/4 neutropenia (12) G3 TCP (3) G3 fatigue (1)	-Ongoing at time of presentation -Study drug did not alter kinetics of carboplatin or paclitaxel
CIV* x 21 days; Doses 1.0, 1.5, 2.0 + (5-FU 425 mg/m ² /day + leucovorin 20mg/m ² x 5 days) Q 28 days (Mani et al, 2002)	Colorectal (8); unknown primary (2); gallbladder (1); ovarian (1); breast (1); pancreatic (1); esophageal (1)	-> 50% reduction (2; colorectal and unknown) -Minor reduction in tumor size (colorectal (3) & pancreatic (1))	G3 chest pain (1) G3 mucositis (3) G3/4 neutropenia (12) G3/4 TCP (3)	-Study drug did not alter kinetics of 5-FU or leucovorin
CIV* x 14 days LY900003 at 2.0 mg/kg/day + (carboplatin AUC 6 + Paclitaxel 175 mg/m ² day 4) Q 21 days (Yeun et al, 2001, Yuen et al, 2000)	NSCLC (12); Unknown (6)	-53% partial response -20% stable disease -Median time to progression: 6.5 months	None	-Trial was expanded to Phase II with a focus on NSCLC patients

* CIV = continuous intravenous infusion

TCP = Thrombocytopenia

B. Phase II

Table II summarizes the published phase II trials completed in LY900003. A dose of 2.0 mg/kg/day was used as either a 21-day or 14-day continuous infusion. This agent showed very little activity as monotherapy in hormone-refractory prostate cancer, advanced colorectal cancer, high-grade astrocytomas, and metastatic breast disease. Modest single-agent activity was demonstrated in non-Hodgkin's lymphoma (Yuen et al, 2000, 2001; Tolcher, et al, 2002; Cripps et al, 2002; Alavi et al, 2000; Gradishar et al, 2001; Emmanouilides et al, 2002; Moore et al, 2002; Ritch et al, 2002). Grade 3 and 4 toxicities were limited with monotherapy. Out of 128 patients treated, 0.8% developed Grade 3 lethargy or Grade 4 elevations in serum glutamic oxaloacetic transaminase (SGOT), 2.3% developed Grade 3 fatigue, 3.1% developed

Grade 3 / 4 infections, and 9.3% developed Grade 3 / 4 thrombocytopenia.

In contrast to the poor efficacy seen with monotherapy, LY900003 showed favorable efficacy in advanced NSCLC in combination with other agents, such as docetaxel, carboplatin, paclitaxel, cisplatin, and gemcitabine (Yuen et al, 2000, Yuen et al, 2001, Moore et al, 2002; Ritch et al, 2002). Specifically, the expanded Phase I/II trial (N=53) of the LY900003, carboplatin, and paclitaxel combination demonstrated a complete or partial response in 42% of patients (Yuen et al, 2000, 2001). The median time to disease progression was 6.6 months and the median overall survival was 19 months. This compares to the standard median survival of six to eight months with chemotherapy treatment (Ginsberg et al, 2001 and Kim and Murren, 2002).

Table II: Phase II trials

* CIV = continuous infusion

Regimen	Type of cancer (number)	Efficacy (number)	Grade 3 & 4 Toxicities (number)	Comments
LY900003 CIV* or ISIS 5132** CIV* x 21 days Q 28 days (Tolcher et al, 2002)	Hormone-refractory prostate cancer (HRPC) (31)	-No objective or PSA responses -Stable disease (3) -Stable PSA levels (5)	G3 lethargy (1)	-No single agent antitumor activity for HRPC
LY900003 CIV* or ISIS 5132** CIV* x 21 days Q 28 days (Cripps et al, 2002)	Untreated advanced colorectal cancer (32)	-No objective response -Stable disease on ISIS 3521 (4)	Not presented	-No single agent antitumor activity for advanced colorectal cancer
LY900003 CIV* x 21 days Q 28 days (Alavi et al, 2000)	High grade astrocytomas (HGA) (21)	-Median time to progression: 35 days -Median survival: 93 days	G3 TCP (3) G4 SGOT (1)	-No single agent antitumor activity for HGA
LY900003 CIV* x 21 days Q 28 days (Gradishar et al, 2001)	Metastatic Breast Cancer (MBC) (15)	-Median time to progression: 1.2 months -Median survival 8.3 months	G3/4 TCP (2) G3/4 infection (4)	-No single agent antitumor activity for MBC
LY900003 CIV* x 21 days Q 28 days (Emmanouilides et al 2002)	Low-grade, non-Hodgkin's lymphoma (NHL)(29)	-73% reduction (1) -stable disease (16) -progressive disease (4)	G3 TCP (6) G4 TCP (1) G3 fatigue (3)	-Observed modest activity in NHL
LY900003 CIV* x 14 days + (docetaxel 75 mg/m ² day 3) Q 21 days (Moore et al. 2002)	Advanced, previously treated NSCLC (57)	-Partial response (8) -Stable (23) -Progressive (21)	G3 neutropenia (11) G4 neutropenia (23) G3 TCP (9) G3/G4 infection (9) G3/G4 dyspnea (11) G3/4 neutropenic fever (7)	-Hematologic toxicity is standard for docetaxel monotherapy -Initial efficacy is favorable
LY900003 CIV* x 14 days + (carboplatin AUC 6 + paclitaxel 175 mg/m ² day 4) Q 21 days ²¹⁻²²	Phase I: all tumors (18) Phase II: advanced NSCLC (53)	-Complete or partial response (42%) -Progressive (17%) -Median time to progression: 6.6 months Median survival: 19 months	G3 neutropenia (16) G4 neutropenia (14) G3 TCP (9) G3 TCP (4)	-Well-tolerated -Initial efficacy is very favorable -Phase III trial in progress
LY900003 CIV* x 14 days + (cisplatin 80 mg/m ² + gemcitabine 1250 mg/m ² days 0 and 8) Q 21 days ²⁹	NSCLC (55)	-Complete response (3%) -Partial (35%) -Stable (50%) - Progressive (13%)	G3/4 neutropenia (57%) G3/4 TCP (43%)	-Well-tolerated -Initial efficacy is very favorable -Phase III trial in progress

TCP = thrombocytopenia

** ISIS 5132 is another antisense oligonucleotide under investigation

Note: All doses of LY900003 were 2.0 mg/kg/day

Another promising outcome of LY900003 in the treatment of advanced NSCLC occurred in the combination of LY900003, cisplatin, and gemcitabine in 55 patients (Ritch et al, 2002). Over 90% of these patients had Stage IV disease. In this trial, 37% of all patients responded, with one complete response, 17 partial responses, and 24 patients with stable disease. Grade 3 and 4 toxicities with combination chemotherapy included a much higher incidence of neutropenia (Yuen et al, 2000, 2001; Moore et al, 2002; Ritch et al, 2002).

C. Phase III

There are currently two Phase III trials initiated with LY900003 in advanced NSCLC patients with a performance status of 0-1, as shown in **Table III** (Ritch et al, 2002; Lynch et al, 2002: The Pink Sheet 2002). The first trial compared the combination of a 14-day continuous infusion of LY900003 2 mg/kg/day over days 1-14 with paclitaxel 175 mg/m² and carboplatin AUC 6 on day 3 repeated every 21 days to paclitaxel 175 mg/m² and carboplatin AUC 6 on day 1 repeated every 21 days (Lynch et al, 2003). Enrollment of over 600 patients was completed in January 2002. Preliminary results were presented at the ASCO annual meeting in May 2003. There was no difference in the treatment groups with regards to prognostic factors, such as age, stage, performance status, weight loss, presence of brain metastases, or adenocarcinoma. Patients randomized to the LY900003 arm were required to have venous access. The primary efficacy measurement was the overall response rate (complete and partial responses) using the intent to treat population. The secondary efficacy measurement was the time to disease progression (TTP). There was no statistically significant difference in either of these outcomes. The overall response rate was 37% and 36% in the LY900003 (n=309) and control arm (n=307), respectively, while the TTP was 4.7 months and 4.5 months, respectively. While there was no difference in treatment-related deaths between the two arms, the LY900003 arm showed significantly more Grade 3 thrombocytopenia and anemia, and Grade 3 / 4 vomiting

and fatigue. Additionally, there were significantly more venous access complications with the LY900003 arm.

The investigators concluded that although LY900003 therapy did not extend survival in this patient population, a 14-day continuous infusion of antisense oligonucleotides is feasible. Additional analyses on the stage of disease, gender, age, histology, or percentage receiving second line therapy did not identify any subset of patients that fared better. Potential reasons why LY900003 failed to demonstrate a favorable outcome compared to the control arm include an inadequate dose or regimen of LY900003 and the lack of targeted patient selection for overexpression of the PKC- protein.

Carboplatin and paclitaxel is the recommended regimen by the Eastern Cooperative Oncology Group (ECOG) for advanced NSCLC, however, they do not have regulatory approval for NSCLC in the United States (Shiller et al, 2002). For this reason, another large-scale Phase III trial was initiated. The second phase III trial includes a 14-day continuous infusion of LY900003 plus one day of cisplatin (Day 1) and two days of gemcitabine (Days 1 & 8) on a 21-day cycle (Ritch et al, 2002). Cisplatin and gemcitabine do have FDA regulatory approval for the treatment of advanced NSCLC. Over 670 patients have been enrolled and analyses are expected sometime in 2004. If the results are favorable, a new drug application (NDA) will be submitted to FDA based on Phase II NSCLC trials and this Phase III trial (The Pink Sheet 2002).

V. Adverse effects and drug interactions

A. Adverse reactions

There are several class effects of phosphorothioate oligonucleotides, including the prolongation of activated partial thromboplastin time (aPTT) and complement activation (Yuen et al, 1999).

Table III: Phase III trials

Regimen	Type of cancer (number)	Efficacy (%) LY900003 vs. control	Grade 3 & 4 Toxicities (%) LY900003 vs. control	Comments
LY900003 CIV* x 14 days + (carboplatin AUC 6 + paclitaxel 175 mg/m ² day 4) Q 21 days (Moore et al, 2002)	Advanced NSCLC (616); previously untreated	-Overall response rate: 37% vs. 36% -Time to tumor progression: 4.7 vs. 4.5 months -Overall survival: 10 vs. 9.7 months	G3 TCP: 44% vs. 15% G3 anemia: 13% vs. 6% G3/4 nausea: 6% vs. 1% G3/4 fatigue: 16% vs. 8%	-Completed enrollment -Results expected in 2003
LY900003 CIV* x 14 days + (cisplatin day 1 + gemcitabine days 1 & 8) Q 21 days (Ritch et al, 2002, FDA 2002)	Advanced NSCLC (670)	--	--	-Currently enrolling

* CIV = continuous intravenous infusion

Although these specific effects were seen in primate studies, no associations were made with the adverse effects seen in all clinical trials. In Phase I and II trials, the majority of observed adverse events appear to be complications of advanced cancer or concurrent therapy rather than associated with the administration of LY900003. As previously discussed, LY900003 monotherapy demonstrated few Grade 3 or 4 toxicities.

The initial results of the Phase III trial investigating LY900003 in combination with paclitaxel and carboplatin showed that patients receiving LY900003 were more likely to develop Grade 3 thrombocytopenia (TCP) (44% vs. 15%, $p < 0.0001$) and Grade 3 anemia (13% vs. 6%, $p = 0.008$) compared to the control (Lynch et al, 2003). However, neither of these hematologic toxicities resulted in any significant adverse drug reactions, such as bleeding. Additionally, thrombocytopenia was not cumulative, in contrast to standard chemotherapy agents. Grade 3 / 4 vomiting (6% vs. 1%, $p = 0.006$) and fatigue (16% vs. 8%, $p = 0.003$) were also significant non-hematologic concerns in the LY900003 arm compared to the control. Generally, these can be controlled with oral 5-HT₃ receptor antagonists & phenothiazines and analgesics, respectively.

Finally, catheter-related complications posed several problems in the LY900003 arm (Lynch et al, 2003). Compared to the control, the LY900003 arm had higher rates of catheter infections (8.2% vs. 0.3%) and thrombotic events (5.4% vs. 1.4%). As a result, the control arm received a median of 5 cycles, while the LY900003 arm received a median of 4 cycles. Overall, there was no difference in the rate of regimen-related deaths (3.4% for each arm).

B. Drug interactions

LY900003 has been combined successfully with several chemotherapeutic agents in Phase I, II, and III trials (Yuen et al, 1999). Specifically, the pharmacokinetics of paclitaxel, carboplatin, leucovorin, docetaxel, cisplatin, and gemcitabine did not change with concomitant use of LY900003. Additionally, cytochrome P450 interactions are not expected, as the drug undergoes metabolism through a chain-shortening exonuclease mechanism (Yuen et al, 1999).

C. Precaution / Contraindications

Due to the antisense phosphorothioate class effects of complement activation and a prolongation of aPTT, exclusion criteria in all clinical trials included patients with any underlying disease states associated with bleeding, complement abnormalities, a past medical history of coagulopathy, and use of anticoagulants (Yuen et al, 1999). Patients without adequate hematopoietic function may also be cautioned from clinical involvement with LY900003, as the drug has been shown to cause thrombocytopenia.

VI. Dosage and administration

Due to the long-term nature of the LY900003 infusion, a venous access device is necessary for continuous administration of the drug. Although, no known physiochemical incompatibilities occurred with LY900003, it is ideal to have a line designated for LY900003. This avoids halting other treatments if an infection were to occur in the long-standing line. Information on the type of venous access device in the phase III trial is unknown.

ISIS Pharmaceuticals is currently supplying LY900003 to ongoing clinical trials (The Pink Sheet 2002). The drug comes in 2 mL or 11 mL vials, holding 1.1 mL or 10 mL of the active drug, respectively (Yuen et al, 1999; Nemunaitis et al, 1999). The volume of drug needed to achieve a dose of 2 mg/kg/day for seven days is calculated based on the patient's actual body weight prior to beginning LY900003 therapy (Moore et al, 2002). This is then withdrawn from the vials. A volume of normal saline equal to the calculated drug volume is removed from a 250 mL normal saline bag and LY900003 is then added to the bag. In Phase II trials, a portable volumetric infusion pump was used to administer the drug via an indwelling CVC with a 0.22 micron inline filter (Yuen et al, 1999).

The fixed dosage regimen of 2 mg/kg/day for 14 days appears to be standard for advanced NSCLC patients in Phase III trials. In one phase II clinical trial in advanced NSCLC patients, this was achieved by administering a daily dose of either 125, 175, or 225 mg based on the patient's actual body weight (Moore et al, 2002). Patients receive a seven-day supply of medication at a time and return to clinic for monitoring and an additional supply of medication to complete the 14-day regimen.

VII. Conclusion

Compared to the promising Phase II results seen with LY900003 in combination with other chemotherapeutic agents in Stage IIIB and IV NSCLC patients, the initial Phase III results are disappointing. While LY900003 appears to break the eight-month survival barrier previously seen with standard chemotherapeutic regimens in advanced NSCLC, the results of the initial Phase III trial with paclitaxel and carboplatin did not demonstrate any efficacy advantage over standard chemotherapy alone. Additionally, there were some toxicity concerns in the LY900003 arm. Although there was no difference in regimen-related deaths, patients on the LY900003 arm were more prone to additional hematological, non-hematological, and catheter-related problems.

The investigators hypothesize that the lack of efficacy seen in the first large-scale Phase III trial with LY900003 may be due to lack of patient selection for the overexpression of PKC- β . Perhaps as drug therapy becomes more focused on the inhibition of specific molecular targets, patient selection must also follow. Certainly drugs like trastuzumab (Herceptin) have already proven this theory in the treatment of metastatic

breast cancer showing an over-expression of the HER-2/neu protein.

The future of LY900003 lies in the results of the second Phase III trial. Regardless of the outcome, the lessons learned from LY900003 have been bountiful. First, a 14-day continuous infusion of an antisense oligonucleotide is possible. The first phase III trial with LY900003 is the largest trial using an oligonucleotide, to date. Second, as drug therapy in oncology becomes increasingly complex, individualized therapy must occur to optimize patient outcome. None of the clinical trials with LY900003 assessed PKC- levels. This may be important in large scale, Phase III trials. Finally, it is essential that properly planned and conducted Phase III trials occur in new chemical molecules prior to their approval by the Food and Drug Administration (FDA). The lack of a survival advantage demonstrated in the initial Phase III results of LY900003 in combination with paclitaxel and carboplatin look similar to results seen with gefinitib (Iressa) in two recent Phase III trials that enrolled over 1000 advanced NSCLC patients per trial (Giaccone, 2002; Johnson 2002). Here, gefinitib failed to demonstrate a survival advantage when combined with a paclitaxel / carboplatin or a gemcitabine / cisplatin combination. Interestingly, subset analyses of these trials investigating stratification and prognostic factors also did not identify a group of patients that benefited from gefinitib, similar to the LY900003 subanalyses (Lynch et al, 2003; Herbst 2003).

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