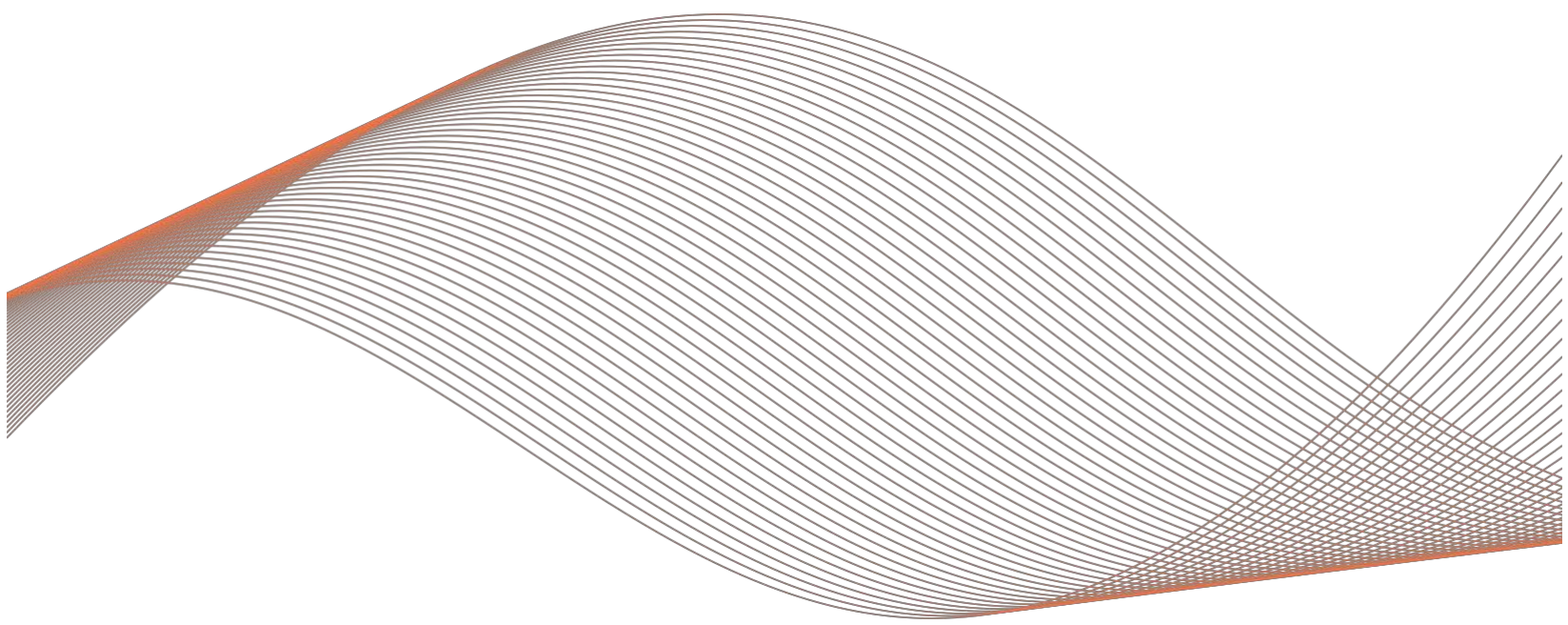
NovoTTF™-100L System

INSTRUCTIONS FOR USE for Unresectable Malignant Pleural Mesothelioma



novocure™

This manual is intended for physicians prescribing the use of NovoTTF-100L System. Additional information is found in the following materials:

- Patient Information and Operation Manual
- Clinical Practice Guidelines: layout optimization in thoracic malignancies

Caution: Federal law restricts this device to sale by or on the order of a physician Humanitarian Device. Authorized by Federal Law for use in the treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma concurrently with pemetrexed and platinum based chemotherapy. The effectiveness of this device for this use has not been demonstrated

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Indications for Use

The NovoTTF-100L System is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy.

Contraindications, Warnings and Precautions

Contraindications

Do not use the NovoTTF-100L System if you have implantable electronic medical devices including a pacemaker, implantable automatic defibrillator, etc. Use of the NovoTTF-100L System together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device.

Do not use the NovoTTF-100L System if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with the NovoTTF-100L System may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

Warning – Use the NovoTTF-100L system only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of NovoTTF-100L without receiving this training can result in breaks in treatment and may rarely cause increased skin irritation, open sores on your chest or back, allergic reactions or even an electric shock.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), use high potency topical steroids (hydrocortisone cream) when replacing transducer arrays. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals.

Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

Caution - Do not use any parts that do not come with the NovoTTF-100L System, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment.

Caution - Do not use NovoTTF-100L if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment.

Caution - Do not wet the device or transducer arrays. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the transducer arrays very wet is likely to cause the transducer arrays to come loose from your skin. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that the NovoTTF-100L power switch is in the OFF position. Disconnecting transducer arrays with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Caution - If you have an underlying serious skin condition on the chest, discuss with your doctor whether this may prevent or temporarily interfere with NovoTTF-100L treatment.

Caution - Do not use NovoTTF-100L if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. NovoTTF-100L was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.

Notices

Notice - The NovoTTF-100L System and transducer arrays will activate metal detectors.

Notice - If you plan to be away from home for more than 1.5 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment.

Notice - Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time you may have a break in your treatment.

Notice - Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1 hour from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment.

Notice - You should carry the Troubleshooting Guide (Section 26 of the patient information and operation manual) at all times. This guide is necessary to ensure the NovoTTF-100L system works properly. If you do not work the system correctly you may have a break in your treatment.

Notice - Do not block the device vents located on the sides of the device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device. In case the vents are blocked with pet hair or dust, return the device for service.

Notice - Do not block the battery charger vents located on the sides of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging. In case the vents are blocked with pet hair or dust, return the charger for service.

Notice - Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice - The transducer arrays are for single use and should not be taken off your body and put back on again. If you put a used transducer array back on your chest again, it may not stick well to your skin and the device could turn off.

Notice - Keep the device out of the reach of children and pets.

Notice - The device has a cord that may cause tripping when connected to an electric socket.

Description

The NovoTTF-100L system, for the first-line treatment of unresectable, locally advanced or metastatic, malignant pleural mesothelioma, is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically- insulated surface transducer arrays. TTFields disrupt the rapid cell division exhibited by cancer cells[1].

The NovoTTF-100L system is comprised of two main components: (1) an Electric Field Generator (the NovoTTF-100L device); and (2) ILE Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included in the NovoTTF-100L System: power supply, portable battery, battery rack, battery charger, connection cable and carrying bag.

Treatment parameters are preset by Novocure such that there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced at least two times per week (every 4 days at most) and the skin re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

[1] Mitotic Spindle Disruption by Alternating Electric Fields Leads to Improper Chromosome Segregation and Mitotic Catastrophe in Cancer Cells. Giladi M, et al. Sci Rep. 2015 Dec 11;5:18046. doi: 10.1038/srep18046.

Principles of Operation

The NovoTTF-100L system produces TTFields within the human body through transducer arrays placed on the chest. TTFields disrupt the rapid cell division exhibited by cancer cells.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 150 kHz for MPM).

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the lungs), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the chest, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown in vitro to inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase[2].

Specifically, TTFields have been shown to inhibit mesothelioma cells in vitro at a frequency of 150 kHz and an intensity of 1 V/cm. Based on realistic finite element mesh simulations, Novocure has concluded that intended TTFields intensities can be generated in the lungs of large animals and humans.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for TTFields has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

2 Kirson, E. D., Z. Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." Cancer Res 64(9): 3288-95.

Clinical Data

UNRESECTABLE MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Potential Adverse Effects of the Device on Health

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Treatment related skin toxicity
- Allergic reaction to the plaster or to the gel
- Electrode overheating leading to pain and/or local skin burns
- Infection at the sites of electrode contact with the skin
- Local warmth and tingling sensation beneath the electrodes
- Medical device site reaction
- Muscle twitching
- Skin breakdown / skin ulcer

Clinical Study in Unresectable MPM

Study Design: The study was a prospective, single-arm study evaluating pemetrexed and cisplatin or carboplatin in combination with TTFields in patients with untreated unresectable malignant pleural mesothelioma. The study was conducted at 13 sites in Europe.

The following were the objectives of the study:

To prospectively determine the overall survival of malignant pleural mesothelioma subjects treated with NovoTTF-100L System in combination with pemetrexed and cisplatin or carboplatin.

To collect evidence of the safety of TTFields applied to subjects with malignant pleural mesothelioma using NovoTTF-100L.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

a. Pathological or histological evidence of mesothelioma.
b. ≥ 18 years of age
c. TNM Stage IV, Not candidate for curative treatment (surgery or radiotherapy)
d. At least 4 weeks since major surgery
e. At least one measurable or evaluable lesion according to modified RECIST criteria for malignant pleural mesothelioma
f. ECOG Performance Status (PS) of 0-1.
g. Life expectancy of at least 3 months.
h. Participants of childbearing age must use effective contraception as indicated by the investigator
i. All subjects must sign written informed consent.
j. Able to operate the NovoTTF-100L System independently or with the help of a caregiver.

Exclusion Criteria

k. Previous chemotherapy or radiation;
l. Prior malignancy requiring anti-tumor treatment or concurrent malignancy;
m. Significant co-morbidities within 4 weeks prior to enrollment, resulting in the following laboratory findings:
    - Significant liver function impairment:
    - AST or ALT >3 times the upper limit of normal
    - Total bilirubin >1.5 upper limit of normal
    - Significant renal impairment (serum creatinine >1.7 mg/dL);
    - Coagulopathy (as evidenced by PT or APTT >1.5 times control in subjects not receiving anticoagulants);
    - Thrombocytopenia (platelet count < 100 x 103/µL);
    - Neutropenia (absolute neutrophil count < 1.5 x 103/µL);
    - Anemia (Hb <10 g/dL);
    - Severe acute infection;
n. Significant comorbidity expected to affect patient's prognosis or ability to receive the combined therapy:
    - History of significant cardiovascular disease unless the disease is well controlled. Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea).
    - History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the trial.
    - Active infection or any serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.
    - History of any psychiatric condition that might impair the patient's ability to understand or comply with the requirements of the study or to provide consent.
o. Untreated brain metastases. Asymptomatic, pretreated brain metastases not requiring steroids are allowed;
p. Implanted pacemaker, defibrillator or other electrical medical devices;
q. Known allergies to medical adhesives or hydrogel;
r. Pregnant or breastfeeding (all patients of childbearing potential must use effective contraception method during the entire period of the study based on the recommendation of the investigator or a gynecologist);
s. Admitted to an institution by administrative or court order.

Study Procedures:

Patients received pemetrexed based doublet in combination with TTFields. For the purpose of this study 3 weeks (21 days) was considered one treatment cycle. Chemotherapy: Treating investigators could choose one of the following regimens: pemetrexed/cisplatin, or pemetrexed/carboplatin. Pemetrexed was administered intravenously at a dose of 500 mg/m^2 day with either cisplatin 75 mg/m^2 intravenously on day 1 or carboplatin intravenously at a dose of AUC 5 on day 1. Cycles were repeated every 21 days for up to 6 cycles in the absence of progression or unacceptable toxicity. In the event of chemotherapy toxicities, dose modifications could be employed.

NovoTTF-100L System: Continuous TTFields for at least 18 hours/day applied to the thorax with output parameters of 150 kHz with two sequential, field direction at a maximal intensity of 1414mA RMS. TTFields were administered until radiological disease progression according to the Modified RECIST criteria for malignant pleural mesothelioma, or unacceptable toxicity based on investigator assessment. There was no dose modification for TTFields but treatment interruptions could occur if recommended by investigator. In the case of chemotherapy discontinuation due to toxicity or the completion of 6 chemotherapy cycles, TTFields therapy could be continued until disease progression or unacceptable toxicity.

Follow-up

All patients were seen every 3 weeks until disease progression. At each visit patients underwent: physical examination, performance status assessment, complete blood count, serum chemistry, adverse event collection, concomitant medication recording and device compliance assessment. CT of the chest and MRI and/or bone scan (if clinically indicated) were performed every 6 weeks until progression. Assessment of local and distant disease progression was performed per the modified RECIST criteria version 1.1. The protocol specified a minimum follow-up of 12 months.

Patients were seen at an outpatient clinic for an additional visit 30 days following treatment discontinuation. Physical examination and blood tests were performed during the visit. Patient performance status and adverse events were documented at this visit. Subsequently, patients were followed monthly for survival by telephone (unless a clinical visit was performed). Patient date of death was captured in the CRFs.

Analysis: The trial endpoints were analyzed in the intent to treat population which included 80 patients.

Protocol Deviations:

Major protocol deviations were defined as deviations that have the potential to influence the primary endpoints of the study. There were no major protocol deviations in the trial.

Subject Characteristics and Treatment Details: 80 subjects with unresectable MPM were enrolled in the study. Eight patients (10%) were lost to follow up before completing the required minimum of 12 months follow up. Baseline characteristics and treatment details in the ITT population were as follows:

Characteristics	NovoTTF-100L/Chemotherapy (N=80)
Age (Years)	
n	80
Mean (SD)	64.8 (9.28)
Median (range)	67.0 (27-78)
Sex, No. (%)	
Female	13 (16%)
Male	67 (84%)
Ethnicity, No. (%)	
Caucasian	80 (100%)
Smoking, No. (%)	
Current Smokers	8 (10%)
Former Smokers	37 (46%)
Never Smokers	35 (44%)
Tumor pathology, No. (%)	
Epithelioid	53 (66%)
Sarcomatoid/Biphasic	21 (26%)
Unknown	6 (8%)
Performance status (ECOG), No. (%)	
0	45 (56%)
1	35 (44%)
Visual Analog Pain Scale at Baseline	
Mean (SD)	15.1 (20.68)
Median (range)	5.0 (0-93)

Treatment Details

Number of TTFields Cycles	
Mean (SD)	8.7 (6.08)
Median (range)	8.0 (2-41)
Number of Chemotherapy Cycles	
Mean (SD)	4.6 (1.81)
Median (range)	6.0 (1-7)
Usage (percentage NovoTTF-100L use per treatment cycle)	
n	72
Median (range)	68.0 (2-91)
Patients with treatment breaks (>=24 hours), No.(%)	70 (88%)
Number of treatment breaks (>=24 hours)	
n	70
Median (range)	6.0 (1-75)
Duration of treatment breaks (>=24 hours) (Days)	
n	70
Median (range)	2.6 (1-101)

Results:

Primary Endpoint: Overall Survival
The median overall survival in the trial was 18.2 months (95%CI 12.1-25.8). The Kaplan Meier overall survival curve for the 80 study patients is shown in Figure 1 below.

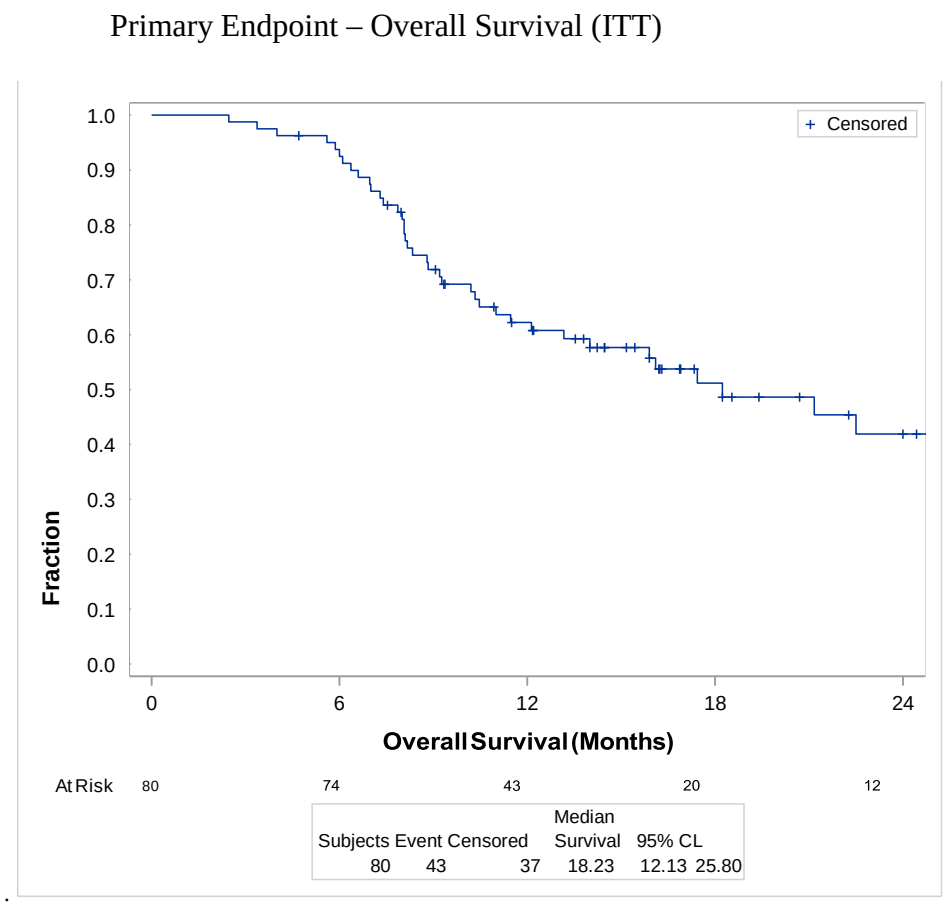

Figure 1: Median OS in STELLAR Study

Patients with epithelioid histology have previously been shown to have better outcomes than those with non-epithelioid histology. OS in the current study also favored patients with epithelioid versus non-epithelioid histology (median OS 21.2 months versus 12.1 months, respectively).

Secondary Endpoints:

Progression Free Survival
The median PFS in the study was 7.6 months (95% CI 6.7-8.6). The Kaplan Meier PFS curve for the 80 study patients is shown in Figure 2 below.

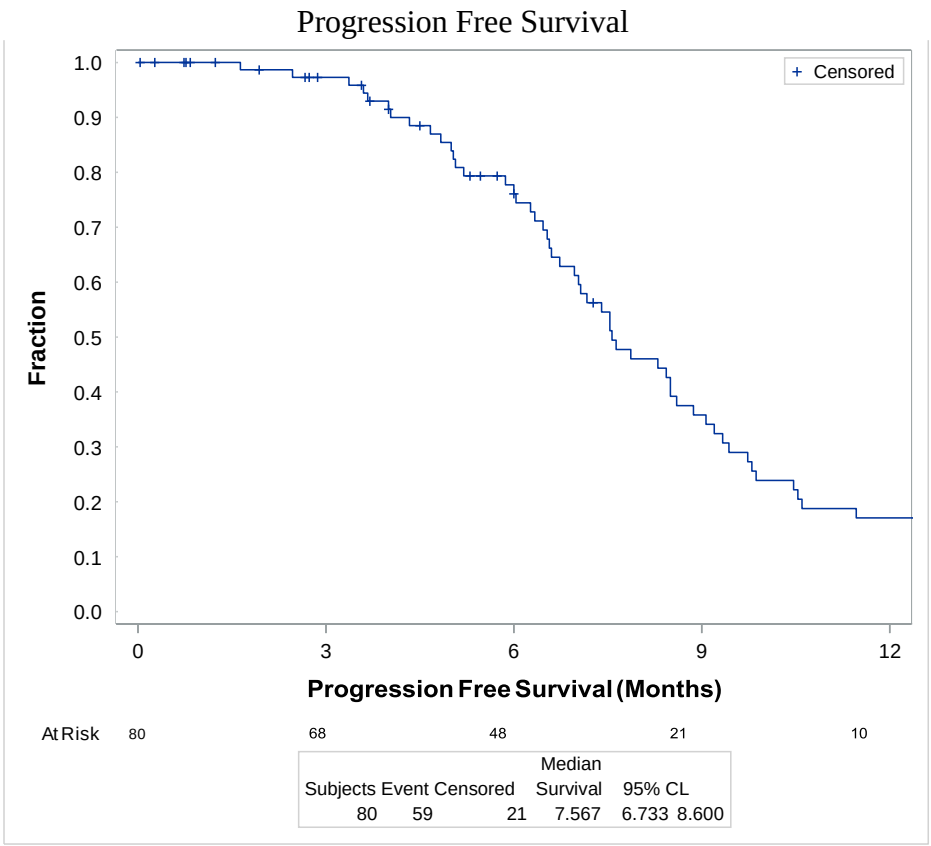

Figure 2: Median PFS in STELLAR Study

PFS in the current study also favored patients with epithelioid versus non-epithelioid histology (median PFS 8.3 months versus 6.5 months, respectively).

One-year and two-year survival rate
1-year survival in the study was 62% (95%CI 50%-72%). 2-year survival in the study was 42%.

Radiological Response Rate
Seventy two patients in the trial had at least one follow up CT scan performed. Of these patients, 29 (40%) experienced a partial response, 41 stable disease (57%) and 2 (3%) patients progressed at their first follow up scan. This represents a disease control rate of 97%.

Summary of Results

Endpoint	NovoTTF-100L / Pemetrexed / Platinum (n=80)
Overall survival	
Median OS, months (95% CI)	18.2 (12.1-25.8)
Survival rate % (95% CI)	
1-year	62.2% (50.3- 72.0)
2-year	41.9% (28.0 ; 55.2)
Progression free survival	
Median PFS, months (95% CI)	7.6 (6.7-8.6)
Available best response, No. (%)	72 (90)
Complete Response	0 (0)
Partial Response	29 (40)
Stable Disease	41 (57)
Progressive Disease	2 (3)
Disease control rate (CR+PR+SD)	70 (97)

Safety Results: A total of 32 patients (40%) reported severe (grade 3-4 adverse events in the trial). None of the grade 3-4 adverse events were considered related to NovoTTF-100L by any of the investigators except for 5% grade 3 skin irritation.

Severe (Grade 3-4) Adverse Events by Body System and Severity seen in > 1 patient

System Organ Class	n=80
Preferred Term	
Number of Patients with >=1 AE	32 (40%)
Blood and lymphatic system disorders	18 (23%)
Anemia	9 (11%)
Leukopenia	3 (4%)
Neutropenia	7 (9%)
Thrombocytopenia	4 (5%)
Cardiac disorders	3 (4%)
Pericardial effusion	2 (3%)
Gastrointestinal disorders	3 (4%)
Vomiting	2 (3%)
General disorders and administration site conditions	6 (8%)
Fatigue	3 (4%)
Infections and infestations	2 (3%)
Investigations	2 (3%)
Respiratory, thoracic and mediastinal disorders	4 (5%)
Dyspnea	2 (3%)
Skin and subcutaneous tissue disorders	4 (5%)
Medical Device Site Reaction (rash beneath transducer arrays)	4 (5%)

The only AEs attributed to use of the NovoTTF-100L System are the known skin irritation seen in 66% of patients in this study (5% severe). No SAEs were considered related to device use.

Conclusions: The NovoTTF-100L is a portable, battery operated device which delivers TTFields to patients with unresectable previously untreated MPM. The results of the trial in MPM showed that NovoTTF-100L, when added to pemetrexed and cisplatin or carboplatin, leads to a median OS of 18.2 months and a median PFS of 7.6 months. No increase in systemic adverse events is seen when NovoTTF-100L treatment is added to pemetrexed and a platinum based chemotherapy. The only common device-related AE was skin irritation seen beneath the transducer arrays in 66% percent of patients. The majority of these events were mild to moderate with only 5% of patients experiencing severe skin irritation.

Directions for Use

Detailed directions for use for NovoTTF-100L for MPM can be found in:
The NovoTTF-100L Patient Information and Operation Manual for MPM

Guidelines for ILE transducer array placement can be found in:
Clinical Practice Guidelines: layout optimization in thoracic malignancies

Abbreviations

AE – Adverse event

MPM – Malignant Pleural Mesothelioma

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

NovoTTF-100L System – A portable battery, or power supply, operated device for delivering 150 kHz TTFields to the lungs of patients with MPM

OS – Overall survival

PFS – Progression free survival

Radiological Response Rate - sum of complete and partial radiological response rates

Disease Control Rate – sum of stable disease, complete and partial radiological response rates

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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Kirson, E. D., Z. Gurvich, et al. (2004). “Disruption of cancer cell replication by alternating electric fields.” Cancer Res 64(9): 3288-95.

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