Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial

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See Comment page 1623

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Summary

Background Tumour Treating Fields (TTFields) are a regional, antimitotic treatment for solid tumours, which is based on the delivery of low-intensity alternating electric fields. The aim of the STELLAR study was to test the activity of TTFields delivered to the thorax in combination with systemic chemotherapy for the front-line treatment of patients with unresectable malignant pleural mesothelioma.

Methods STELLAR was a prospective, single-arm, phase 2 trial done at 12 European academic and non-academic sites (five in Italy, three in Poland, one in France, one in Belgium, one in Spain, and one in the Netherlands) for treatment-naive patients with histologically confirmed unresectable malignant pleural mesothelioma. Patients were aged at least 18 years, had an Eastern Cooperative Oncology Group performance status of 0–1, and at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Patients received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with intravenous pemetrexed (500 mg/m² on day 1) plus intravenous platinum (either cisplatin 75 mg/m² on day 1 or carboplatin area under the curve 5 on day 1) every 21 days for up to six cycles. Patients not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, patient or physician decision, or unacceptable toxic effects. The primary endpoint of the trial was overall survival. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all patients who received at least 1 day of TTFields treatment. This trial is registered with ClinicalTrials.gov, NCT02397928.

Findings Between Feb 9, 2015 and March 21, 2017, 80 patients were enrolled in the study. Median follow-up was 12·5 months (IQR 7·4–16·6). Median overall survival was 18·2 months (95% CI 12·1–25·8). The most common grade 3 or worse adverse events were anaemia (nine [11%] patients), neutropenia (seven [9%]), and thrombocytopenia (four [5%]). Skin reaction was the only adverse event associated with TTFields and was reported as grade 1–2 in 53 (66%) patients, and as grade 3 in four (5%) patients. No treatment-related deaths were observed.

Interpretation The trial showed encouraging overall survival results, with no increase in systemic toxicity. TTFields (150 kHz) delivered to the thorax concomitant with pemetrexed and platinum was an active and safe combination for front-line treatment of unresectable malignant pleural mesothelioma. Further investigation in a randomised trial is warranted.

Funding Novocure.

Introduction

Malignant pleural mesothelioma is a rare cancer, commonly associated with asbestos exposure.[1] Its incidence has already peaked in the USA, with approximately 3000 new cases diagnosed annually, but is still increasing in most European and Asian countries.[2] Because of the insidious presentation, most patients are diagnosed with a diffuse disease, unamenable to radical resection. The median survival time for patients with unresectable malignant pleural mesothelioma is around 12 months, with platinum and an antifolate being the accepted standard of care since 2003.[3,4] Carboplatin has had similar efficacy and objective responses as cisplatin, but has had a better toxicity profile and ease of administration,[5] so it has often been used in combination with pemetrexed for the treatment of patients who might not be able to tolerate cisplatin, including older patients.[6] The addition of bevacizumab to cisplatin and pemetrexed has been reported to increase median survival time by more than 2 months, with an expected higher incidence of severe adverse events.[7]

Tumour Treating Fields (TTFields) are a non-invasive, regional, antimitotic treatment for solid tumours, that is based on the delivery of low-intensity alternating

Research in context

Evidence before this study

We searched PubMed for reports published from Jan 1, 2003, to June 30, 2019, using the terms "mesothelioma", "chemotherapy", "tumor treating fields" and "Novo-TTF". Additionally, we examined abstracts from major international conferences of the same period (American Society of Clinical Oncology, American Association for Cancer Research, and International Association for the Study of Lung Cancer annual meetings). We also searched clinical trial registers (ClinicalTrials.gov). Malignant pleural mesothelioma is a tumour with a poor prognosis and few effective treatment options. Because of its pattern of local spread, few patients are candidates for multimodality treatments including chemotherapy, surgery, and radiotherapy. Upfront treatment of patients with unresectable malignant pleural mesothelioma has not changed in the past 15 years, since the establishment of pemetrexed and cisplatin as the standard of care. Aiming to reduce cisplatin toxicity, treatment schedules with carboplatin have been implemented, with similar results in terms of disease control and survival outcomes, but with a more favourable toxicity profile. The addition of targeted agents (particularly anti-angiogenic compounds) to standard chemotherapy has shown no or marginal improvement in overall survival so far, mostly with increased systemic toxicity. Immunotherapy with immune checkpoint inhibitors is still under evaluation. Tumour Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment for solid tumours, which is based on the delivery of low-intensity alternating electric fields by a portable home-use medical device. The US Food and Drug Administration has approved TTFields for newly diagnosed glioblastoma in combination with maintenance temozolamide. Preclinical studies have shown an anti-proliferative effect of TTFields on mesothelioma cell lines at a frequency of 150 kHz, also suggesting additivity with chemotherapy. Based on these promising preclinical results, as well as on the safety profile of TTFields applied to the upper torso, the STELLAR study was designed as a multicentre, single-arm, phase 2 study to identify a signal for the activity of 150 kHz TTFields in combination with pemetrexed and cisplatin or carboplatin, in patients with unresectable malignant pleural mesothelioma.

Added value of this study

The results of the phase 2 STELLAR trial show that the combination of TTFields with pemetrexed and cisplatin or carboplatin is an active and safe first-line treatment for patients with unresectable malignant pleural mesothelioma. Notably, the activity reported in the STELLAR trial was achieved without an increase in systemic toxicity. As expected from previous trials with TTFields in other cancers, the only toxic effects related to this treatment were medical device site reactions beneath the transducer arrays. Skin reactions were mostly mild to moderate, and were generally managed with topical corticosteroids, regular shifting of the arrays applied to the skin, and short treatment breaks.

Implications of all the available evidence

There is a substantial unmet need for new therapeutic strategies in malignant pleural mesothelioma. TTFields are an innovative treatment modality which has so far been unexplored in patients with malignant pleural mesothelioma. Although our results require further confirmation in a larger randomised trial, STELLAR data support the use of TTFields in combination with chemotherapy in patients with newly diagnosed unresectable malignant pleural mesothelioma.

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electric fields to the tumour.[8–11] The fields act by disrupting the assembly of the mitotic spindle at metaphase and by dielectrophoretic dislocation of organelles essential for mitosis at cytokinesis. The field frequency can be tuned to achieve a maximal antimitotic effect in different types of cancer cells.[10] TTFields were also shown to alter cellular membrane structure in glioblastoma cell models, thus potentially increasing permeability to chemotherapeutics.[12] TTFields are delivered continuously through a portable home-use medical device and have minimal toxic effects apart from localised skin irritation underneath the transducer arrays, which are applied to the skin near the location of the tumour.[11,13] In a phase 3 trial, TTFields in combination with maintenance temozolomide significantly increased the survival of patients with newly diagnosed glioblastoma compared with that for maintenance temozolomide alone,[14] without leading to a decline in patients' quality of life.[15] TTFields at frequencies of 150–200 kHz have been tested in pilot studies in non-small-cell lung cancer, pancreatic cancer, and ovarian cancer, demonstrating their safety when applied to the torso.[11,16]

TTFields had an optimal antiproliferative effect on mesothelioma cell lines in vitro at a frequency of 150 kHz, leading to a decrease in clonogenicity.[17] The reduction in cell count in clonogenic survival assays was significantly higher in human mesothelioma cells than in other tumour models, including glioblastoma, suggesting particularly high susceptibility of the tumour to TTFields. Combining TTFields with different concentrations of cisplatin or pemetrexed resulted in a shift to the left of the dose–response curve, suggesting additivity between these treatment modalities.[17] Using Finite Element Mesh simulations, therapeutic-level distribution of field intensities (≥1 V/cm) were demonstrated within the pleura and lung parenchyma.[17] Based on promising preclinical results in mesothelioma models and the safety profile of 150 kHz TTFields applied to the upper torso, the STELLAR study aimed to identify a signal for the activity of 150 kHz TTFields in combination with pemetrexed and cisplatin or

carboplatin, in patients with unresectable malignant pleural mesothelioma.

Methods

Study design and participants

STELLAR was a prospective, multicentre, single-arm, phase 2 trial for treatment-naive patients with histologically confirmed malignant pleural mesothelioma, who were not candidates for curative surgery according to the local multidisciplinary board of each site, which included a thoracic surgeon. Patients were enrolled at 12 European academic and non-academic sites (five in Italy, three in Poland, one in France, one in Belgium, one in Spain, and one in the Netherlands; appendix p 1). Patient were aged at least 18 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and at least one measurable or evaluable lesion according to the modified Response Evaluation Criteria for Solid Tumors (mRECIST) for mesothelioma.[18] Adequate hepatic, renal, and haematological functions were required, as well as life expectancy of at least 3 months. Participants had to be able to operate the NovoTTF-100L System independently or with the help of a caregiver. Patients with substantial comorbidities that were expected to affect prognosis or ability to receive the study treatments (including uncontrolled cardiovascular disease, active infection, or psychiatric condition) were excluded, as well as patients with implanted electrical medical devices. Additional exclusion criteria were concurrent or previous malignancy requiring anti-tumour treatment (apart from in-situ cervical cancer, in-situ breast cancer, non-melanoma skin cancer, or any malignancy for which treatment was received and there was no evidence of disease for at least 5 years). The study was done according to the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the ethics committees of all study sites. All patients provided written informed consent before enrolment. The study protocol is available in the appendix (pp 3–42).

See Online for appendix

Procedures

Patients received continuous TTFields for at least 18 h per day applied to the thorax with output parameters of 150 kHz with two sequential, perpendicular field directions at a maximal device output of 1414 milliampere root mean square, using the NovoTTF-100L System (Novocure, Haifa, Israel; appendix p 2). TTFields were administered concomitantly with chemotherapy. Investigators could choose for each patient either cisplatin or carboplatin. Pemetrexed was administered intravenously at a dose of 500 mg/m² together with intravenous platinum (cisplatin 75 mg/m² or carboplatin area under the curve [AUC] 5) on day 1 of a 21-day cycle for up to six cycles in the absence of radiological progression according to mRECIST criteria for malignant pleural mesothelioma[18] or unacceptable toxic effects based on investigator assessment. Patients not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, patient or physician decision, or unacceptable toxic effects.

All patients were supplemented with folic acid and vitamin B12. Folic acid was taken orally (350–1000 µg daily), beginning approximately 1 week before the first dose of chemotherapy and was continued throughout the duration of chemotherapy until 3 weeks after the last dose of pemetrexed. 1000 µg vitamin B12 was administered intramuscularly at least 1 week before the first dose of chemotherapy and approximately every 9 weeks until discontinuation of chemotherapy. Patients were also required to take a corticosteroid equivalent to 4 mg of dexamethasone given orally twice daily, the day before, the day of, and the day after pemetrexed dosing. Dose reductions of chemotherapy were predefined to allow management of adverse events. Dose adjustments at the start of a subsequent cycle of therapy were based on haematological and non-haematological toxic effects observed during the preceding course. Patients with grade 4 haematological toxicities received 75% of the previous pemetrexed and cisplatin dose or AUC 4 for carboplatin. In the event of grade 3 or 4 non-haematological toxicities, treatment was delayed until resolution to grade 1 or less before proceeding. Therapy was then resumed at 75% of the previous dose level (AUC 4 for carboplatin), if deemed appropriate by the treating physician. No dose modifications were planned for TTFields. The maximum allowed duration of treatment break from TTFields for adverse events was 3 weeks.

Patients were followed up every 3 weeks during the study period. Follow-ups consisted of physical examination and evaluation of performance status, adverse events, and concomitant medication. Complete blood cell count and chemistry tests (creatinine, glucose, electrolytes, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, and bilirubin) were collected. Chest and abdomen CT scans were done every 6 weeks, followed by local radiological disease assessment according to mRECIST criteria for malignant pleural mesothelioma. PET scans, bone scans, and CT or MRI of the brain were done if clinically indicated. If patients had radiological progression, they were followed up every 2 months for survival. Toxic effects were recorded prospectively according to version 4.0 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTCAE). Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day, and information was reviewed and transferred at the follow-up visits.

Outcomes

The primary endpoint of the trial was overall survival, defined as the time from study treatment initiation to death. Secondary endpoints were progression-free survival (defined as the time from study treatment initiation to disease progression or death, whichever occurred first),

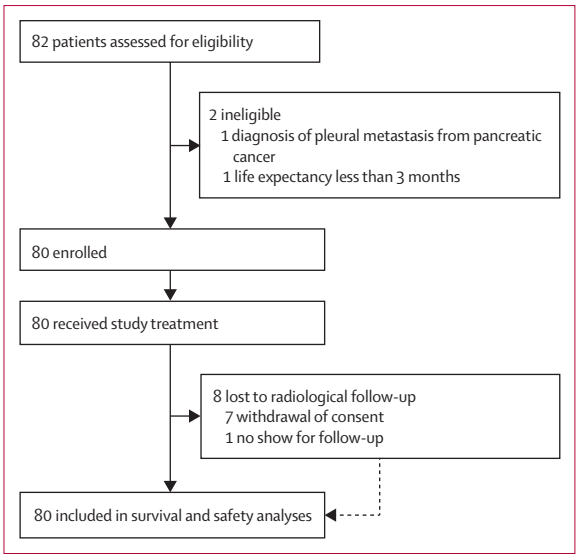

Figure 1: **Trial profile**
Patients who withdrew their consent to radiological follow-up could still agree to have their survival data collected on the study.

	Study population (n=80)
Age, years	67 (61–71)
Sex	
Female	13 (16%)
Male	67 (84%)
Ethnicity	
Caucasian	80 (100%)
Smoking	
Current	8 (10%)
Former	37 (46%)
Never	35 (44%)
Tumour stage	
Locally advanced	67 (84%)
Metastatic	13 (16%)
Tumour histology	
Epithelioid	53 (66%)
Sarcomatoid or biphasic	21 (26%)
Unknown	6 (8%)
ECOG performance status	
0	45 (56%)
1	35 (44%)
Number of TTFields cycles	8 (5–10)
Number of chemotherapy cycles	6 (3–6)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics of the study population**

objective response (defined as the proportion of assessable patients achieving complete or partial response based on mRECIST criteria for malignant pleural mesothelioma), and toxicity. No independent central radiological review was planned. Patients lost to radiological follow-up were censored for progression-free survival at the last date they were known to be alive and progression-free. Patients lost to follow-up had their overall survival censored at the last date they were known to be alive.

Statistical analysis

Because of the uncertainty of radiological assessment in malignant pleural mesothelioma due to its pattern of local spread and the lack of a survival benefit with existing second and further-line therapies, overall survival was set as the primary endpoint of the trial. The sample size calculation was based on the asymptotic distribution of the log of the hazard rate. The population reported by Vogelzang and colleagues[4] was assumed to have an exponential distribution with a constant hazard rate of 0·05728, calculated from the median survival of 12·1 months. A sample size of 71 patients provides 80% power with a two-sided α of 0·05 to detect an increase of 5·5 months in median overall survival (ie, overall survival of 17·6 months would have an exponential hazard rate of 0·03938) compared with this published population. This increase in median overall survival would be equivalent to a hazard ratio (HR) of 0·67 compared with the historical control data for overall survival. To allow for a 12% loss to follow-up, a total of 80 patients were planned to be recruited. Median overall survival was calculated with the Kaplan-Meier method. Secondary endpoints and adverse events were presented descriptively. An unplanned, post-hoc analysis of overall survival and progression-free survival by histological subtype was also done.

Survival analyses were done in the intention-to-treat population, and safety analyses were done in all patients who received at least 1 day of TTFields treatment. All analyses were done using SAS software (version 9.4).

This trial is registered with ClinicalTrials.gov, NCT02397928.

Role of the funding source

Novocure designed the trial and collected the data, and was involved in data analysis and data interpretation. Novocure was not involved in writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 9, 2015 and March 21, 2017, 80 patients were enrolled in the STELLAR study (figure 1) and included in survival and safety analyses. Two patients who were screened for the study did not meet eligibility criteria, one because of a pathological diagnosis of pleural metastasis from pancreatic cancer, and another because his life expectancy was less than 3 months. Baseline characteristics of the enrolled patients are summarised in table 1.

The median number of chemotherapy cycles was 6 (IQR 3–6); 50 (63%) patients were treated with the

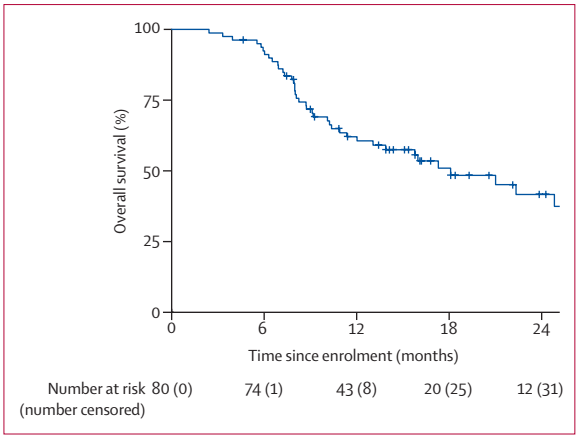

Figure 2: **Overall survival**
Kaplan-Meier analyses of overall survival in the intention-to-treat population.

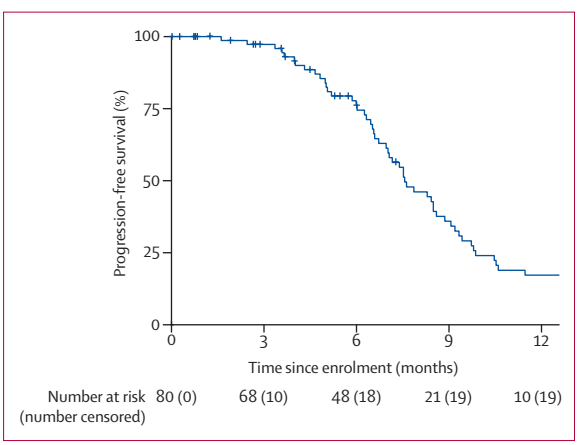

Figure 3: **Progression-free survival**
Kaplan-Meier analyses of progression-free survival in the intention-to-treat population.

	Study population (n=78)
Any treatment	44 (56%)
Pemetrexed re-challenge	
Pemetrexed and platinum	5 (6%)
Pemetrexed only	4 (5%)
Other chemotherapy	
Vinorelbine	17 (22%)
Gemcitabine	11 (14%)
Doxorubicin	5 (6%)
Carboplatin	1 (1%)
Immunotherapy	7 (9%)
Investigational drugs	7 (9%)

Data are n (%). Post-study treatments refer to any systemic anticancer treatments that the patients received after progression in this trial. Patients could have more than one subsequent anticancer treatment. Data were not available for two patients.

Table 2: **Post-study treatments**

carboplatin and pemetrexed combination and 30 (37%) received cisplatin and pemetrexed. Seven (9%) patients had dose reductions due to: grade 3 thrombocytopenia (in two patients, both treated with carboplatin); grade 3 anaemia (in one patient treated with carboplatin), grade 4 leukopenia (in one patient treated with carboplatin), grade 3 hepatotoxicity (in one patient treated with carboplatin), grade 3 renal toxicity (in one patient treated with cisplatin), and grade 3 fatigue (in one patient treated with cisplatin). Four (5%) patients treated with carboplatin discontinued chemotherapy as a result of chemotherapy-related toxic effects: grade 4 anaemia (in one patient), grade 4 respiratory failure (in one patient), grade 3 dyspnoea (in one patient), and grade 3 gastric ulcer (in one patient). The median number of 3-week TTFields cycles was 8 (IQR 5–10). Median compliance with TTFields in the first 3 months was 16·3 h per day (IQR 12·7–18·2), which is 68% (53–76) of the potential daily duration. Four (5%) patients had to temporarily reduce the use of TTFields treatment because of device-related skin toxic effects, and 38 (47%) took a temporary break of at least 3 days throughout the entire treatment period because of reasons unrelated to toxic effects, but all resumed the treatment. Four (5%) patients permanently interrupted TTFields before having progressive disease.

Median follow-up was 12·5 months (IQR 7·4–16·6); 43 patients had follow-up beyond 12 months. Median overall survival was 18·2 months (95% CI 12·1–25·8; figure 2). 1-year overall survival was 62·2% (95% CI 50·3–72·0) and 2-year overall survival was 41·9% (28·0–55·2). Median progression-free survival was 7·6 months (95% CI 6·7–8·6; figure 3). The numbers of events were 43 for overall survival and 59 for progression-free survival.

In the post-hoc analysis of overall survival and progression-free survival by histological subtypes, both overall survival and progression-free survival were longer in patients with epithelioid histology than in patients with other subtypes. Median overall survival was 21·2 months (95% CI 13·2–25·8) in 53 patients with epithelioid histology and 12·1 months (7·9–not reached [NR]) in 27 patients with non-epithelioid histology. The numbers of events were 29 for patients with epithelioid histology and 14 for patients with non-epithelioid histology. Median progression-free survival was 8·3 months (95% CI 7·1–9·7) in 53 patients with epithelioid histology and 6·5 months (5·0–8·5) in 27 patients with non-epithelioid histology. The numbers of events were 39 for patients with epithelioid histology and 20 for patients with non-epithelioid histology.

72 patients in the trial had at least one follow-up CT scan and were therefore evaluable for response according to mRECIST criteria. Of these patients, 29 (40%) had a partial response, 41 (57%) had stable disease and two (3%) progressed at their first follow-up scan. Median duration of response was 5·7 months (IQR 3·0–9·3). After progression, 44 (56%) patients went on to receive post-study therapy (table 2), mostly with progressive or

short-lived stable disease as a best response. Of 44 patients receiving post-study therapy, 27 (61%) had progressive disease as best response, 15 (34%) had stable disease, and two (5%) had a partial response.

The safety results are summarised in table 3. The most common mild to moderate (grade 1–2) adverse event was skin reaction at the site of the medical device, manifesting as localised dermatitis underneath the transducer arrays, which occurred in 53 (66%) of 80 patients. 29 (36%) patients had severe (grade 3–4) adverse events during the study period, and three (4%) died due to an adverse event (Candida sepsis [n=1], pneumonia [n=1], and epilepsy [n=1]). 20 (25%) patients had at least one grade 3 or worse adverse event. The most common grade 3 or worse adverse events (seen in ≥5% of patients) were anaemia (nine [11%] patients), neutropenia (seven [9%] patients), thrombocytopenia (four [5%] patients), and treatment-related medical device site reactions (4 [5%] patients with grade 3 skin reactions). Anaemia was the most common serious adverse event, leading to hospital admission of two (3%) patients. None of the serious adverse events leading to hospital admission were related to NovoTTF-100L treatment. See appendix (pp 43–44) for the full list of serious adverse events and for serious adverse events leading to hospital admission. Skin-related adverse events resolved in all cases after treatment with topical corticosteroids and, in the most severe cases, with temporary or permanent interruption of treatment with the NovoTTF-100L device. No treatment-related deaths were observed. Out of the 43 deaths at the study cut-off, 40 (93%) were the result of disease progression, and 3 were caused by intercurrent disease (table 3) not related to treatment.

Discussion

Our multicentre, single-arm, prospective, phase 2 study shows an encouraging signal of activity of 150 kHz TTFields in combination with standard chemotherapy as first-line treatment of unresectable malignant pleural mesothelioma, with a median overall survival of 18·2 months (95% CI 12·1–25·8). These data have been obtained in a malignant pleural mesothelioma population with a high prevalence of non-epithelioid cancers, who have mostly been treated with carboplatin and pemetrexed. Moreover, no increase in systemic toxicity was observed.

Malignant pleural mesothelioma is a tumour with a dismal prognosis and few effective therapeutic options. Upfront treatment of patients who are not candidates for curative surgery has not changed in the past 15 years, since the establishment of chemotherapy containing pemetrexed and a platinum agent as the standard of care.[3–5] Multiple phase 2 and phase 3 studies have not reported improvements in patient outcome.[19] Clearly, new treatment strategies are needed. TTFields, a therapeutic modality previously approved by the US Food and Drug Administration (FDA) for the treatment of newly diagnosed glioblastoma based on survival superiority in a

	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients with ≥1 adverse event	43 (54%)	24 (30%)	5 (6%)	3 (4%)
Blood and lymphatic system disorders	27 (34%)	16 (20%)	2 (3%)	0
Anaemia	25 (31%)	8 (10%)	1 (1%)	0
Febrile neutropenia	0	1 (1%)	0	0
Leukopenia	0	2 (3%)	1 (1%)	0
Neutropenia	0	6 (8%)	1 (1%)	0
Thrombocytopenia	0	4 (5%)	0	0
Cardiac disorders	0	2 (3%)	1 (1%)	0
Atrial fibrillation	0	1 (1%)	0	0
Cardiac tamponade	0	0	1 (1%)	0
Pericardial effusion	0	2 (3%)	0	0
Gastrointestinal disorders	30 (38%)	3 (4%)	0	0
Constipation	8 (10%)	0	0	0
Gastric ulcer haemorrhage	0	1 (1%)	0	0
Nausea	17 (21%)	..	0	0
Vomiting	0	2 (3%)	0	0
General disorders and administration site conditions	34 (43%)	6 (8%)	0	0
Asthenia	11 (14%)	1 (1%)	0	0
Chest pain	10 (13%)	1 (1%)	0	0
Fatigue	10 (13%)	3 (4%)	0	0
Pain	0	1 (1%)	0	0
Hepatobiliary disorders	0	1 (1%)	0	0
Cholelithiasis	0	1 (1%)	0	0
Infections and infestations	17 (21%)	0	1 (1%)	2 (3%)
Bronchopneumonia	0	0	1 (1%)	..
Candida sepsis	0	0	0	1 (1%)
Oral candidiasis	0	1 (1%)	0	..
Pneumonia	0	0	0	1 (1%)
Investigations	15 (19%)	2 (3%)	0	0
Neutrophil count decreased	0	1 (1%)	0	0
Platelet count decreased	0	1 (1%)	0	0
White blood cell count decreased	0	1 (1%)	0	0
Metabolism and nutrition disorders	8 (10%)	0	0	0
Musculoskeletal and connective tissue disorders	0	1 (1%)	0	0
Neck pain	0	1 (1%)	0	0
Nervous system disorders	12 (15%)	0	0	1 (1%)
Epilepsy	0	0	0	1 (1%)
Renal and urinary disorders	0	1 (1%)	0	0
Oliguria	0	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders	17 (21%)	3 (4%)	1 (1%)	0
Cough	8 (10%)	0	0	0
Dyspnoea	0	2 (3%)	0	0
Pulmonary embolism	0	1 (1%)	0	0
Respiratory failure	0	..	1 (1%)	0
Skin and subcutaneous tissue disorders	54 (68%)	4 (5%)	0	0
Medical device site reaction	53 (66%)	4 (5%)	0	0
Pruritus	11 (14%)	0	0	0
Vascular disorders	8 (10%)	0	0	0

Data are n (%). Patients shown for each grade represent patients who had that grade as the highest for that specific adverse event. Grade 1 or 2 adverse events occurring in at least 10% of patients and all grade 3–5 adverse events are reported.

Table 3: **Adverse events in the study population (n=80)**

phase 3 study,[20] have a strong rationale for application in malignant pleural mesothelioma. The alternating electric fields used to target mitotic events in the tumour are distributed regionally in the thorax, and can therefore cover the entire disease burden of malignant pleural mesothelioma without causing systemic toxicity. Additionally, preclinical data[17] show high sensitivity of mesothelioma cells to TTFields, with and without chemotherapy. The safety of applying TTFields to the thorax has been shown in a previous pilot study[21] on non-small-cell lung cancer.

Because of the well-known difficulties of radiological response assessment in malignant pleural mesothelioma, and the lack of proven survival improvements with current second-line therapies (including immunotherapy with immune checkpoint inhibitors), overall survival was set as the primary outcome measure of the STELLAR trial, with the aim to identify a signal of efficacy with a novel approach to treating malignant pleural mesothelioma. The sample size calculation of the study was based on a comparison with the historical control of standard chemotherapy reported in the EMPHACIS study,[4] which included a minority of patients not supplemented with folic acid and vitamin B12. This could have led to a possible underestimation of the expected survival in supplemented patients.

The median overall survival of 18·2 months reached in our study is promising. Moreover, the 1-year and 2-year overall survival estimates suggest a meaningful benefit in long-term outcome in patients treated with TTFields and standard chemotherapy. Of note, 50 (63%) patients were treated with pemetrexed and carboplatin as the chemotherapy backbone, which is a regimen mostly used in patients who might not be able to tolerate cisplatin, including older patients.[22] The signal for activity achieved with the addition of TTFields to standard chemotherapy in the STELLAR study is further validated by comparison with two recent randomised trials in malignant pleural mesothelioma, the MAPS[7] and the LUME-Meso trials.[23,24] In both these studies, only patients with a good ECOG performance status score were included (0–1 in LUME-Meso and 0–2 in MAPS, but only 4% of the control cohort in the MAPS study had an ECOG performance status score of 2), similar to the STELLAR study. A better performance status is a well-known prognostic factor in malignant pleural mesothelioma,[25] and could partially contribute to the better overall survival observed in the control groups of recent trials. The MAPS study[7] tested the addition of bevacizumab to cisplatin and pemetrexed in the treatment of unresectable malignant pleural mesothelioma, showing a median overall survival of 18·8 months (95% CI 15·9–22·6) in the experimental group, compared with 16·1 months (14·0–17·9) with the standard treatment group. However, the percentage of patients with epithelioid histology, another strong prognostic factor in malignant pleural mesothelioma,[26] was higher in both groups of the MAPS trial than in the STELLAR study (80% in the experimental group and 81% in the control group, compared with 66% in the STELLAR study). As expected with VEGF-targeted therapies, higher frequencies of hypertension, cardiovascular events, and arterial and venous thromboembolic events were reported with bevacizumab.[27] The phase 2 part of the LUME-Meso study,[23] which tested the addition of nintedanib to pemetrexed and cisplatin in 87 patients with unresectable malignant pleural mesothelioma with epithelioid and biphasic histology, reported an overall survival of 14·2 months (95% CI 12·3–20·9) in the control group and 18·3 months (15·2–28·8) in the experimental group. This study included an even greater proportion of patients with epithelioid histology (88% in the experimental group and 89% in the control group). Median overall survival of patients with epithelioid histology in the control group of the LUME study was 15·2 months (95% CI 12·2–23·6) compared with 20·6 months (16·2–28·8) in the experimental group, similar to the median overall survival of 21·2 months (13·2–25·8) of patients with epithelioid histology in the STELLAR study. However, more recently, the phase 3 part of the LUME-Meso study showed no difference in overall survival between chemotherapy-naive patients with epithelioid histology treated with nintedanib plus cisplatin and pemetrexed and those treated with cisplatin and pemetrexed alone.[24] Median overall survival was 16·1 months (95% CI 13·7–19·3) in the control group and 14·4 months (12·2–17·9) months in the experimental group, so both groups had a shorter overall survival than patients in the STELLAR trial which comprised patients with tumours with both epithelioid and non-epithelioid histology.

Objective response and progression-free survival results in the STELLAR study were similar to results reported in other trials of malignant pleural mesothelioma.[7,23,24] However, the absence of independent radiological review limits the interpretation of these data in our study. Importantly, the overall survival results in the STELLAR trial were achieved without an increase in systemic toxicity related to chemotherapy. The expected mild to moderate TTFields-related skin reactions were reported in 53 (66%) patients, but only four (5%) had severe skin reactions that required temporary or permanent discontinuation of TTFields. Skin irritation, probably the result of chronic exposure to irritants contained in the transducer arrays, has been reported in all other studies involving TTFields so far, and is normally treated with topical corticosteroids and regular shifting of the arrays applied to the skin.[11,13,16]

In conclusion, 150 kHz TTFields applied to the thorax in combination with pemetrexed and platinum was an active and safe option in the front-line treatment of unresectable malignant pleural mesothelioma. Our results have the obvious limitations of a single-arm phase 2 design, and need confirmation in a larger randomised trial. However, the STELLAR study represents a novel approach to treating malignant pleural mesothelioma, which has received FDA approval on

For the **US Food and Drug Administration approval of the NovoTTF-100L System** see https://www.fda.gov/medical-devices/recently-approved-devices/novottftm-100l-system-h180002

May 23, 2019, under the Humanitarian Device Exemption pathway. To the best of our knowledge, this is the first FDA approval to be granted for a mesothelioma clinical trial since 2004.

Contributors

All investigators were involved in data collection and reviewed the radiological data at their respective sites. All authors contributed to the writing of the manuscript, and reviewed and approved the final draft.

Declaration of interests

GLC reports personal fees for advisory roles, speaker engagements, and travel and accommodation expenses from Boehringer-Ingelheim, Merck Sharp & Dohme, Astellas, Pfizer, and Novocure, outside the submitted work. JGA reports personal fees and non-financial support from Merck Sharp & Dohme, and personal fees from Bristol-Myers Squibb, Boehringer-Ingelheim, Amphera, Eli Lilly, Takeda, Bayer, Roche, and AstraZeneca, outside the submitted work. He also has a patent allogenic tumour cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending. RD reports personal fees for advisory roles, speaker engagements, and travel and accomodation expenses from Roche and AstraZeneca, and personal fees from Novartis, Pfizer, Boehringer-Ingelheim, Merck Sharp & Dohme, Takeda, and Foundation Medicine, outside the submitted work. SC reports personal fees from Bristol-Myers Squibb, Roche, Pfizer, and Boehringer Ingelheim, outside the submitted work. DP reports participation as principal or co-investigator in clinical trials with institutional financial interests from AstraZeneca, Bristol-Myers Squibb, Abbvie, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Medimmune, Sanofi-Aventis, Taiho Pharma, Novocure, and Daiichi Sankyo. MM reports participation as principal or co-investigator in clinical trials with institutional financial interests from from Roche, Jannsen-Cylag, and AstraZeneca, and personal fees for advisory roles, speaker engagements, and travel and accommodation expenses from Merck Sharp & Dohme, Roche, Jannsen-Cylag, AstraZeneca, Italfarmaco, and Novartis, outside the submitted work. FG reports travel support from Novocure. All other authors declare no competing interests.

Data sharing

The study protocol and site enrolment data will be available to anyone who wishes to access them in the appendix of this Article, immediately following publication and with no end date. Individual patient data underlying the results reported in this Article will not be available.

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