Systemic therapy in malignant mesothelioma: treat it or leave it

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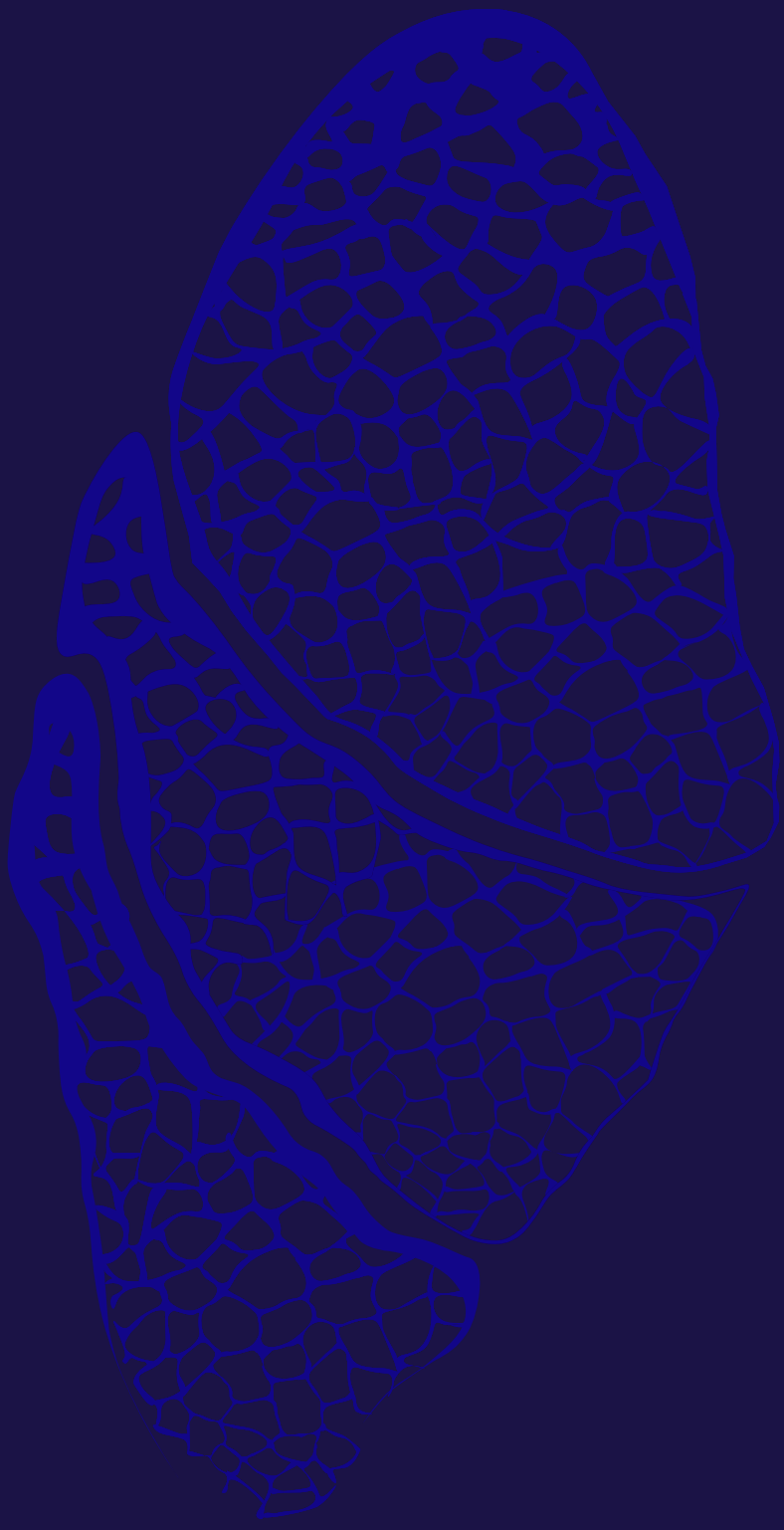

Chapter 3

Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma (NVALT19): an investigator-initiated, randomised, open-label, phase 2 trial

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CLINICAL TRIAL.

ABSTRACT

Background

Almost all patients with malignant mesothelioma eventually have disease progression after first-line therapy. Previous studies have investigated maintenance therapy, but none has shown a great effect. We aimed to assess the efficacy and safety of switch-maintenance gemcitabine in patients with malignant mesothelioma without disease progression after first-line chemotherapy.

Methods

We did a randomised, open-label, phase 2 trial in 18 hospitals in the Netherlands (NVALT19). We recruited patients aged older than 18 years with unresectable malignant mesothelioma with no evidence of disease progression after at least four cycles of first-line chemotherapy (with platinum and pemetrexed), who had a WHO performance status of 0–2, adequate organ function, and measurable or evaluable disease. Exclusion criteria were active uncontrolled infection or severe cardiac dysfunction, serious disabling conditions, symptomatic CNS metastases, radiotherapy within 2 weeks before enrolment, and concomitant use of any other drugs under investigation. Patients were randomly assigned (1:1), using the minimisation method, to maintenance intravenous gemcitabine (1250 mg/m^2 on days 1 and 8, in cycles of 21 days) plus supportive care, or to best supportive care alone, until disease progression, unacceptable toxicity, serious intercurrent illness, patient request for discontinuation, or need for any other anticancer agent, except for palliative radiotherapy. A CT scan of the thorax or abdomen (or both) and pulmonary function tests were done at baseline and repeated every 6 weeks. The primary outcome was progression-free survival in the intention-to-treat population. Safety was analysed in all participants who received one or more doses of the study drug or had at least one visit for supportive care. Recruitment is now closed; treatment and follow-up are ongoing. This study is registered with the Netherlands Trial Registry, NTR4132/NL3847.

Findings

Between March 20, 2014, and Feb 27, 2019, 130 patients were enrolled and randomly assigned to gemcitabine plus supportive care (65 patients [50%]) or supportive care alone (65 patients [50%]). No patients were lost to follow-up; median follow-up was 36·5 months (95% CI 34·2 to not reached), and one patient in the supportive care group withdrew consent. Progression-free survival was significantly longer in the gemcitabine group (median 6·2 months [95% CI 4·6–8·7]) than in the supportive care group (3·2 months [2·8–4·1]; hazard ratio [HR] 0·48 [95% CI 0·33–0·71]; p=0·0002). The benefit was confirmed by masked independent central review (HR 0·49 [0·33–0·72]; p=0·0002). Grade 3–4 adverse events occurred in 33 (52%) of 64 patients in the gemcitabine group and in ten (16%) of 62 patients in the supportive care group. The most frequent adverse events were anaemia, neutropenia, fatigue or asthenia, pain, and infection in the gemcitabine group, and pain, infection, and cough or dyspnoea in the supportive care group. One patient (2%) in the gemcitabine group died, due to a treatment-related infection.

Interpretation

Switch-maintenance gemcitabine, after first-line chemotherapy, significantly prolonged progression-free survival compared with best supportive care alone, among patients with malignant mesothelioma. This study confirms the activity of gemcitabine in treating malignant mesothelioma.

Funding

Dutch Cancer Society (Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding) and Stichting NVALT studies.

INTRODUCTION

Malignant mesothelioma is highly therapy resistant, and is almost impossible to completely resect, resulting in more stringent indications for surgery in the past 10 years.[1] Palliative systemic therapy is the only treatment option in most patients to prevent tumour progression and prolong survival without compromising quality of life.[2] Since 2003, platinum and pemetrexed has been the standard treatment, and the only registered, first-line therapy for patients with unresectable mesothelioma.[3] Only the addition of bevacizumab to this regimen has shown a small, potential survival benefit. Nevertheless, almost all patients who received this treatment developed a disease recurrence in time, resulting in a median overall survival of 12·1–16·1 months.[3,4]

Maintenance therapy is an effective strategy in treating solid tumours and is known to prolong progression-free survival.[5,6] However, in malignant mesothelioma, several maintenance strategies, such as pemetrexed and nintedanib, have shown no benefit in progression-free survival or in overall survival.[7,8] Switch-maintenance therapy using a non–cross-resistant drug such as thalidomide or defactinib also proved unsuccessful (appendix p 17).[9,10] However, these drugs had little single-agent activity. By contrast, phase 2 trials of gemcitabine have shown single-agent activity with partial response rates of up to 31% in patients with malignant mesothelioma, with a manageable toxicity profile.[11,12]

We aimed to assess the efficacy and safety of switch-maintenance gemcitabine in patients with malignant mesothelioma without disease progression after first-line platinum and pemetrexed therapy.

METHODS

Study design and participants

We did a prospective, investigator-initiated, randomised, open-label, phase 2 trial in 18 hospitals in the Netherlands (NVALT19; appendix p 18).Eligible patients were aged 18 years or older and had a histologically or cytologically confirmed unresectable malignant mesothelioma and a WHO performance status of 0–2. Patients were required to have completed at least four cycles of first-line platinum (cisplatin or carboplatin) and pemetrexed combination chemotherapy within 21–42 days before study entry, with no evidence of disease progression following first-line treatment. Absence of progression at inclusion was determined by the investigators and based on radiological and clinical criteria. Patients were required to have measurable or evaluable disease, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for pleural mesothelioma. In addition, adequate organ function within 14 days before study enrolment was mandatory, and was defined as haemoglobin of at least 6·2 mmol/L, platelets of at least 100×10^9 per L, and neutrophils of at least $1{\cdot}5 \times 10^9$ per L; serum bilirubin no more than 1·25 times the upper limit of normal (ULN), and alanine aminotransferase and aspartate aminotransferase no more than 2·5 times the ULN (except with liver metastases); and serum creatinine no more than 1·25 times the ULN, or a creatinine clearance of at least 50 mL/min.

Exclusion criteria included active uncontrolled infection or severe cardiac dysfunction, symptomatic CNS metastases, and radiotherapy within 2 weeks before enrolment. Patients with an unstable peptic ulcer, unstable diabetes, or other serious disabling conditions, or who were receiving any other concomitant experimental drug, were also excluded (appendix p 37).

All patients provided written informed consent. This study was done in accordance with

the Declaration of Helsinki and the International Council for Harmonisation Harmonised Tripartite Guideline on Good Clinical Practice, and the protocol (appendix pp 23–59) was approved by the central ethical committee of the Netherlands Cancer Institute and local institutional review boards.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either maintenance gemcitabine plus supportive care, or best supportive care alone. Patients were centrally randomised by an online randomisation system (ALEA version 17.1, ALEA Clinical, Abcoude, Netherlands), using a strict minimisation method. The randomisation sequence was concealed. Minimisation factors were histology (epithelioid vs biphasic or sarcomatoid disease) and response to first-line treatment (complete or partial response vs stable disease). Patients were assigned to the allocated treatment group according to randomisation done by the local research team. As this was an open-label study, neither patients nor the investigators were masked to treatment allocation.

Procedures

Patients assigned to the active treatment group were treated with intravenous gemcitabine (1250 mg/m^2) on days 1 and day 8, in cycles of 21 days, plus supportive care. Toxicities were managed by treatment interruption or dose reduction. If dose reduction was needed due to toxicity, the dose of gemcitabine was reduced by 25% of the starting dose for gemcitabine. A second dose reduction was permitted to a dose of 50% of the starting dose for gemcitabine. In patients experiencing toxicity after two dose reductions, treatment was discontinued (appendix p 39). The supportive care group received scheduled supportive care visits every 3 weeks only (appendix p 41). Supportive care was defined as adequate management of pain and pleural effusions, psychosocial therapy, and managing other needs. For example, supportive care could include palliative radiotherapy for pain control, or pleural fluid drainage. Patients who were off-study for any reason

Research in Context

Evidence before this study

We searched PubMed on Dec 5, 2019, for articles published in English from database inception to Dec 1, 2019, using the search terms "mesothelioma", "maintenance", and "gemcitabine". The main results of the identified studies are summarised in the appendix. Platinum and pemetrexed is the standard first-line therapy and the only registered therapy for malignant mesothelioma since the randomised phase 3 study by Vogelzang and colleagues in 2003. The MAPS trial in 2014 showed a small but significant overall survival benefit of combining standard first-line chemotherapy with maintenance bevacizumab. Although immunotherapy seems to be a potentially active treatment in malignant mesothelioma, no randomised studies have, to our knowledge, reported activity for immunotherapy as a first-line treatment. Only two studies have been done in a switch-maintenance setting, using alternative agents that were not administered during the firstline therapy; one study investigated thalidomide and one defactinib, after first-line platinum and pemetrexed. The studies found neither a progression-free survival benefit nor an overall survival benefit. The activity of gemcitabine, whether as a single agent or in combination with a platinum compound, has been shown in phase 2 trials, with a tolerable safety profile.

Added value of this study

To our knowledge, this is the first randomised trial to investigate the efficacy and safety of switch-maintenance gemcitabine in patients with malignant mesothelioma. Our study showed that switch-maintenance gemcitabine after standard first-line platinum and pemetrexed therapy significantly improved the length of progression-free survival (confirmed by independent central review), with a manageable toxicity profile.

Implications of all the available evidence

We report evidence of the activity of gemcitabine after first-line chemotherapy in patients with unresectable malignant mesothelioma, an aggressive malignancy with few therapeutic options. Although a benefit in terms of overall survival was not seen, our finding of improved progression-free survival has important consequences for the treatment of patients with malignant mesothelioma.

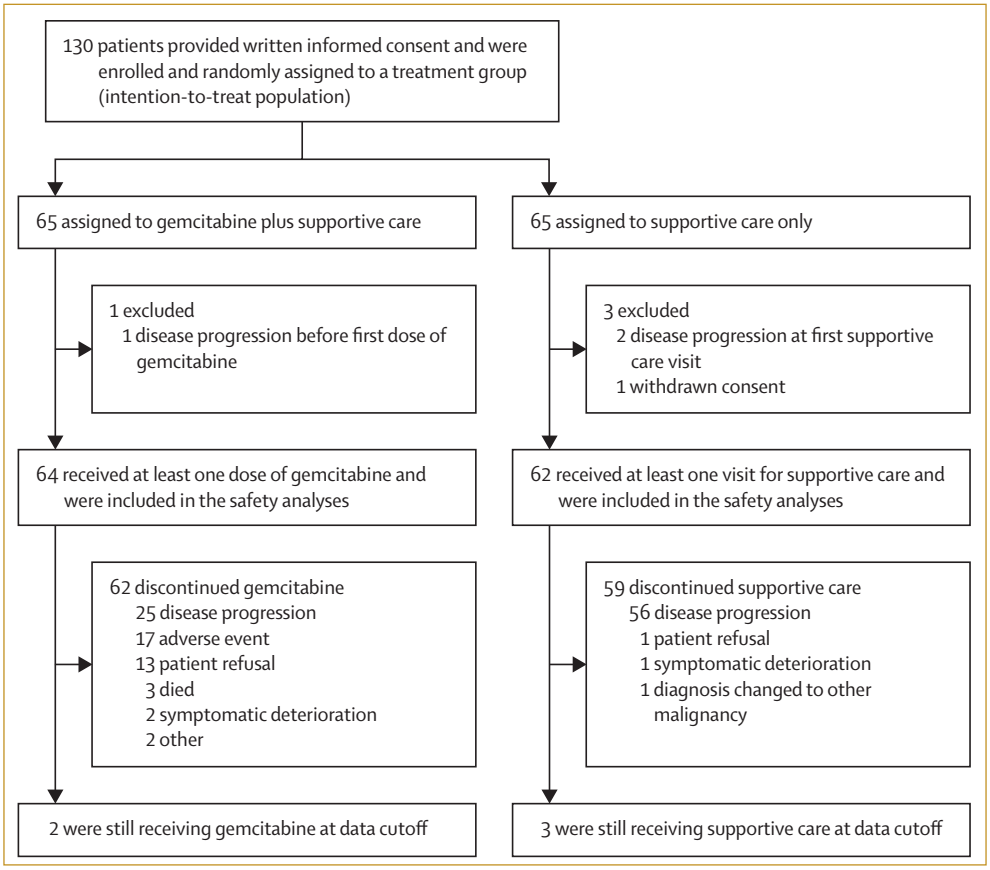

Figure 1: Inclusion of patients. One patient in the gemcitabine group had disease progression before the first dose of gemcitabine and received gemcitabine off-study. One patient, who was randomly assigned to the best supportive care group, had a change of diagnosis to another malignancy other than malignant mesothelioma; this patient was censored at the moment the diagnosis changed. One patient withdrew informed consent before the first cycle of supportive care, but agreed to be followed-up for progression-free survival.

were followed-up every 12 weeks for survival.

Study treatment, in both the gemcitabine group and the supportive care group, continued until disease progression (defined by the local investigator, using mRECIST criteria for malignant mesothelioma), unacceptable toxicity, serious intercurrent illness, patient request for discontinuation, or need for any other anticancer agent other than protocol treatment (except for palliative radiotherapy). Second-line treatment could be used at the judgement of the investigator. Gemcitabine was one of the preferred treatment options for patients in the supportive care group; that is, either gemcitabine monotherapy or a gemcitabine and platinum combination.

A CT scan of the thorax or abdomen (or both) and pulmonary function tests were done at baseline and repeated every 6 weeks at the investigation site. Clinical (laboratory) assessments, including biochemistry, haematology, physical examination, WHO performance status, and body weight were captured at baseline and repeated every 3 weeks (at the start of every treatment cycle in the gemcitabine group) and at the end-of-treatment visit in both groups. Full blood count was also assessed at day 8 of each treatment cycle in patients in the

gemcitabine group.

Adverse events of grade 2–5, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, were recorded from the first study visit until 30 days after the end-of-treatment visit, and were monitored by the data safety monitoring board. Grading for serious adverse events was the same as the grading of adverse events. Classification of serious adverse events was according to protocol definitions (appendix p 47). Toxicity was analysed and reported in patients who received at least one dose of gemcitabine or had at least one visit for supportive care.

Outcomes

The primary endpoint was progression-free survival, determined by the local investigator and defined as time from randomisation to disease progression (according to mRECIST criteria for malignant mesothelioma), clinical progression (as determined by the local physician), death (in absence of documented progression), or until censored on cutoff date. The primary analysis was done in the intention-to-treat population (including all patients who underwent randomisation). All CT scans were centrally reviewed by an independent radiologist (FL) who was masked to treatment allocation after patients' disease progression was assessed by the local investigator. Secondary endpoints were adverse events, objective radiological response rate (defined according to mRECIST criteria for malignant mesothelioma; assessed in patients with measurable disease at

Table 1. Baseline characteristics of the intention-to-treat population*

	Gemcitabine group (n=65)	Supportice care group (n=65)
Sex		
Female	7 (11%)	11 (17%)
Male	58 (89%)	54 (83%)
Age		
Median (years)	69	69
Range	43-84	35-82
WHO performance score		
0	37 (57%)	38 (58%)
1	27 (42%)	25 (38%)
2	0	2 (3%)
Unknown	1 (2%)	0
Histological subtype		
Epithelial	57 (88%)	57 (88%)*
Biphasic	5 (8%)	6 (9%)
Sarcomatoid	3 (4%)	2 (3%)
Best response to first-line treatment		
Complete response	2 (3%)	1 (2%)
Partial response	25 (38%)	26 (40%)
Stable disease	38 (58%)	38 (58%)
Disease site		
Pleural	65 (100%)	64 (98%)
Peritoneal and pleural	0	1 (2)
Measurable disease according to local physician	48 (74%)	50 (77%)
Measurable disease according to central review	46 (71%)	46 (71%)
Tumor stage		
Stages I-II	31 (48%)	30 (46%)
Stages III-IV	25 (39%)	27 (42%)
Unknown	9 (14%)	8 (12%)
First line treatment		
Cisplatin-pemetrexed	26 (40%)	26 (40%)
Carboplatin- pemetrexed	31 (48%)	27 (42%)
Cisplatin and carboplatin- pemetrexed	8 (12%)	12 (19%)

Data are n (%) or median (IQR). *The diagnosis of one patient was changed to another malignancy while participating in the study. †One patient received nivolumab and ipilimumab before first-line chemotherapy, one patient received nintedanib together with first-line chemotherapy, and one patient received GSK3052230 together with first-line chemotherapy.

Table 2. Adverse Events

	Gemcitabine (n= 64)				BSC (N=62)		
Grade	2	3	4	5	2	3	Total
Neutropenia	12(18%)	19 (29%)	2 (3%)		1 (2%)		34 (26%)
Anaemia	23 (35%)	2(3%)			5 (8%)		30 (23%)
Pain	14 (22%)	2(3%)			6 (9%)	4 (6%)	26 (20%)
Infection	6 (9%)	8(12%)		1 (2%)	6 (9%)	2 (3%)	23 (18%)
Fatigue/asthenia	17 (26%)	2(3%)			3 (5%)		22 (17%)
Cough/dyspnoea	11 (17%)	2(3%)			4 (6%)	1 (2%)	18 (14%)
Nausea/ vomiting/ anorexia or dyspepsia	9 (14%)	5(8%)			4 (6%)		18 (14%)
Cardiovascular disorder	6 (9%)	7(11%)			2 (3%)	1 (2%)	16 (12%)
Other*	6 (9%)	1(2%)			2 (3%)	2 (3%)	11 (8%)
Fever	7 (11%)	1(2%)			1 (2%)		9 (7%)
Pleural effusion	4 (6%)	1(2%)			2 (3%)	1 (2%)	8 (6%)
Flu like symptoms/ fatigue and rash	6 (9%)				1 (2%)		7 (5%)
Leukopenia	5 (8%)	1(2%)					6 (5%)
Metabolic disorders	4 (6%)				2 (3%)		6 (5%)
Constipation or diarrhoea	2 (3%)				1 (2%)		3 (2%)
Kidney insufficiency	1 (2%)	1(2%)			1 (2%)		3 (2%)
Nervous system disorders	1 (2%)				2 (3%)		3 (2%)
Thrombocytopenia	2 (3%)	1(2%)					3 (2%)
Infusion related symptoms	2 (3%)						2 (2%)
Second malignancy	1 (2%)	1(2%)					2 (2%)
Febrile neutropenia	1 (2%)						1 (1%)

* No grade 4 or 5 events were noted in the Best Supportive Care group. The events marked 'Other' were pneumothorax, edema, dry skin, pneumothorax, gastrointestinal disorders ,hernia inguinalis, ascites, dry skin, ggt increased (2), rib fracture, insomnia, urination problems, vasovagal reaction, weight loss, cataract and alopecia and second malignancies; one patient developed both a melanoma and renal cell carcinoma and one patient a melanoma.

baseline), overall survival, changes in forced vital capacity (lung function) and weight, and translational research regarding immune cell profiling and potential tumour markers (to be reported elsewhere). Overall survival was analysed in the intention-to-treat population. Lung function and weight were analysed and reported in patients who received at least one dose of gemcitabine or had at least one visit of supportive care.

Statistical analysis

In the previous NVALT5 study,[9] a median progression-free survival of 3·6 months was observed in patients who had no disease progression after receiving first-line chemotherapy for mesothelioma. 118 progression events were computed to give 90% power to detect an increase in progression-free survival from median 3·5 months to median 6·0 months at a 90% CI (hazard ratio [HR] of 0·58). Therefore, we estimated that approximately 124 patients would be needed to complete the study. Patients were censored for follow-up on Feb 28, 2020. Independent data monitoring was done at every study site after inclusion of the first patient and the last patient.

Efficacy analyses were done in the intention-to-treat population. Progression-free survival and overall survival were estimated using the Kaplan-Meier method, and the randomised groups were compared using the log-rank test (stratified by the stratification factors used

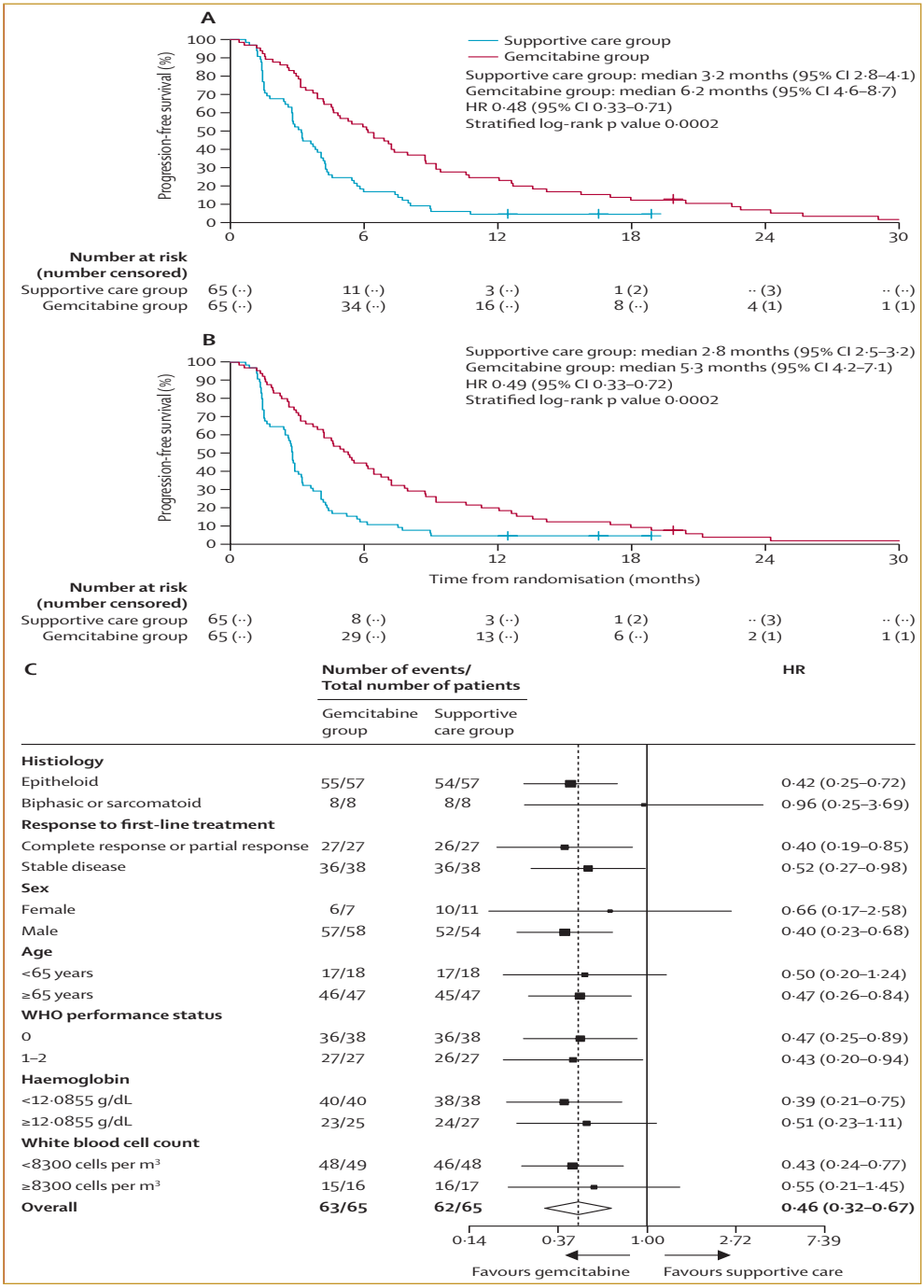

Figure 2: Progression-free survival analyses (A) Kaplan-Meier estimates as assessed by the local investigator. (B) Kaplan-Meier estimates as assessed by masked independent central review. (C) Forest plot of subgroup analyses; the dashed line indicates the point of overall effect across subgroups; HRs are presented with 99% CI, and with 95% CI for the overall effect. HR=hazard ratio.

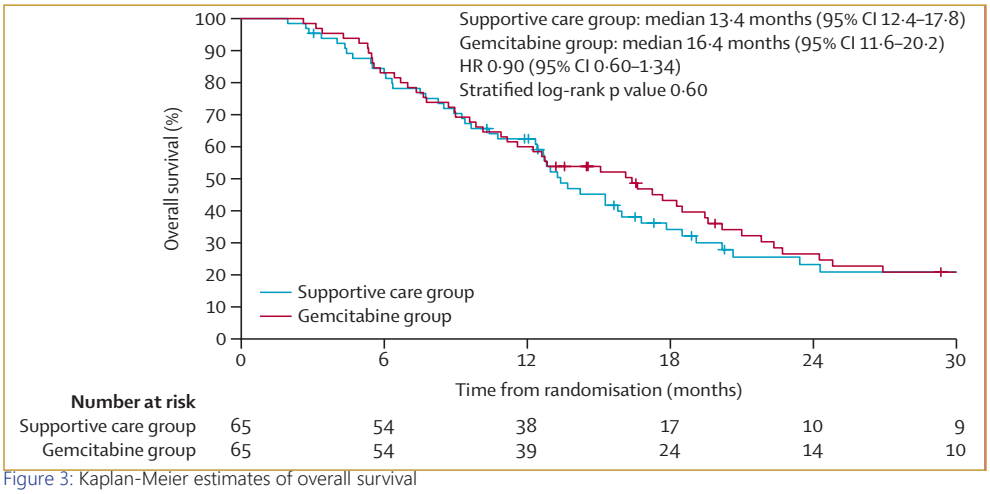

Figure 3: Kaplan-Meier estimates of overall survival

in the randomisation). Cox proportional hazard regression analyses were used to estimate HRs in the entire population as well as in subgroups determined by the stratification factors and to explore potentially confounding factors. All secondary endpoints were analysed by descriptive statistics.

Exploratory post-hoc analyses of progression-free survival (by histology, response to first-line treatment, sex, age group, WHO performance status, haemoglobin and white blood cell count) and overall survival (by post-study treatment) were done. For post-hoc sensitivity analyses within each subgroup, the unadjusted 95% CIs were reported.[13] In all analyses, a two-tailed p value of less than 0·05 was deemed to be significant. Statistical analyses were done in R version 3.6.1.

Weight and forced vital capacity during treatment were expressed as a percentage of baseline values. Development over time of the relative values was assessed graphically for each patient. This study is registered with the Netherlands Trial Registry, NTR4132/NL3847.

Role of the funding source

The Dutch Cancer Society (Koningin Wilhelmina Fonds voor de Nederlandse Kankerbestrijding) had no role in study design, data collection, data analyses, data interpretation, or writing of the report. The NVALT study group investigators and staff had a role in the study design and collected the data, but had no role in data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between March 20, 2014, and Feb 27, 2019, 130 patients were enrolled and randomly assigned to gemcitabine plus supportive care (65 patients [50%]) or supportive care alone (65 patients [50%]; figure 1). The groups were well balanced with respect to baseline patient and disease characteristics (table 1, appendix p 3). The median duration of follow-up was 36·5 months (95% CI 34·2 to not reached). No patients were lost to follow-up. At the data cutoff for analyses (Feb 28, 2020), two patients (3%) in the gemcitabine group and three patients (5%) in the supportive care group were still in the study (figure 1, appendix p 8). Three patients (3%) in the gemcitabine group received palliative radiotherapy.

At the data cutoff, 125 (96%) of 130 patients had disease progression or died due to disease progression (appendix p 9). Patients receiving gemcitabine had a significantly longer median progression-free survival (median 6·2 months [95% CI 4·6–8·7]) than did patients in the supportive care group (3·2 months [2·8–4·1]; HR 0·48 [95% CI 0·33–0·71]; p=0·0002; figure 2A). The progression-free survival benefit in the gemcitabine group was confirmed by masked independent central review (median 5·3 months [95% CI 4·2–7·1] in the gemcitabine group vs 2·8 months [2·5–3·2] in the supportive care group; HR 0·49 [95% CI 0·33–0·72]; p=0·0002; figure 2B).

An objective radiological response was recorded in eight (17%) of 48 patients with measurable disease at baseline in the gemcitabine group, and in two (4%) of 50 patients in the supportive care group (p=0·048). In the independent central review, an objective response was recorded in five (11%) of 46 patients with measurable disease at baseline in the gemcitabine group, and in one (2%) of 46 patients in the supportive care group (p=0·20; appendix p 7).

The results of the post-hoc subgroup analyses for progression-free survival were similar across all subgroups (figure 2C). The benefit of gemcitabine was especially similar among patients who had stable disease and those who had a complete or partial response to first-line therapy. There was no difference in progression-free survival between patients with a performance status of 0 and those with a performance status of 1; no patients in the gemcitabine group had a performance status of 2.

At data cutoff (Feb 28, 2020), 102 (78%) of 130 patients had died. The median overall survival was 13·4 months (95 CI% 12·4–17·8) for supportive care alone and 16·4 months (95 CI% 11·6–20·2) for the gemcitabine group (HR 0·90 [0·60–1·34]; p=0·60; figure 3).

After disease progression, 38 (61%; including seven who received gemcitabine after disease progression) of 63 patients in the gemcitabine group and 45 (72%) of 65 patients in the supportive care group received post-study treatment. In the gemcitabine group, nivolumab was the most common post-study treatment (18 patients [28%]) and gemcitabine was most common in the supportive care group (20 patients [31%]; appendix pp 10–13; note that patients could have more than one line of post-study treatment). Exploratory post-hoc subgroup analyses of overall survival did not reveal a superior treatment strategy (appendix p 21).

59 (92%) of 64 patients in the gemcitabine group and 30 (48%) of 62 patients in the supportive care group experienced adverse events. The most frequent adverse events were anaemia, neutropenia, fatigue or asthenia, pain, and infection in the gemcitabine group, and pain, infection, and cough or dyspnoea in the supportive care group (table 2). Two patients in the gemcitabine group developed a second primary tumour during the study; one patient developed both melanoma and renal cell carcinoma; and one patient developed melanoma. Grade 3–4 adverse events occurred in 33 (52%) of 64 patients in the gemcitabine group and in ten (16%) of 62 patients in the supportive care group. Treatment-related adverse events in the gemcitabine group were grade 3 in 27 patients (42%) and grade 4 in two patients (3%; appendix p 14). Grade 3 or higher serious adverse events were reported in 15 patients (23%) in the gemcitabine group and in two patients (3%) in the supportive care group. Infection was the most frequent serious adverse event in the gemcitabine group (8 patients [13%]; appendix p 15). One patient (2%) in the gemcitabine group died from a treatment-related serious adverse event (grade 5 infection; appendix p 16). Gemcitabine dose reductions were required in 15 patients (23%), 39 patients (61%) had one or more doses omitted, and dose delays occurred in 27 patients (42%; appendix p 6). Changes in lung function and weight over time.

DISCUSSION

In this study, patients who had switch-maintenance treatment with gemcitabine plus supportive care after first-line platinum and pemetrexed therapy had a significantly longer progression-free survival compared with those who had supportive care only. The median progression-free survival benefit was approximately 3 months, with a 21% risk reduction of disease progression or death in the first year after starting maintenance gemcitabine treatment. This progression-free survival improvement was seen in all subgroups, even in the groups with known poor prognostic factors, and was confirmed by masked independent central review.

NVALT19 is the second positive randomised study to provide a new treatment strategy for malignant mesothelioma since the landmark study by Vogelzang and colleagues.[3] Previously, only the MAPS trial[4] had shown a 2·7-month survival benefit with the addition of maintenance bevacizumab to platinum and pemetrexed. Our data support the role of gemcitabine as a therapy for malignant mesothelioma.

The progression-free survival benefit for patients treated with gemcitabine was not accompanied by an overall survival benefit. Although the baseline characteristics were balanced between the groups, overall survival might have been confounded by post-study treatments, with 20 patients in the supportive care group who received gemcitabine and more patients who received other post-study treatments (appendix pp 10, 21).

No new safety concerns were noted about gemcitabine in the maintenance setting.[14–17] Gemcitabine was generally well tolerated, and patients were able to receive a median of five cycles of gemcitabine (appendix pp 4–5).

Our study has some limitations. Similar to the MAPS trial, NVALT19 was not placebo controlled. Frequent intravenous placebo infusions would have hampered the inclusion rate.[4] The open-label study design probably did not affect the study outcome, because the progression-free survival benefit was confirmed by an independent radiological reviewer, who was masked as to the study groups, and CT scans were collected until start of a new treatment or death to minimise potential informative censoring.[18] Moreover, the median progression-free survival in the best supportive care group (3·2 months) was similar to historical data from the placebo group of the LUME-Meso trial8 (3·0 months). The study accrual was slow, but was representative of the population with malignant mesothelioma in the Netherlands. 1921 patients were diagnosed with pleural mesothelioma during 2015–18 in the Netherlands, of which 783 patients (41%) started chemotherapy and 527 patients (27%) completed at least four cycles.[19] Historical data showed that approximately 60% of patients with malignant mesothelioma are eligible for maintenance therapy after first-line chemotherapy.[8] Therefore, we estimate that around 40% of the eligible patients with malignant mesothelioma in the Netherlands were included in this study. The non-epithelioid pathological subtype was represented in 16 patients (12%) in our study population, which is comparable with historical data in other maintenance setting populations.[9,10] We did not measure quality of life. However, because lung function, weight, and performance status (data not shown) changed similarly over time in the treatment and supportive care groups, we assume that no major quality-of-life differences occurred between the study groups (appendix p 19).[20–22] This study was designed to explore the potential benefit of maintenance gemcitabine, which needs to be confirmed in a phase 3 trial. Although immunotherapy has not proven to be effective in mesothelioma thus far, several randomised immunotherapy studies are underway and their results should

be taken into consideration before initiating new studies in the maintenance setting. As maintenance therapy might mainly prolong progression-free survival as opposed to overall survival, quality of life is paramount and should be monitored in a confirmatory phase 3 study. As malignant mesothelioma is a rare disease, we strongly recommend selecting agents for large phase 3 trials on the basis of the response rate from single-agent phase 2 data and positive randomised phase 2 results.

CONTRIBUTORS

JAB and HvT designed the study. CJdG and JAB did the literature search. VvdN, CJdG, and JAB analysed and interpreted the data. CJdG wrote the first version of the manuscript. All authors contributed to the writing, review, and approval of the final manuscript.

DECLARATION OF INTERESTS

PB has participated in advisory boards of Merck Sharp & Dohme (MSD), AstraZeneca, Takeda, and Bristol-Myers Squibb (BMS), outside of the submitted work. RC has participated in advisory boards of MSD and Roche and has received a speaker fee from Roche, Pfizer, and BMS, outside of the submitted work. HJMG has received research funding from Eli Lilly and Boehringer-Ingelheim, and has participated in advisory boards of BMS, Merck, and Novartis. JGA reports personal fees and non-financial support from MSD, and personal fees from BMS, Boehringer Ingelheim, Amphera, Eli Lilly, Takeda, Bayer, Roche, and AstraZeneca, outside of the submitted work; and has a patent for allogeneic tumour cell lysate licensed to Amphera, a patent for combination immunotherapy in cancer pending, and a patent for a biomarker for immunotherapy pending. JAB reports reimbursement from BMS and F Hoffmann-La Roche for the Netherlands Cancer Institute, and financial support for an investigator-initiated trial from MSD, outside of the submitted work. All other authors declare no competing interests.

DATA SHARING

Qualified researchers can request access to anonymised individual patient level data by sending a request to the corresponding author (JAB). Data will be shared after approval of a submitted proposal with a signed data access agreement.

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Table S1. Baseline characteristics; prognostic laboratory tests

	Gemcitabine (N=65)	Best supportive care (N=65)
Platelets		
< 4 *10^5 cells/m3	59 (91%)	56 (86%)
≥ 4 * 10^5 cells/m3	40 (62%)	38 (58%)
Hemoglobin		
< 12 g/dL	40 (62%)	38 (58%)
≥ 12 g/dL	16 (25%)	17 (26%)
White Blood Cell Count		
< 8300 cell/mm3	49 (75%)	48 (74%)
≥ 8300 cells/mm3	16 (25%)	17 (26%)

cells/m3; cells per cubic meter, cells/mm3; cells per cubic millimeter, g/dl: gram per deciliter. Data are number (%) unless otherwise stated.

Table S2. Treatment characteristics; Treatment cycles before progression		
	Maintenance gemcitabine	Best Supportive Care
Median number of cycles before disease progression IQR	5 (0-50)	4 (0-26)
Time between visits days, mean, (range)	22 (5-48)	24 (1-89)

Table S3. Treatment characteristics; Gemcitabine-arm before disease progression	
Duration of treatment, weeks, median (range)	15·1 (3·0-151·0)
Total dose of gemcitabine, per patient, milligram, median (range)	2249 (1200-3015)
Dose per square meter body surface area per patient, milligram, median (range)	1232 (644-1308)

Table S4. Reasons for dose modification of gemcitabine					
Reason for modification	Delay (N=67)	Omitted (N=132)	Dose reduction (N=54)	Dose reduction and delay (N=20)	Total (N=273)
Bone marrow suppression (other than neutropenia)	3 (4%)	4 (3%)	4 (7%)	0	11(4%)
Cardiovascular disorder	1 (1%)	2 (2%)	0	0	3 (1%)
Concurrent radiotherapy	0	1 (1%)	0	0	1 (0%)
Fatigue/asthenia/dyspnea	1 (2%)	38 (29%)	1 (2%)	5 (25%)	45 (16%)
Fever	3 (4%)	3 (2%)	0	0	6 (2%)
Flu like symptoms	0	1 (1%)	0	0	1 (0%)
Holiday	16 (24%)	4 (3%)	0	0	20 (7%)
Hospitalization	0	7 (5%)	0	0	7 (3%)
Infection	7 (10%)	6 (5%)	0	0	13 (5%)
Infusion related symptoms	0	2 (2%)	1 (2%)	0	3 (1%)
Liver toxicity	0	0	27 (50%)	13 (65%)	40 (15%)
Logistic reasons	3 (4%)	11 (8%)	2 (4%)	1 (5%)	17 (6%)
Nausea	0	1 (1%)	0	0	1 (0%)
Neutropenia	8 (12%)	48 (36%)	18 (33%)	1 (5%)	75 (27%)
Pain	1 (1%)	0	1 (2%)	0	2 (1%)
Patient's request	21 (32%)	3 (2%)	0	0	24 (9%)
Pneumothorax	1 (2%)	0	0	0	1 (0%)
Unknown	2 (3%)	1 (1%)	0	0	3 (1%)

Dose modifications are reported per patient. Per patient more than one dose modification could occur. Seventeen (27%) patients had no dose modification at all. Data are number (%) unless otherwise stated.

Table S5. Best Overall Response

According to local investigator		Gemcitabine (N=48*)	Best Supportive Care (N=50*)
	Missing	1 (2%)	1 (2%)
	PR	8 (17%)	2 (4%)
	SD	29 (62%)	27 (55%)
	PD	10 (21%)	20 (41%)
According to central review		Gemcitabine (N=46**)	Best Supportive Care (N=46**)
	PR	5 (11%)	1 (2%)
	SD	32 (70%)	25 (54%)
	PD	9 (20%)	20 (43%)

Best overall response according to the local investigator and by central review using modified RECIST for malignant mesothelioma. Best response is only determined in patients with measurable disease at baseline. PD; Progressive disease, PR: Partial response, SD: Stable disease. * Number of patients with measurable disease according to the local investigator and ** according to the independent radiological reviewer. Data are number (%) unless otherwise stated.

Table S6. End of study reason

	Gemcitabine (N=63)	Best Supportive Care (N=62)
End of study reason		
Adverse event	17 (27%)	0
Disease progression	26 (41%)	58 (93%)
Patient refusal	13 (21%)	2 (3%)
Death	3 (5%)	0
Doctor's decision	0	1 (2%)
Symptomatic deterioration	2 (3%)	1 (2%)
Other	2 (3%)	0

Other: 'adverse events and stable disease for a long time' and 'social reasons.' Five patients (4%; 2 in the gemcitabine arm and 3 in the BSC arm) were still on treatment at data- cutoff. Data are number (%) unless otherwise stated.

Table S7. Progression type

	Gemcitabine (N=65)	Best Supportive Care (N=65)
No PFS event	2 (3%)	3 (5%)
Radiological progression	55 (85%)	61 (94%)
Clinical progression	2 (3%)	1 (1%)
Progression at time of death (death cause)	5 (8%)	0
Death without progression	1 (1%)	0

Data are number (%) unless otherwise stated.

Table S8. Post study treatments

Treatment –no (%)	Gemcitabine (N=87)	Best supportive Care (N=93)
No further treatment	25 (29%)	17 (18%)
Chemotherapy		
Docetaxel	0	1 (1%)
Gemcitabine	9 (10%)*	19 (20%)
Pemetrexed	4 (5%)	1 (1%)
Platinum + Etoposide	0	1 (1%)
Platinum + Gemcitabine	0	1 (1%)
Platinum + Pemetrexed	6 (7%)	6 (7%)
Vinorelbine	5 (6%)	0
Participated in phase I trial	4 (8%)	10 (11%)
Immunotherapy		
Nivolumab + Ipilimumab	2 (2%)	4 (4%%)
PD-1 inhibitor (study treatment)	19 (29%)	18 (20)
Radiotherapy	13 (15%)	14 (15%)

Patients could have subsequent more lines of treatment. *This includes 7 patients who continued gemcitabine after progression because of clinical benefit, plus one patient (pat 125) who had progressive disease before the first cycle of gemcitabine, and one patient (pat 75) who stopped gemcitabine treatment due to patient refusal and restarted later, after progression. Data are number (%) unless otherwise stated.

Table S9. Post-study treatment individual patients

Patient number	Treatment arm	Type of treatment	Treatment details
1	BSC	No further treatment	
2	BSC	No further treatment	
3	Gemcitabine	No further treatment	
4	Gemcitabine	Chemotherapy	Gemcitabine
4	Gemcitabine	Radiotherapy	thoracic ingrowth
5	BSC	Chemotherapy	Carboplatin pemetrexed
6	Gemcitabine	No further treatment	
7	BSC	Chemotherapy	Gemcitabine
8	BSC	No further treatment	
9	Gemcitabine	No further treatment	
10	Gemcitabine	Chemotherapy	Gemcitabine
11	BSC	No further treatment	
12	Gemcitabine	Radiotherapy	thoracic ingrowth
12	Gemcitabine	Chemotherapy	Vinorelbine
13	BSC	Chemotherapy	Gemcitabine
14	Gemcitabine	Targeted therapy	phase I study drug
14	Gemcitabine	Targeted therapy	Anetumab ravtansine
14	Gemcitabine	Chemotherapy	Carboplatin pemetrexed
14	Gemcitabine	Radiotherapy	Distant metastasis
15	BSC	Chemotherapy	Gemcitabine
15	BSC	Radiotherapy	Thoracic ingrowth
16	Gemcitabine	Immunotherapy	Nivolumab + ipilimumab
16	Gemcitabine	Chemotherapy	Carboplatin pemetrexed
16	Gemcitabine	Radiotherapy	Thoracic ingrowth

17	BSC	Immunotherapy	Nivolumab
17	BSC	Radiotherapy	Thoracic ingrowth
18	BSC	No further treatment	
19	Gemcitabine	No further treatment	
20	Gemcitabine	No further treatment	
21	BSC	Chemotherapy	Gemcitabine
22	Gemcitabine	No further treatment	
23	BSC	No further treatment	
24	BSC	Immunotherapy	Nivolumab
24	BSC	Immunotherapy	Nivolumab
24	BSC	Radiotherapy	Thoracic ingrowth
25	Gemcitabine	Radiotherapy	Thoracic ingrowth
25	Gemcitabine	Radiotherapy	Thoracic ingrowth
26	Gemcitabine	No further treatment	
27	BSC	No further treatment	
28	BSC	Targeted therapy	Anetumab ravtansine
28	BSC	Combination strategy	Phase I study drug + platinum + gemcitabine
28	BSC	Immunotherapy	Nivolumab
29	Gemcitabine	Chemotherapy	Pemetrexed
30	Gemcitabine	No further treatment	
31	BSC	Targeted therapy	Anetumab ravtansine
32	Gemcitabine	Chemotherapy	Carboplatinum pemetrexed
32	Gemcitabine	Immunotherapy	Nivolumab
32	Gemcitabine	Chemotherapy	Vinorelbine
33	BSC	Chemotherapy	Carboplatinum pemetrexed
34	Gemcitabine	No further treatment	
35	BSC	Chemotherapy	Carboplatin+ gemcitabine
35	BSC	Radiotherapy	Thoracic ingrowth
36	Gemcitabine	No further treatment	
37	Gemcitabine	Chemotherapy	Gemcitabine
38	BSC	Immunotherapy	Nivolumab
38	BSC	Radiotherapy	Thoracic ingrowth
39	Gemcitabine	Chemotherapy	Vinorelbine
40	Gemcitabine	Targeted therapy	Anetumab ravtansine
41	BSC	Chemotherapy	Gemcitabine
42	Gemcitabine	Targeted therapy	Anetumab ravtansine
42	Gemcitabine	Radiotherapy	Distant metastasis
43	BSC	No further treatment	
44	BSC	Targeted therapy	Anetumab ravtansine
46	Gemcitabine	Chemotherapy	Pemetrexed
47	BSC	Chemotherapy	Gemcitabine
48	Gemcitabine	Immunotherapy	Nivolumab
49	Gemcitabine	Immunotherapy	Nivolumab + ipilimumab
49	Gemcitabine	Chemotherapy	Carboplatin pemetrexed
50	BSC	Combination strategy	Phase I study drug + platinum
51	BSC	No further treatment	
52	Gemcitabine	Chemotherapy	Gemcitabine
52	Gemcitabine	Radiotherapy	Thoracic ingrowth
53	BSC	Chemotherapy	Docetaxel
54	Gemcitabine	Immunotherapy	Nivolumab
54	Gemcitabine	Radiotherapy	Thoracic ingrowth
55	Gemcitabine	No further treatment	
56	BSC	Targeted therapy	Anetumab ravtansine
56	BSC	Targeted therapy	Phase I study drug
57	Gemcitabine	Chemotherapy	Gemcitabine
58	Gemcitabine	No further treatment	

59	BSC	No further treatment	
60	BSC	Immunotherapy	Nivolumab + ipilimumab
60	BSC	Chemotherapy	Gemcitabine
61	BSC	Targeted therapy	Anetumab ravtansine
61	BSC	Chemotherapy	Gemcitabine
61	BSC	Radiotherapy	Distant metastasis
62	Gemcitabine	Chemotherapy	Gemcitabine
62	Gemcitabine	Immunotherapy	Nivolumab
63	Gemcitabine	No further treatment	
64	BSC	Chemotherapy	Carboplatin pemetrexed
64	BSC	Radiotherapy	Thoracic ingrowth
64	BSC	Chemotherapy	Gemcitabine
65	BSC	No further treatment	
66	BSC	No further treatment	
67	Gemcitabine	Chemotherapy	Gemcitabine
68	Gemcitabine	Chemotherapy	Gemcitabine
68	Gemcitabine	Immunotherapy	Nivolumab
69	Gemcitabine	No further treatment	
70	BSC	Immunotherapy	Nivolumab + ipilimumab
71	BSC	Targeted therapy	Phase I study drug
72	Gemcitabine	Chemotherapy	Carboplatin pemetrexed
72	Gemcitabine	Immunotherapy	Nivolumab
74	BSC	No further treatment	
75	Gemcitabine	Chemotherapy	Gemcitabine
75	Gemcitabine	Chemotherapy	Pemetrexed
75	Gemcitabine	Immunotherapy	Nivolumab
76	BSC	Immunotherapy	Nivolumab + ipilimumab
77	BSC	Immunotherapy	Pembrolizumab
78	Gemcitabine	No further treatment	
79	BSC	Immunotherapy	Nivolumab + ipilimumab
79	BSC	Chemotherapy	Gemcitabine
80	Gemcitabine	Immunotherapy	Nivolumab
81	Gemcitabine	Chemotherapy	Gemcitabine
82	Gemcitabine	No further treatment	
83	Gemcitabine	Chemotherapy	Gemcitabine
83	Gemcitabine	Immunotherapy	Pembrolizumab
84	BSC	Chemotherapy	Gemcitabine
84	BSC	Combination strategy	Phase I study drug + pembrolizumab
85	BSC	Chemotherapy	Gemcitabine
85	BSC	Immunotherapy	Pembrolizumab
85	BSC	Chemotherapy	Carboplatin pemetrexed
86	Gemcitabine	Chemotherapy	Gemcitabine
86	Gemcitabine	Chemotherapy	Vinorelbine
87	BSC	Chemotherapy	Gemcitabine
88	Gemcitabine	Chemotherapy	Carboplatin-pemetrexed
89	BSC	Chemotherapy	Gemcitabine
89	BSC	Chemotherapy	Carboplatin pemetrexed
89	BSC	Radiotherapy	Local ingrowth
90	Gemcitabine	No further treatment	
91	BSC	No further treatment	
92	Gemcitabine	Chemotherapy	Vinorelbine
93	Gemcitabine	Chemotherapy	Pemetrexed
94	BSC	Chemotherapy	Gemcitabine
95	BSC	Chemotherapy	Gemcitabine
95	BSC	Immunotherapy	Nivolumab
95	BSC	Radiotherapy	Thoracic ingrowth

96	Gemcitabine	Immunotherapy	Nivolumab
97	Gemcitabine	No further treatment	
98	BSC	Immunotherapy	Nivolumab
99	BSC	Immunotherapy	Nivolumab
99	BSC	Chemotherapy	Gemcitabine
100	Gemcitabine	Immunotherapy	Nivolumab
100	Gemcitabine	Radiotherapy	Thoracic ingrowth
101	BSC	Immunotherapy	Nivolumab
102	Gemcitabine	Chemotherapy	Gemcitabine
102	Gemcitabine	Immunotherapy	Nivolumab
103	Gemcitabine	Immunotherapy	Nivolumab
105	BSC	No further treatment	
106	Gemcitabine	Immunotherapy	Nivolumab
106	Gemcitabine	Radiotherapy	Thoracic ingrowth
109	BSC	Radiotherapy	Thoracic ingrowth
109	BSC	Chemotherapy	Gemcitabine
109	BSC	Immunotherapy	Nivolumab
110	BSC	No further treatment	
111	Gemcitabine	No further treatment	
112	BSC	Radiotherapy	Unknown
113	Gemcitabine	Immunotherapy	Nivolumab
113	Gemcitabine	Radiotherapy	Thoracic ingrowth
114	BSC	Immunotherapy	Nivolumab
114	BSC	Chemotherapy	Gemcitabine
115	Gemcitabine	Immunotherapy	Nivolumab
116	BSC	Immunotherapy	Nivolumab
117	Gemcitabine	Immunotherapy	Nivolumab
118	BSC	Immunotherapy	Nivolumab
119	Gemcitabine	Chemotherapy	Gemcitabine
119	Gemcitabine	Radiotherapy	Thoracic ingrowth
120	Gemcitabine	No further treatment	
121	BSC	Chemotherapy	Carboplatin pemetrexed
121	BSC	Immunotherapy	Nivolumab
123	BSC	No further treatment	
125	Gemcitabine	Chemotherapy	Gemcitabine
125	Gemcitabine	Immunotherapy	Nivolumab
126	Gemcitabine	No further treatment	
127	BSC	Immunotherapy	Nivolumab
127	BSC	Radiotherapy	Thoracic ingrowth
128	BSC	Immunotherapy	Nivolumab
129	Gemcitabine	No further treatment	
130	BSC	Radiotherapy	Distant metastasis
130	BSC	Immunotherapy	Nivolumab

Table S10. Treatment related adverse events in the gemcitabine arm

Grade	2	3	4	5
Neutropenia	11 (17%)	19 (29%)	2 (3%)	
Anemia	19 (29%)	2 (3%)		
Fatigue/asthenia	16 (25%)	2 (3%)		
Nausea/ vomiting/ anorexia or dyspepsia	8 (12%)	4 (6%)		
Infection	6 (9%)	4 (6%)		1 (2%)
Pain	7 (11%)			
Fever	5 (8%)	1 (2%)		

Leucopenia	5 (8%)	1 (2%)
Cough/dyspnea	4 (6%)	1 (2%)
Flu like symptoms/ fatigue and rash	5 (8%)	
Other	5 (8%)	
Thrombocytopenia	2 (3%)	1 (2%)
Infusion related symptoms	2 (3%)	
Cardiovascular disorder		1 (2%)
Constipation or diarrhea	1 (2%)	
Febrile neutropenia		1 (2%)
Kidney insufficiency		1 (2%)
Data are number (%) unless otherwise stated.		

Table S11. All grade Serious Adverse events

	Gemcitabine					BSC	
Grade	1	2	3	4	5	2	3
Infection		1 (2%)	6 (9%)		1 (2%)		
Fever	2 (3%)	4 (6%)	1 (2%)				
Cardiovascular disorder		2 (3%)	2 (3%)			2 (3%)	
Pain		2 (3%)	1 (2%)				2 (3%)
Cough/dyspnea		1 (2%)	2 (3%)				
Nausea/ vomiting/ anorexia or dyspepsia			3 (5%)				
Kidney insufficiency		1 (2%)	1 (2%)				
Fatigue/asthenia			1 (2%)				
Febrile neutropenia			1 (2%)				
Metabolic disorders		1 (2%)					
Pneumothorax		1 (2%)					
Pleural effusion			1 (2%)				
Second malignancy		1 (2%)					
Data are number (%) unless otherwise stated.							

Table S12. Treatment related serious adverse events in the gemcitabine arm

Grade	1	2	3	4	5
Fatigue/asthenia			1 (2%)		
Nausea/ vomiting/ anorexia or dyspepsia			3 (5%)		
Infection		1 (2%)	2 (3%)		1 (2%)
Pain		1 (2%)			
Fever	2 (3%)	3 (5%)	1 (2%)		
Cough/dyspnea		1 (2%)	1 (2%)		
Cardiovascular disorder			1 (2%)		
Febrile neutropenia			1 (2%)		
Kidney insufficiency			1 (2%)		
Data are number (%) unless otherwise stated.					

Table S13. Overview studies on maintenance therapy in Malignant Mesothelioma

Author	Study type	Induction therapy	Maintenance therapy	Progression free survival (months)	Overall survival (months)
Planting[1]	Single arm phase II	Cisplatin + oral etoposide	Oral etoposide	Not reported	Not reported.
Kindler[2]	Randomized phase II	Gemcitabine + cisplatin + bevacizumab or placebo	Bevacizumab or placebo	GC+ Bevacizumab 6.9 GC+ Placebo 6.0	GC+ Bevacizumab 15.6 GC+ Placebo 14.7
Meerbeeck et all[3]	Randomized Phase III	Cisplatin +/- raltitrexed	Cisplatin +/- raltitrexed	CR 5.3 Cisplatin 4	CR 11.4 Cisplatin 8.8
Zalcman[4]	Randomized phase III	Cisplatin + pemetrexed +/- bevacizumab	Bevacizumab	CP+ Bevacizumab 9.2; CP 7.3	CP+ Bevacizumab 18.8; Placebo 16.1
Ceresoli[5]	Single arm phase II	Carbo-pemetrexed+ bevacizumab	Bevacizumab	6.9	15.3
Scagliotti[6]	Randomized phase III	Cisplatin + pemetrexed + nintedanib or placebo	Nintedanib or placebo	CP+ Nintedanib 6.8 vs placebo 7.0	Not reported
Buikhuizen[7]	Randomized phase III	Platinum- pemetrexed	Thalidomide vs BSC	3.6 vs 3.5	10.6 vs 12.9
Purohit[8]	Single arm phase II	Cisplatinum+ IFN Alpha 2a	IFN alpha 2a	6.4	16.5
Halme[9]	Single arm phase II	Interferon -gamma, high-dose methotrexate	interferon -gamma	Not reported	17
Bogaert[10]	Single arm phase II	Platinum+ petemetrexed	Pemetrexed	3.4	6.0
Fennall[11]	Randomized phase II	Platinum + pemetrexed	Defactinib or placebo	4.1 vs placebo 4.0	12.7 vs placebo 13.6
Hassan[12]	Single arm phase II	Amatuximab + pemetrexed + cisplatin	Amatuximab	6.1	14.8
Tsao[13]	Phase I	Cediranib + pemetrexed + cisplatin	Cediranib	8.6	16.2
Tsao [14]	Phase II	Cediranib + pemetrexed + cisplatin or placebo	Cisplatin or placebo	Cediranib 7.2 vs placebo 5.6 (HR 0.69 (p = 0.096)	Cediranib 10 vs 8.5 (HR 0.84, p = 0.44)
Nowak[15]	Phase Ib	Cisplatin +pemetrexed + cp-870,893	CP-870,893 (max 12 total)	6.3	16.5
Nowak[16]	Single arm phase II	Cisplatin +pemetrexed +durvalumab	Durvalumab	6.9	Not reported
Calabro[17]	Single arm phase II	Tremelimimab + durvalumab	Durvalumab	5.7	16.6

BSC: Best supportive care, CP: Cisplatin –pemetrexed, CR: Cisplatin-raltitrexed, GC: Gemcitabine-cisplatin.

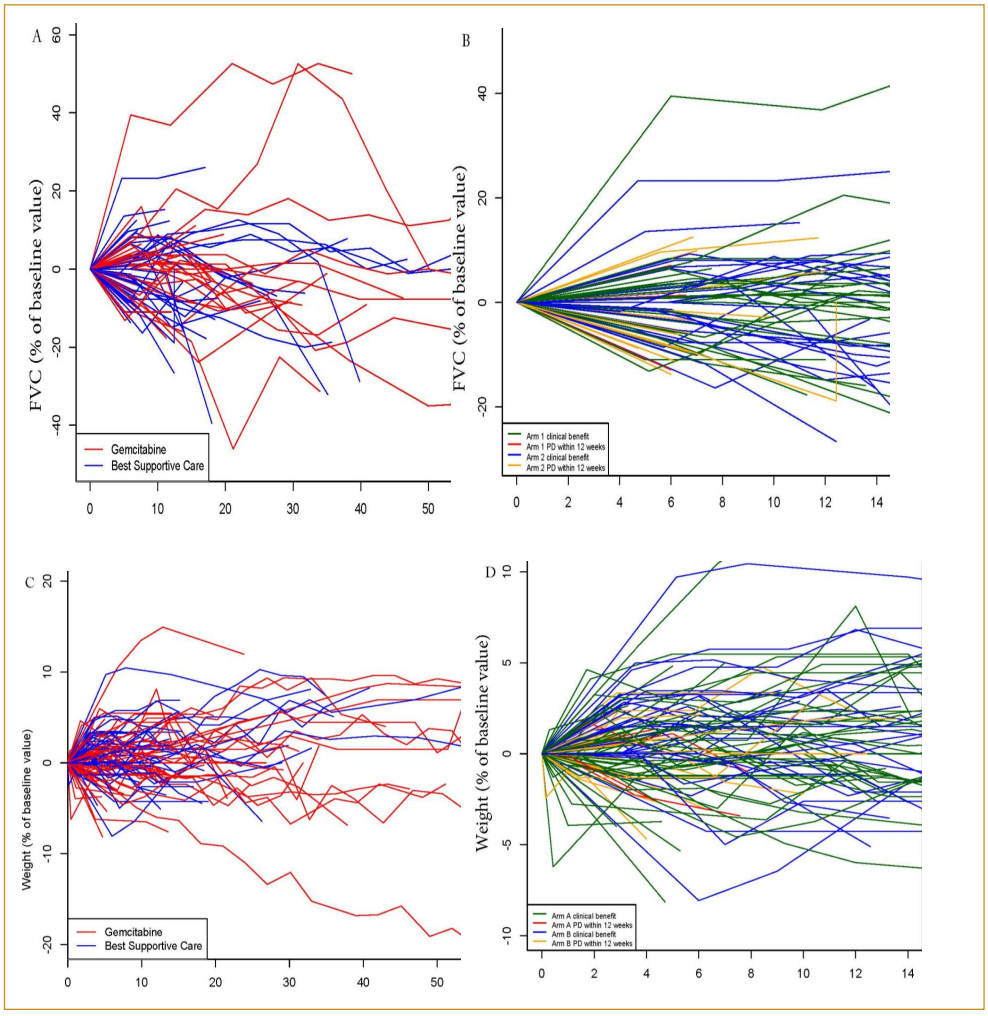

Figure S1.
Panel A shows the changes in forced vital capacity (FVC) during treatment expressed as percentage of baseline values and development over time values for each patient.

Panel B shows the changes in forced vital capacity (FVC)during treatment expressed as percentage of baseline values and development over time of the relative values for each patient. Patients groups are subsided in groups with clinical benefit (no progression (PD) within the first 12 weeks after randomization and patients with progression within the first 12 weeks after randomization.

Panel C shows the changes in weight during treatment expressed as percentage of baseline values and development over time of the relative values for each patient.

Panel D shows the changes in weight during treatment expressed as percentage of baseline values and development over time of the relative values for each patient. Patients groups are subsided in groups with clinical benefit (no progression within the first 12 weeks after randomization) and patients with progression within the first 12 weeks after randomization.

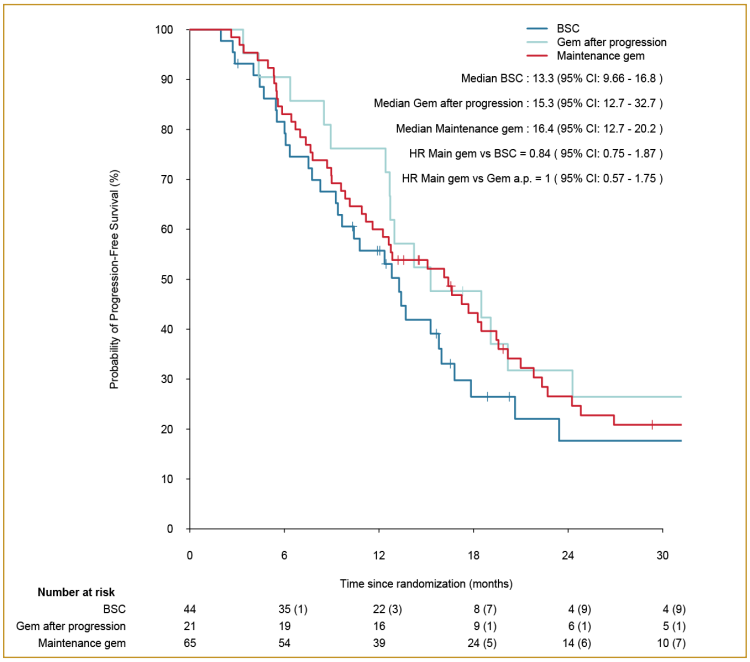

Figure S2.
Kaplan-Meijer estimation of overall survival of patients in the maintenance gemcitabine arm (Main Gem), in the maintenance BSC arm who got gemcitabine at progression (Gem a.p), and in the maintenance BSC arm who did not get gemcitabine at progression (BSC).

Table S14. Patient numbers included per center

Study Center	Number of patients
Antoni van Leeuwenhoek Hospital	52
Isala Hospital	10
Erasmus Medical Center	9
Jeroen Bosch Hospital	8
Amphia Hospital	8
Deventer Hospital	7
Maxima Medical Center	6
University Medical Center Groningen	6
Zorggroep Twente	6
Zuyderland Hospital	5
Sint Elisabeth Hospital	3
Catherina Hospital	2
Laurentius Hospital	2
Noort West Ziekenhuisgroep Alkmaar	2
Gelre Hospital	1
Groene Hart Hospital	1
Maasstad Hospital	1
Haaglanden Medical Center	1

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