Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Amrubicin in previously treated patients with malignant pleural mesothelioma: A phase II study

Takaya Ikeda[1,2], Shinnosuke Takemoto[2], Hiroaki Senju[3], Hiroshi Gyotoku[2], Hirokazu Taniguchi[2,4], Midori Shimada[2,3], Yosuke Dotsu[2], Yasuhiro Umeyama[2], Hiromi Tomono[3,5], Takeshi Kitazaki[6], Masaaki Fukuda[6], Hiroshi Soda[3], Hiroyuki Yamaguchi[2], Minoru Fukuda[2,7] & Hiroshi Mukae[2]

1 Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan
2 Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
3 Department of Respiratory Medicine, Sasebo City General Hospital, Sasebo, Japan
4 Molecular Pharmacology Program and Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA
5 Department of Medicine, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan
6 Department of Respiratory Medicine, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan
7 Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan

Keywords
Amrubicin; chemotherapy; mesothelioma.

Correspondence
Minoru Fukuda, Clinical Oncology Center, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan.
Tel: +81 95 819 7779
Fax: +81 95 819 7776
Email: mifukuda@nagasaki-u.ac.jp

Received: 10 April 2020;
Accepted: 29 April 2020.

doi: 10.1111/1759-7714.13490

Thoracic Cancer **11** (2020) 1972–1978

Abstract

Background: The aim of this study was to assess the efficacy and safety of amrubicin for previously treated malignant pleural mesothelioma.

Methods: The eligibility criteria were: previously treated unresectable malignant pleural mesothelioma; performance status 0–1; age ≤ 75; adequate hematological, hepatic, and renal function. The patients were injected with 35 mg/m^2 amrubicin on days one, two, and three every 3–4 weeks. The planned number of patients was 32.

Results: The study was terminated due to delay in enrollment and 10 patients were subsequently enrolled (nine males and one female; median age 67 [range 49–73]), of which four had epithelioid tumors, three had sarcomatoid tumors and three had biphasic tumors, respectively. According to the International Mesothelioma Interest Group (IMIG), one, four, and four patients had stage II, III, and IV, respectively, and one had postoperative recurrence. There was one (10%) partial response, four (40%) had stable disease, and five (50%) patients exhibited disease progression. The overall response and disease control rates were 10% (95% CI: 0.3–44.5%) and 60% (95% CI: 26.2–87.8%), respectively. The median progression-free survival time was 1.6 months. The median overall survival time was 6.6 months, and the one-, two-, and three-year survival rates were 23%, 23%, and 0%, respectively. The observed grade 3 or 4 toxicities included neutropenia in six (60%) patients; leukopenia in five (50%) patients; and febrile neutropenia, thrombocytopenia, anemia, and pneumonia in one (10%) patient each.

Conclusions: There was not enough data to evaluate the efficacy because the study was terminated early. However, amrubicin showed limited activity and acceptable toxicities when used in previously treated malignant pleural mesothelioma patients.

Introduction

Malignant pleural mesothelioma is a rare disease, which is almost exclusively linked to asbestos exposure. There are few effective treatments for the condition, but it has a poor prognosis (two-year survival: from 19% to 43%).[1–3] Phase III trials have shown that combination chemotherapy with

cisplatin and pemetrexed or cisplatin, pemetrexed, and bevacizumab improved the prognosis of unresectable malignant pleural mesothelioma patients in the first-line setting,[4,5] and phase II trials showed that nivolumab exhibited promising efficacy against unresectable malignant pleural mesothelioma in the second-line setting.[6,7] However, there is still no standard treatment for malignant pleural mesothelioma after the second-line, and chemotherapy with vinorelbine or gemcitabine, or enrollment in a clinical trial is recommended in some guidelines.[8]

Amrubicin (SM-5887, 9-amino-anthracycline) is a chemically synthesized anthracycline-based anticancer drug, which inhibits cell growth by stabilizing DNA-protein complexes that can be cleaved by topoisomerase II. Amrubicin also displays strong antitumor effects in tumor cells and is converted to amrubicinol, an active metabolite with a 5–220 times stronger cytostatic effect than amrubicin.[9,10] Adriamycin, another anthracycline, was one of the key drugs for treating mesothelioma prior to the development of pemetrexed, but the efficacy of amrubicin against mesothelioma has not previously been elucidated.[11,12]

Therefore, we conducted a phase II study of amrubicin therapy for malignant pleural mesothelioma. The main objectives of this study were to determine the efficacy and safety of amrubicin therapy in previously treated patients with malignant pleural mesothelioma.

Methods

Patients

The study protocol was reviewed and approved by the Nagasaki Thoracic Oncology Group (NTOG) and the ethics committee of each institution. Written informed consent was obtained from all study participants. This study was an independent collaborative (unsponsored) group study and was registered with the University Hospital Medical Information Network (UMIN) in Japan under the registration number UMIN000006381.

Patient criteria

The patient eligibility criteria for this study were as follows: having a histologically confirmed diagnosis of malignant pleural mesothelioma, having unresectable disease, having previously undergone chemotherapy, having a life expectancy of >12 weeks, having measurable lesions, being aged ≥20, having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, and having adequate organ function (leukocyte count of ≥4000/μL, platelet count of ≥10.0×10^4/μL, hemoglobin level of ≥9.0 g/dL, serum bilirubin level of ≤1.5 mg/dL, alanine transaminase and aspartate transaminase levels of ≤2 times the normal limit, and serum creatinine level of less than, or equal to, the normal upper limit). The exclusion criteria included medical problems that were severe enough to prevent compliance with the protocol, interstitial pneumonia, brain metastases that required treatment, and superior vena cava syndrome that required treatment. The International Mesothelioma Interest Group (IMIG) staging system was used.[13]

Treatment

The patients were injected with 35 mg/m^2 amrubicin on days 1, 2, and 3. The amrubicin was diluted in 50 mL normal saline and administered as an intravenous injection. Granulocyte colony-stimulating factor (G-CSF) was administered if the patient's neutrophil count fell below 1000/μL and was discontinued if the patient's neutrophil count recovered to >5000/μL. The next cycle commenced after the patient's leukocyte and platelet counts reached at least 3000/μL and 100 000/μL, respectively. If their leukocyte or platelet count fell below these limits, the next cycle was postponed until their counts had recovered. The dose of amrubicin was reduced to 75% if grade 4 hematological toxicities had occurred during the previous treatment cycle. The chemotherapy was repeated every three weeks and continued until the criteria for treatment discontinuation were met, such as progressive disease, unacceptable toxicities, or other difficulties affecting the continuation of treatment.

Toxicity and response evaluation

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Before the first cycle of chemotherapy, a blood cell count, urinalysis, and biochemistry tests were performed to assess the patients' renal and hepatic function and electrolyte levels. Radiographic imaging was performed every four weeks. These tests/examinations were repeated during the treatment. Tumor responses were classified according to the modified Response Evaluation Criteria in Solid Tumors (RECIST),[14] and confirmation was done more than six weeks. For all patients, evaluations of the objective tumor response were conducted by external reviewers.

Statistical analysis

The primary endpoint of this study was the estimated objective response rate. The secondary endpoints were safety, the progression-free survival (PFS) time, and the overall survival (OS) time. Simon's "minimax" design was

used to determine the required number of patients. Assuming an overall response rate of 5% as the threshold response rate, a target response rate of 20% was established. Based on an alpha value of 0.10 and a beta value of 0.10, the estimated required number of patients was 32. The upper limit of rejection was three responses. The Kaplan-Meier method was used to calculate PFS and OS.

Results

Between December 2009 and January 2017, a total of 10 patients from three institutions were enrolled. Although the target number of cases was 32, case registration was delayed, and enrollment for this trial was terminated. All of the enrolled patients received the planned treatment and had their treatment responses, toxicities, and survival evaluated. The patients' baseline characteristics are shown in Table 1. Their median age was 67 years (range: 49–73 years), and there were nine male patients and one female patient. Four patients had epithelioid tumors, three had sarcomatoid tumors, and three had biphasic tumors. One patient had stage II disease, four had stage III disease, and four had stage IV disease, and one had postoperative recurrent disease. The previous first-line chemotherapy regimens included pemetrexed plus cisplatin in eight patients and pemetrexed plus carboplatin in two patients, second line included pemetrexed plus carboplatin in one patient, gemcitabine in one patient, and gemcitabine plus vinorelbine in one patient, and third-line included gemcitabine plus vinorelbine in one patient. There was no patient received nivolumab before or after amrubicin therapy.

Table 1 Patient characteristics

Patient characteristics	*N* = 10
Age, years	
Median (range)	67 (49–73)
Sex	
Male	9
Female	1
ECOG PS	
0	0
1	10
Asbestos exposure	
Yes	9
No	1
Histology	
Epithelioid	4
Sarcomatoid	3
Biphasic	3
Stage (IMIG)	
I	0
II	1
III	4
IV	4
Recurrence	1
Number of prior treatments	
1	7
2	2
3	1

ECOG PS, Eastern Cooperative Oncology Group performance status; IMIG, International Mesothelioma Interest Group.

Treatment

A total of 24 cycles of amrubicin therapy were administered with a median of two cycles administered to each patient (one cycle in two [20%] patients; two cycles in four [40%] patients; three cycles in two [20%] patients; and four cycles in two [20%] patients). Among the two patients that were only administered one cycle of amrubicin therapy, the treatment was terminated because of progressive disease in one patient and because of interstitial pneumonia in the other patient. The treatment was terminated because of disease progression in the remaining patients.

Efficacy

An objective tumor response was observed in one patient, and stable disease was seen in four patients, resulting in an overall response rate of 10.0% (95% CI: 0.3–44.5%) and a disease control rate of 50.0% (95% CI: 18.7–81.3%). No complete responses were achieved, and progressive disease was observed in five patients. At the survival assessment conducted in February 2020, one patient had changed hospitals (on day 89), and the other nine patients had died. The PFS of the 10 patients is shown in Fig 1a. The median PFS time was 1.6 months. The OS of the 10 patients is shown in Fig 1b. The median OS time was 6.6 months, and the one-, two-, and three-year survival rates were 23%, 23%, and 0%, respectively. A 67-year-old male with sarcoma-type stage III (cT3N2M0) disease and a PS of one was enrolled in the present study after four cycles of first-line pemetrexed plus cisplatin. He received four cycles of amrubicin, achieved a partial response, 121 days of progression-free survival time and 262 days of overall survival time. After the protocol therapy, he did not receive chemotherapy for malignant pleural mesothelioma. The chest computed tomography (CT) images obtained before and after the amrubicin treatment are shown in Fig 2.

Toxicities

Of the 10 patients, seven (70%) experienced grade 3 or 4 hematological toxicities, and five (50%) experienced grade 4 toxicities. The principal grade 3 or 4 toxicity was

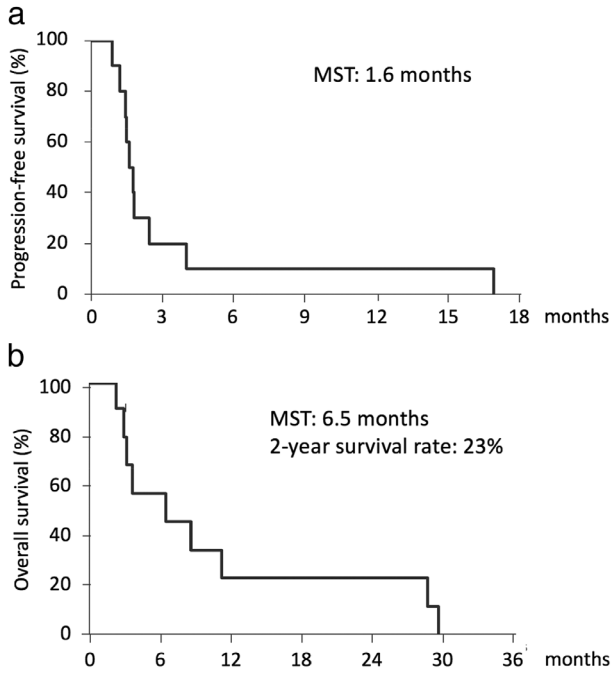

Figure 1 Kaplan-Meier curves of (**a**) progression-free survival and (**b**) overall survival for the patients (n = 10) enrolled in the present study.

neutropenia (n = 6, 60%), whereas the main grade 4 toxicity was neutropenia (n = 5, 50%). The most common nonhematological adverse events were grade 2 nausea (n = 3, 30%), grade 2 fatigue (n = 2, 20%), grade 2 appetite loss (n = 2, 20%), a grade 3 lung infection (n = 1, 10%), grade 3 pneumonitis (n = 1, 10%), and grade 2 dizziness (n = 1, 10%). There were no treatment-related deaths. The grade 3 or 4 toxicities experienced by the patients are listed in Table 2.

Discussion

In the present study, amrubicin therapy was administered to 10 previously treated patients with malignant pleural mesothelioma, which yielded one partial response and stable disease in five cases. The overall response rate was 10%, and the disease control rate was 50%. Although the number of enrolled cases was lower than planned, the present study demonstrated the limited efficacy of amrubicin therapy for previously treated malignant pleural mesothelioma, although it exhibits tolerable toxicity.

A previous study examined the use of second-line treatment for patients with malignant pleural mesothelioma that had previously participated in a phase III trial of pemetrexed plus cisplatin versus cisplatin alone.[15] The median survival time ranged from 12.2 to 15.3 months in patients that received second-line (post-study) chemotherapy, whereas it ranged from 6.8 to 9.8 months in patients that did not receive second-line treatment. Furthermore, a multiple regression analysis adjusted for baseline prognostic factors and treatment interventions revealed that second-line chemotherapy was significantly correlated with prolonged survival ($P < 0.01$). Second-line gemcitabine, vinorelbine, or pemetrexed treatment for previously treated unresectable malignant pleural mesothelioma have all been investigated in previous studies, which resulted in response rates of 7%, 16%–24%, and 19%, respectively.[16–19] Although the response rate for pemetrexed was relatively high, pemetrexed is often used as a first-line treatment in combination with platinum. As another trial in which gemcitabine was used for first-line treatment reported that there were no responders,[20] and the present study included a high proportion of patients with sarcoma-type disease, amrubicin chemotherapy seems to be a useful treatment option for malignant pleural mesothelioma.

Recently, immune checkpoint inhibitors (ICIs) have been shown to be effective against various malignancies. Nivolumab achieved response rates of 26% to 29%, disease control rates of 47% to 68%, median PFS times of 2.6 to 6.1 months, and median OS times of 11.8 to 17.3 months in 34 previously treated malignant pleural mesothelioma patients.[7,21] Based on these results, nivolumab was first approved in Japan as a treatment for unresectable advanced or recurrent malignant pleural mesothelioma that progressed after chemotherapy in August 2018. In addition, pembrolizumab and nivolumab plus ipilimumab achieved response rates of 20% to 37%[22,23] and 52%,[24] respectively. These trials of single or combination treatment with ICIs demonstrated promising results compared with amrubicin (in the present study) or other single cytotoxic agents; therefore, ICIs are now considered to be the standard second-line treatment for malignant pleural mesothelioma. Cytotoxic anticancer agents might be expected to have a greater effect against malignant pleural mesothelioma when used in combination with ICIs.

The main toxicities associated with amrubicin involve myelosuppression, with neutropenia seen more frequently than thrombocytopenia or anemia. In the present study, the incidence of grade 3 or 4 neutropenia was 60%, which is comparable to the 62% incidence rate reported for vinorelbine,[19] but higher than the incidence rates of 9% and 12% reported for pemetrexed and gemcitabine, respectively.[20,25] Careful control of hematological toxicities is essential during amrubicin treatment, and in the current study myelosuppression was manageable with protocol-specific dose reductions, treatment delays, and G-CSF support, and there were no treatment-related deaths. The most common nonhematological toxicities in the present study were nausea, fatigue, and appetite loss, which were also manageable. Pneumonitis, which is a problematic toxicity during cancer chemotherapy and has also been reported

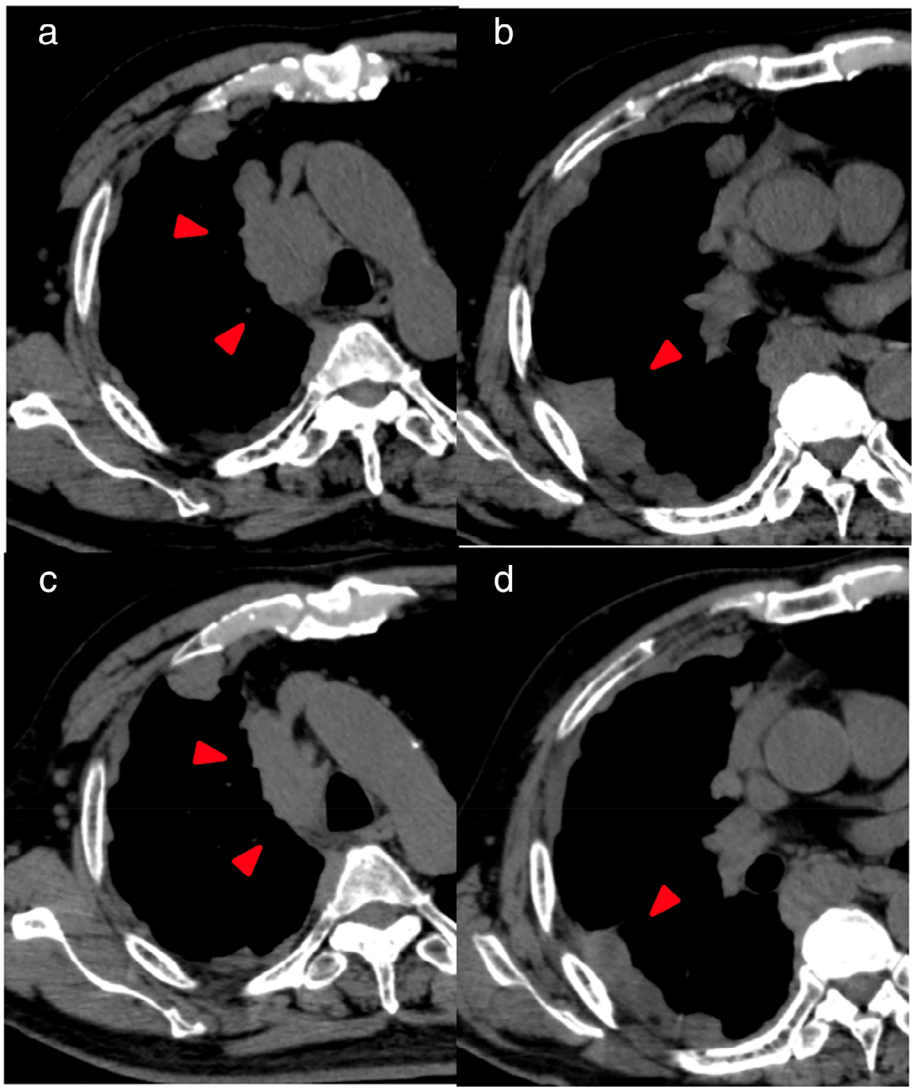

Figure 2 Images of the case in which the tumor reduced in size. Chest computed tomography (CT) scans obtained before (**a**, **b**) and after two cycles of amrubicin therapy (**c**, **d**) are shown.

Table 2 Grade 3 or 4 toxicities experienced by patients in the study

Adverse events	Grade 3/4 (%)
Hematological toxicities	
Leukocytopenia	2 (20)
Neutropenia	6 (60)
Anemia	1 (10)
Thrombocytopenia	1 (10)
Febrile neutropenia	1 (10)
Nonhematological toxicities	
Anorexia	0
Nausea/vomiting	0
Lung infection	1 (10)
Pneumonitis	1 (10)

during amrubicin treatment,[26,27] was observed in one patient (10%), who terminated the protocol therapy and was managed with corticosteroid therapy. Amrubicin at a dose of 40 mg/m^2 was initially administered in previously treated patients in the study by Onoda *et al.* It is highly myelotoxic and in their report, 83.3% of patients had neutropenia of grade 3 or higher.[28] Therefore, amrubicin is sometimes administered at a dose of 35 mg/m^2 in general practice and at this rate in the clinical trials of Igawa *et al.*[29,] and Hellyer *et al.*[30] We also adopted the dose of 35 mg/m^2 in the present study.

In conclusion, because the study was terminated early there was not enough data to evaluate the efficacy, but single-agent amrubicin exhibited limited activity and an acceptable toxicity profile when used for previously treated malignant pleural mesothelioma. Further treatment strategies for malignant pleural mesothelioma involving combinations of cytotoxic agents or ICIs are needed.

Disclosure

No authors report any conflict of interest.

References

1 Peto J, Hodgson JT, Matthews FE *et al.* Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995; **345**: 535–9.
2 Hasegawa S, Okada M, Tanaka F e a. Trimodality strategy for treating malignant pleural mesothelioma: Results of a feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy and postoperative hemithoracic radiation (Japan mesothelioma interest group 0601 trial). *Int J Clin Oncol* 2016; **21**: 523–30.
3 Borasio P, Berruti A, Bille A *et al.* Malignant pleural mesothelioma: Clinicopathologic and survival characteristics in a consecutive series of 394 patients. *Eur J Cardiothorac Surg* 2008; **33**: 307–13.
4 Vogelzang NJ, Rusthoven JJ, Symanowski J e a. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21**: 2636–44.
5 Zalcman G, Mazieres J, Margery J e a. Bevacizumab for newly diagnosed pleural mesothelioma in the mesothelioma avastin cisplatin pemetrexed study (MAPS): A randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; **387**: 1405–14.
6 Scherpereel A, Mazieres J, Greillier L e a. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): A multicenter, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol* 2019; **20**: 239–53.
7 Okada M, Kijima T, Aoe K e a. Clinical efficacy and safety of nivolumab: Results of a multicenter, open-label, single-arm, Japanese phase II study in malignant pleural mesothelioma (MERIT). *Clin Cancer Res* 2019; **25**: 5485–92.
8 Baas P, Fennell D, Kerr KM e a. Malignant pleural mesothelioma: ESMO clinical practice guide-lines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26**: v31–9.
9 Yamaoka T, Hanada M, Ichii S, Morisada S, Noguchi T, Yanagi Y. Cytotoxicity of amrubicin, a novel 9-aminoanthracycline, and its active metabolite amrubicinol on human tumor cells. *Jpn J Cancer Res* 1998; **89**: 1067–73.
10 Hanada M, Mizuno S, Fukushima A, Saito Y, Noguchi T, Yamaoka T. A new antitumor agent amrubicin induces cell growth inhibition by stabilizing topoisomerase II-DNA complex. *Jpn J Cancer Res* 1998; **89**: 1229–38.
11 Harvey VJ, Slevin ML, Ponder BA *et al.* Chemotherapy of diffuse malignant mesothelioma. Phase IItrials of single-agent 5-fluorouracil and adriamycin. *Cancer* 1984; **54**: 961–4.
12 Sorensen PG, Bach F, Bork E *et al.* Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. *Cancer Treat Rep* 1985; **69**: 1431–2.
13 Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. *Lung Cancer* 1996; **14**: 1–12.
14 Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15**: 257–60.
15 Manegold C, Symanowski J, Gatzemeier U e a. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005; **16**: 923–7.
16 Van Meerbeeck JP, Baas P, Debruyne C *et al.* A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer* 1999; **85**: 2577–82.
17 Stebbing J, Powles T, McPherson K e a. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009; **63**: 94–7.
18 Jassem J, Ramlau R, Santoro A e a. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008; **26**: 1698–704.
19 Steele JPC, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. *J Clin Oncol* 2000; **18**: 3912–7.
20 Kindler HL, Millard F, Herndon JE II *et al.* Gemcitabine for malignant mesothelioma: A phase II trial by the Cancer and Leukemia Group B. *Lung Cancer* 2001; **31**: 311–7.
21 Quispel-Janssen J, van der Noort V, de Vries JF e a. Programmed deeath 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. *J Thorac Oncol* 2018; **13**: 1569–76.
22 Alley EW, Lopez J, Santoro A e a. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): Preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017; **18**: 623–30.
23 Metaxas Y, Rivalland G, Mauti LA e a. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. *J Thorac Oncol* 2018; **13**: 1784–91.
24 Scherpereel A, Mazieres J, Greillier L e a. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): A multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol* 2019; **20**: 239–53.
25 Scagliotti GV, Shin DM, Kindler HL e a. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. *J Clin Oncol* 2003; **21**: 1556–61.
26 Ettinger DS, Jotte R, Lorigan P e a. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2598–603.

27 Taniguchi H, Yamaguchi H, Dotsu Y e a. Phase II study of nedaplatin and amrubicin as first-line treatment for advanced squamous cell lung cancer. *Thorac Cancer* 2019; **10**: 1764–9.
28 Onoda S, Masuda N, Seto T e a. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic oncology research group study 0301. *J Clin Oncol* 2006; **24**: 5448–53.
29 Igawa S, Yamamoto N, Ueda S e a. Evaluation of the recommended dose and efficacy of amrubicin as second- and third-line chemotherapy for small cell lung cancer. *J Thorac Oncol* 2007; **2**: 741–4.
30 Hellyer JA, Gubens MA, Cunanan KM e a. Phase II trial of single agent amrubicin in patients with previously treated advanced thymic malignancies. *Lung Cancer* 2019; **137**: 71–5.

