Systemic therapy in malignant mesothelioma: treat it or leave it

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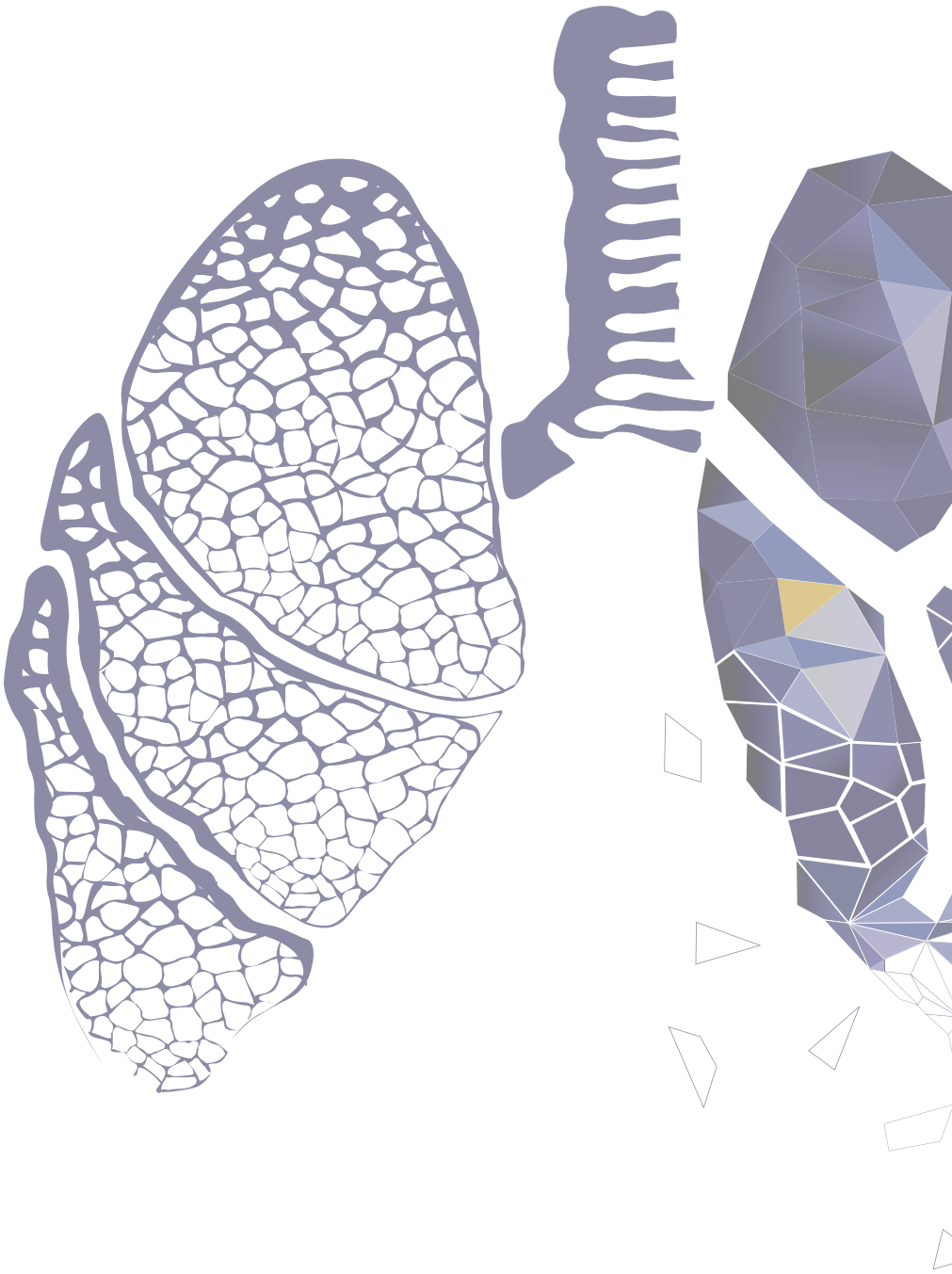

Chapter 1

General introduction to systemic therapy in malignant mesothelioma

OVERVIEW.

GENERAL BACKGROUND

Malignant mesothelioma is a rare aggressive malignancy, mostly linked to asbestos exposure, with limited treatment options. In the majority of patients malignant mesothelioma arises of the of the pleura (MPM) and more rare from the peritoneum (MpeM) and exceptionally from the pericardium or tunica vaginalis testes. In general, malignant mesothelioma can be divided into three major pathological subtypes; epithelial mesothelioma with the best prognosis, mixed- or biphasic mesothelioma, and sarcomatoid mesothelioma with the worst prognosis.[1]

Only a minority of patients with MPM is fit enough to be a surgical candidate and the indication for surgery has become stricter in the last years.[2-4] Opposite to MPM, the mainstay of treatment of malignant peritoneal mesothelioma MPeM is surgery existing of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). Eventually, the majority of patients with malignant mesothelioma is treated with palliative systemic therapy.

Chemotherapy was the backbone of systemic therapy regimes in malignant mesothelioma for over fifteen years. Although systemic therapy based on genetic stratification has revolutionised treatment in other solid tumours like lung cancer, malignant mesothelioma is far behind in targeted therapy options. Mainly because malignant mesothelioma is mostly driven by loss of tumour suppression genes like CDKN2A, NF2 and BAP1, rather than activation of oncogenes, evidence of efficacy of targeted therapy in malignant mesothelioma is lacking.[5] Immunotherapy had recently a breakthrough, improving survival in a subgroup of patients with malignant mesothelioma[6] So, chemotherapy, immunotherapy and combination therapies will be the focus of treatment in malignant mesothelioma in the next decades.

FIRST LINE THERAPY

Chemotherapy

Platinum with pemetrexed, a multitargeted antifolate which interferes with purine and pyrimidine synthesis, was the standard first line treatment in malignant mesothelioma until recently. In 2003, Vogelzang et al reported on a phase III study comparing cisplatin to cisplatin-pemetrexed in 448 treatment naïve patients. The median OS prolonged from 9.3 months in the control arm to 12 months.[1] in the cisplatin-pemetrexed arm (hazard ratio (HR) 0.77, P = .020). Also the median progression free (PFS) survival prolonged significantly in the combination arm (5.7 months versus 3.9 months; P =.001), with response rates of 41.3% in the combination arm versus 16.7% in the control arm (P <.0001).[7]

The additional value of a (multitargeted) antifolate to cisplatin monotherapy was confirmed by a phase III study in 250 treatment naïve patients with MPM, comparing cisplatin vs cisplatin-raltitrexed. The combination therapy was superior to single agent therapy with a median survival of 11.4 months in de cisplatin-raltitrexed arm vs 8.8 months for cisplatin alone, and the one-year survival was 46 versus 40 percent (p =0 .048). The median time to progression was significantly longer in the cisplatin-raltitrexed arm; 5.7 months versus 3.9 months (P = .001). The health-related quality of life was measured, and despite the toxicity of the treatment the quality of life was not affected and was equal in both treatment arms. Also, in both arms the dyspnoea improved.[8] Unfortunately, raltitrexed was barely registered in European countries for this indication.

Most patients with malignant mesothelioma are diagnosed at a high age.[9] The typical high emetic non-haematological toxicity profile of cisplatin is not optimal in this patients population. Therefore, carboplatin had been explored as option to reduce toxicity. Replacement of cisplatin by carboplatin did neither influence the PFS in patients with MPM, nor the 1-year survival (63.1% versus 64.0%) and time to progression (7 months versus 6.9 months), with an acceptable burden of toxicity.[10]

Gemcitabine, a pyrimidine antagonists, combined with a platinum compound, including cisplatin, carboplatin, and oxaliplatin have been tested in several phase II studies[11-16] Response rates for these combinations ranged from 15 to 48 percent, with acceptable levels of toxicity. Gemcitabine and pemetrexed have never been compared head-to-head, but it is generally accepted that malignant mesothelioma patients should receive pemetrexed-based therapy in the first-line setting. The combination of platinum/pemetrexed is also preferable from a logistic point of view; gemcitabine is given on day 1 and 8 of a three-week cycle and pemetrexed is given only on day 1 of a three-week cycle adds to this approach.

First line platinum-pemetrexed chemotherapy has never been compared head-to-head to best supportive care alone. In 2008 a study was reported in the UK, which compared a BSC arm with two chemotherapy strategies; a triple therapy of mitomycin, vinblastine, cisplatin and single-agent vinorelbine. Because of slow accrual, the study closed early, and data of the two chemotherapy groups were merged. A trend was reported towards better survival in the combination chemotherapy arms, even though chemotherapy schedules were used that are considered as inferior.[17]

Angiogenesis inhibition

Vascular endothelial growth factor (VEGF) signalling is an important concept in malignant mesothelioma cell pathophysiology.[18] The phase III MAPS study, the addition of bevacizumab (VEGF inhibitor) to standard of care was investigated. four hundred forty eight treatment naïve patients were randomized (1:1) to receive cisplatin-pemetrexed or cisplatin-pemetr-

exed + bevacizumab. The OS was significantly increased with the triple combination with a median 18.8 versus 16.1 months; HR 0.77, 95% CI 0.62-0.95) without compromising quality of life.[19] The PFS and OS of 7.3- and 16.1 months in the control arm were superior to the study of Vogelzang. This improvement might be related to several factors: use of rechallenge of pemetrexed, stricter inclusion criteria (like excluding patients with cardiovascular comorbidities) and the use of thoracoscopy as the diagnostic procedure which led to 90% efficient pleurodesis procedures. Efficient pleurodesis could have avoided recurring abundant pleural effusion which could impair general condition or systemic treatment administration because of progressive respiratory insufficiency.[20] Bevacizumab is used only to a limited extent in daily practice. To date, bevacizumab is not approved in malignant mesothelioma by US Food and Drug Administration (FDA) nor by the European Medicines Agency (EMA) since the MAPS study was not designed for registration purposes.[1]

A phase II study examined the additional value of bevacizumab to cisplatin-gemcitabine in patients with MPM. The study resulted in a similar response rate of 24.5% in the bevacizumab arm and 21.8% in the placebo arm. Also the median PFS and OS did not improve in the bevacizumab arm compared with the placebo arm (PFS 6.9 vs. 6.0 months, OS 15.6 vs. 14.7 months).[21] It is still not clear why bevacizumab resulted in a survival benefit in combination with cisplatinum-pemetrexed and not with cisplatin-gemcitabine.

Nintedanib is a tyrosine kinase inhibitor (TKI) which targets i.e. the VEGF receptor. In the phase II LUME-Meso trial with chemotherapy-naïve patients with MPM, PFS was higher in the combination arm (cisplatin-pemetrexed- nintedanib median 9.4 months), compared to the cisplatin-pemetrexed- placebo arm median 5.7 months. Unexpectedly, the randomized phase III LUME-Meso trial, in 542 patients could not confirm a PFS or OS benefit of nintedanib combined with platinum-pemetrexed.[22]

Further research is required to reveal the optimal combination strategy of angiogenesis inhibition in malignant mesothelioma.

Immunotherapy

In 2020, finally a new effective first line treatment regime proved to provide a survival benefit in patients with MPM: Nivolumab (anti-programmed cell death 1; PD-1)- ipilimumab (anti-cytotoxic T-lymphocyte 4 ;CTLA-4) combination therapy in the CheckMate 743 trial. This strategy significantly extended overall survival versus platinum-pemetrexed chemotherapy (mOS 18·1 months vs 14·1 months; HR 0·74 [96·6% CI 0·60–0·91]; p=0·0020) in 605 patients. In an underpowered exploratory subgroup analysis, patients with an epithelial subtype had no survival benefit, while in patients with a non-epitheloid subtype survival was vastly prolonged from median 8.8 months to 18.1 months (HR 0.46 [95% CI 0.31-0.68]).[6]

MAINTENANCE THERAPY

Unlike in other solid tumors like lung cancer, there is currently no evidence for maintenance chemotherapy in MPM. Maintenance pemetrexed is feasible, but studies showing a PFS- or survival benefit are lacking.[23] The CALGB 30901 trial randomized 53 MPM patients 1:1 to observation or continuation of pemetrexed until progression after first line therapy. In this trial, maintenance pemetrexed did improve neither PFS nor OS.[24] Single center experiences with maintenance pemetrexed without progression on carboplatin- pemetrexed induction or pemetrexed monotherapy have been described.

The previously mentioned studies with cisplatin-pemetrexed with bevacizumab provide the first evidence for maintenance therapy with an anti-VEGF agent. Thalidomide (a well-known antiangiogenic agent), was tested in a large phase III study, randomizing patients to

maintenance thalidomide or BSC. Unfortunately, no improvement was observed in progression free survival (3.6 months active agent arm vs 3.0 in the BSC arm).[25] The combination strategy of nivolumab- ipilimumab provided evidence for maintenance immunotherapy, as patients were treated until progression in the experimental arm of the CheckMate 743 trial.[6]

SECOND LINE THERAPY

Chemotherapy

No standard second line treatment is registered in malignant mesothelioma. The NCCN guidelines recommends consideration of re-challenge of pemetrexed if there was a good sustaining response at the time of initial chemotherapy interruption. Other options like vinorelbine or gemcitabine could be considered.[2] The additional value of pemetrexed in second line is doubtful. In a phase III study in 243 previously treated MM patients (excluding pemetrexed) were randomized to BSC or pemetrexed. Pemetrexed prolonged the progression free survival (3.6 months vs 1.5 months, p=0.0148), although there was no effect on the primary endpoint OS (pemetrexed 8.4 vs 9.7 in the BSC arm, p=0.7434). The authors suggested that this was due to the imbalance in post study therapies. Patients in the BSC arm were allowed to receive chemotherapy after discontinuation of the study. The percentage of BSC patients who received pemetrexed after discontinuation of study treatment was also much higher (18.3% v 3.3%, respectively; P = .0001). Furthermore, BSC patients received chemotherapy, after discontinuation of the study, significantly earlier than P+BSC patients (median time to initiation, 4.3 v 15.7 months,respectively; log-rank P < .0001).[26]

Immunotherapy

Several PD-(L)1 inhibitors have been tested in patients with progressive disease after first line chemotherapy. The KEYNOTE-028 phase I trial was the first study testing a PD-1 inhibitor (pembrolizumab) in 25 patients with a PD-L1 immunohistochemistry expression (IHC) ≥1%. The trial reported a response rate of 20%, a disease control rate (DCR) of 72% with a median duration of response of 12 months.[29] Desai et al reported similar results in 65 patients treated with pembrolizumab, in a unselected patient population.[30] The response rate was 19%, a DCR of 47% and with a median progression free survival of 4.5 months (95% CI 2.3, 6.2). Metaxas et al. reported the efficacy of this checkpoint inhibitor using real world data. In 93 patients, they observed an objective response rate (ORR) of 18%. However, the mPFS was only 3.1 months with an OS of 7.2 months.[31]

Single agent nivolumab has been tested in 2 single arm phase II trials and in the MAPS2 trial, a randomized, non-comparative phase II study of nivolumab and nivolumab-ipilimumab. All three studies showed activity with an ORR between 15-29% and a DCR between 44 and 68%.[32-34] Although in one of the phase II trials (NivoMes) the objective response was 24% and the mPFS was only 2.6 months.[32] The second study that tested nivolumab monotherapy (MERIT) showed a higher mPFS of 6.1 months.[33] In the combination study of the MAPS-2, the nivolumab monotherapy reported a mPFS of 4.0 months.[34] The study with avelumab, a PD-L1 blocker, showed less efficacy with a response rate of 9.4% in 53 patients and a mPFS of 3.9 months.[35]

The first comparative randomized study in patients with recurrent MPM was the PROMISE-meso trial in which patients were randomized to chemotherapy (gemcitabine or vinorelbine) versus pembrolizumab. The primary endpoint, PFS, was not met. The median PFS in the pembrolizumab arm was 2.5 months (95% CI 2.1-4.2) vs 3.4 months (2.2-4.3) in the chemo arm, HR=1.06 [.73–1.53], p=0.76. Surprisingly, the response rate was significantly

higher in the pembrolizumab arm (22%) compared to chemotherapy (6%; p=0.004), despite an equal PFS. The median OS was 10.7 months for patients in the pembrolizumab arm versus 11.7 months for chemotherapy, HR=1.05 ([0.66-1.67]; p=0.85). Forty-five patients out of the chemotherapy arm crossed over to pembrolizumab after progression on chemotherapy. Accounting for crossover yielded a similar OS result. Treatment-related adverse events were similar in both groups. (TrAE) grade ≥3 were experienced by 19% in the pembrolizumab arm versus 24% chemotherapy arm.[36]

The CONFIRM trial in UK was recently presented at the WCLC 2021. Three hundred twenty-three patients with progression after at least 2 treatment lines were randomized to 12 months treatment with nivolumab or placebo.[37] The randomization was 2:1. The primary endpoint of OS in the nivolumab arm was 9.2 months versus 6.6 months (HR 0.72 95% CI 0.55-0.94). Grade 3-4 treatment-related adverse events were reported in 19% of patients who received nivolumab and in 6.3% who received placebo. These trials confirm evidence of the potential benefit of the use of PD-1 blocking in the treatment of relapsed mesothelioma.[38]

Combination immunotherapy

The non-comparative MAPS-II trial, randomizing patients between nivolumab alone or nivolumab with ipilimumab showed clinical activity in both arms with a DCR of 40% and 52%, an ORR of 19% vs 28% and mPFS of 4.0 and 5.6, months respectively. The combination group had a slightly higher proportion of drug-related adverse events (93% with combination vs 89% with monotherapy) and 3 toxicity-related deaths (vs none in the monotherapy group). The French investigators concluded that nivolumab monotherapy with or without ipilimumab provided a clinically meaningful response.[34] Updated results showed a median OS of 11.9 months (6.7-17.4) in the nivolumab arm and 15.9 months (10.7-22.2) in the combination arm.The occurrence of hyper progression disease (HPD) was assessed by two formulae; Tumor Growth Rate (TGR) and Tumor Growth Kinetics (TGK). The TGK definition of HPD did impact OS after pooling data from both treatment arms. There was no significant correlation of HPD defined by TGR and OS.[39]

Clinical activity of the combination ipilimumab-nivolumab was also seen in the Dutch INITIATE trial with a response rate of 38% and a DCR of 68% at three months. The mPFS was 6.2 months (6.4-NR) and the mOS was NR (12.7- NR) with a 64% OS at 1-year. However, the combination treatment was more toxic with 94% of patients experiencing an adverse event (Grade 3 was 35% and grade 4 was 3% gGT increase). Most side effects were easily managed and no grade 5 toxicity was observed.[40]

Tremelimumab, another CTLA-4 blocker was also tested with a PD-L1 blocker (durvalumab) in 40 patients (in first and second line) in the NIBIT trial. The ORR of 28% was comparable to the MAPS-2 trial with a DCR of 65%, a median PFS of 8.0 months and an OS of 16.6 months.[41] The combination of PD-1 blocking and chemotherapy is an effective first line treatment in NSCLC. The first results of combining durvalumab (PD-L1 blocking) with cisplatin-pemetrexed in the first line are hopeful. In the Australian DREAM study, a single arm phase II in 54 first line patients reported an ORR of 48% by mRECIST but a mPFS of 6.9 months only. The PFS at 6 months (PFS6) was 57% (90% CI 45-68%).[42] An international world-wide phase III randomized study with this combination is planned, led by the USA and Australia.

BIOMARKERS

To be able to distinguish between patients with and without benefit from immunothera-

py, better biomarkers are urgently needed. Similar to NSCLC, melanoma and other cancers, biomarkers to predict the response (or toxicity) to treatment in patients, are a crucial issue. In MPM, PD-L1 is expressed in 40-60% of the tumors, mostly in patients with sarcomatoid histology. PD-L1 expression is a negative prognostic factor for overall response to standard care but not for PFS or OS. In a retrospective study, the PD-L1 positive patients exhibited a mOS of 5 months, while median survival in PD-L1 negative patients was 14.5 months[43], while other studies and trials results had discrepancies on this finding.[44]

In several studies, PD-L1 expression was correlated with response to PD-L1 inhibitors, with or without CTLA-4 inhibitors. In the PD(L)-1 monotherapy studies responses to PD-L1 >1% varied between 19 to 44%.[30-33,35] Generally, PD-L1 negative tumors showed responses up to 10%, with only one study reporting an ORR of 56%; although in a small group of 9 patients.[32] In the studies combining PD-(L)1 inhibitors with CTLA-4 inhibitors, a correlation between response and PD-L1 positive expression on tumors was found. In these studies PDL-1 > 1% showed a response rate of 23 to 73%.36,40,42 Patients with PD-L1 negative tumors showed an ORR of 27 to 33%. Interestingly, the study of Scherpereel et al[34] showed that the PD-L1 negative tumors had a similar response compared to the PD-L1 positive tumors to the combination therapy. In a subgroup analyses of the CheckMate 743 trial, patients with a PD-L1 status <1% did not benefit of ipilimumab-nivolumab in contrast to patients with a PD-L1 status ≥ 1% (HR 0.69 [95% CI 0.55-0.87]). [6]

PD-L1 immunohistochemistry (IHC) might not to be a very reliable biomarker as in multiple studies a relatively low number of CD8+ tumor infiltrating lymphocytes (TIL) in MPM.[45,46] MPM is also known to have an increased suppressive immune environment, with a high amount of CD4+, FOXP3 and CD25+RO+ TILs. Marcq et al showed in MPM with low numbers of CD8+TILs, that their function was either moderately or severely suppressed.[47] A high number of CD8+TILs on the other hand correlates with more tumor cell apoptosis, lower N-stage and higher overall survival.[46,48,49] Higher numbers of PD-L1+CD8+TIL were found in sarcomatoid subtypes47, which might explain the slightly better results in PD-(L)1 checkpoint inhibitor therapy. High CD8+TILs is a prognostic biomarker[49], it is not clear if this can also be used as a predictive biomarker in checkpoint inhibitors. CTLA-4 is expressed in a little more than half of the MPM tissues. In the study of Roncella et al., CTLA-4 expression was measured in tissue, serum and pleural effusion of 45 patients. CTLA-4 expression seems a favorable prognostic factor, but this was only statistically significant in pleural fluid with a dead-rate reduction of 60% when a cut-off at 67 pg/ml soluble CTLA-4 was applied. Whether a positive finding of CTLA-4 expression in MPM will have therapeutic implications has not been investigated yet.[50]

In NSCLC, tumor mutational burden (TMB) is a suggested biomarker to predict the efficacy in immunotherapy, in particular for the ipilimumab-nivolumab combination. As MPM harbors a low average TMB[51], this is thought to be of little prognostic use. One of the newer findings indicate that chromothripsis and chromoplexy; which is chromosome scattering followed by random chromosome rearrangement, occurs more often in MPM and cannot be identified with whole genome sequencing. It is believed that the large parts of spliced DNA will accumulate in the cytoplasm and give rise to neoantigens.[52] Other factors that might correlate with response to checkpoint inhibitors such as HLA class I phenotype, foregut microbiome composition are investigated but no results were reported yet.[53]

In conclusion, immunotherapy brings hope for a selected group of MPM patients but several crucial questions remain unanswered to date. In addition, there is an urgent need for biomarkers to select the optimal candidates for immunotherapy among MPM patients in terms of efficacy and tolerance.

THESIS OUTLINE

Chapter **1** provides an overview of systemic treatment options in malignant mesothelioma, both as single agent therapy or as combination therapy strategy in first- and later line setting.

PART I of this thesis focuses on chemotherapy treatment malignant mesothelioma. **Chapter 2** focuses on chemotherapy strategies in malignant pleural mesothelioma until March 2018. **Chapter 3** presents the NVALT19 trial, a Dutch multicentre randomized trial in which patients with malignant mesothelioma which examined the additional value of switch-maintenance gemcitabine after platinum-pemetrexed chemotherapy. The study confirmed the activity of gemcitabine in treating malignant mesothelioma. As malignant peritoneal mesothelioma is even more rare than malignant pleural mesothelioma no prospective phase II or III clinical trials of systemic therapy regimen have been conducted. **Chapter 4** describes trends in the clinical treatment decision making in malignant peritoneal mesothelioma and focusses on the outcomes of patients in relation to centralization of care.

In PART II the challenges of immunotherapy in malignant mesothelioma are described. **Chapter 5** immerses on immunotherapy and (potential) biomarkers in malignant mesothelioma. No second line treatment is registered for patients with recurrence malignant mesothelioma. Although several small single arm phase II trials showed promising results of PD(L)-1 blocking in malignant pleural mesothelioma, a randomized phase II trial showed no superiority of pembrolizumab compared to chemotherapy. **Chapter 6** sets the results of a retrospective study of pembrolizumab in real-world setting in the light of previous studies in malignant mesothelioma. **Chapter 7** reports the clinical outcomes, and potential predictive factors of second and later line nivolumab in patients with malignant mesothelioma treated outside a study setting.

PART III focusses on predictive and prognostic factors in patients with malignant mesothelioma who start a systemic treatment. **Chapter 8** presents an additional analyses in the NVALT19 in which we examined the predictive- and prognostic value of CYFRA 21-1 in patients treated with gemcitabine. **Chapter 9** reports subgroup analyses of the NVALT19 showing a widespread effects on circulating immune cells of gemcitabine in patients with malignant mesothelioma which were correlated with (progression free) survival and provides guidance for potential combination therapy in malignant mesothelioma. **Chapter 10** presents a clinical prediction model for the prognosis of individual malignant mesothelioma patients at the start of a new systemic treatment.

Finally, PART IV with **Chapter 11** discusses the results obtained in this thesis and provides suggestions for future research projects.

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