Systemic therapy in malignant mesothelioma: treat it or leave it

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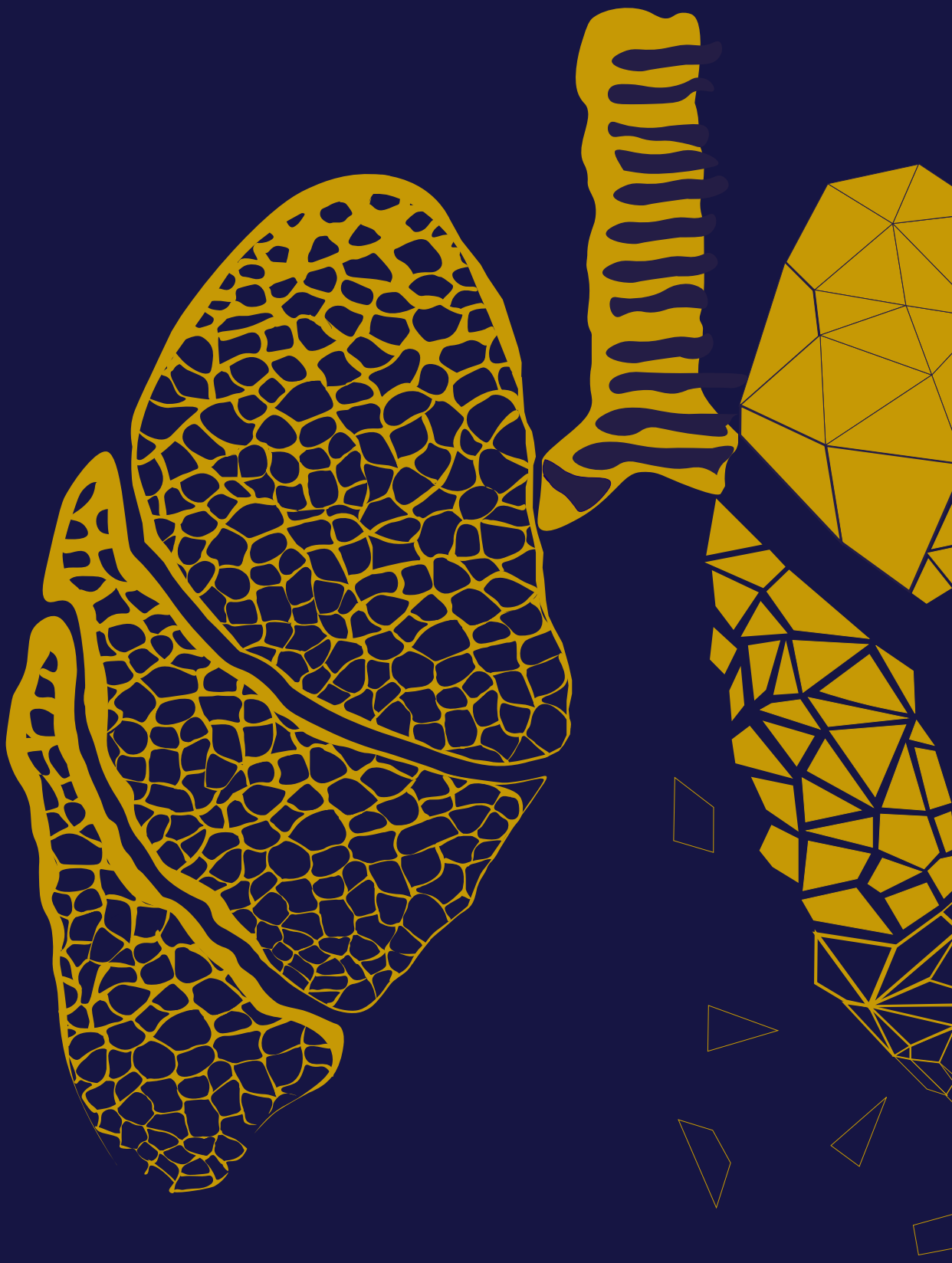
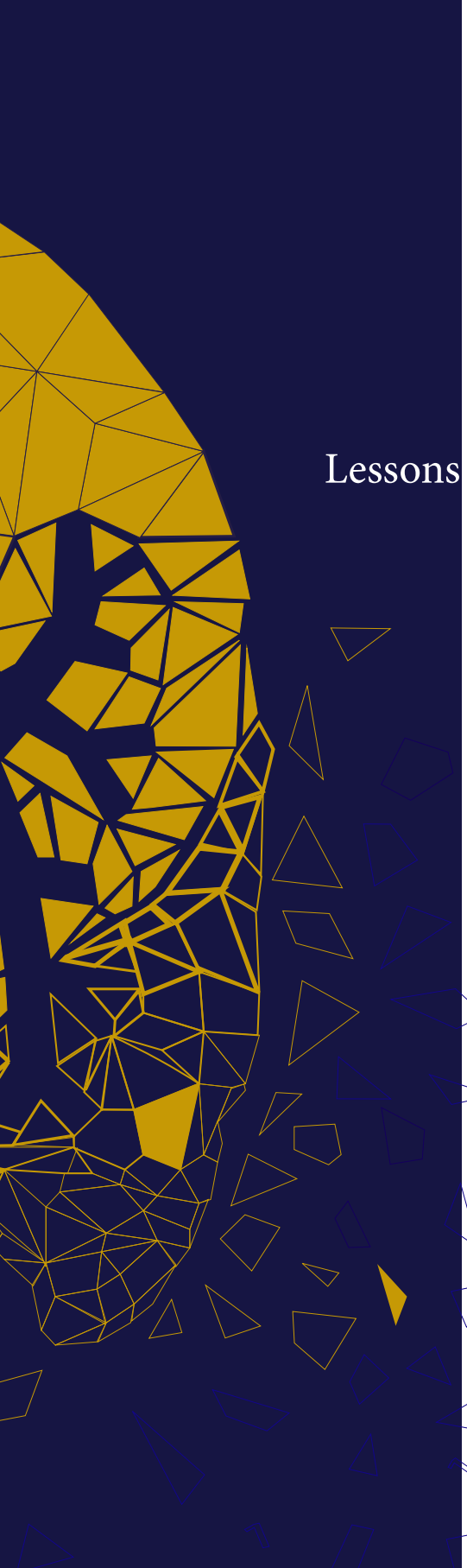
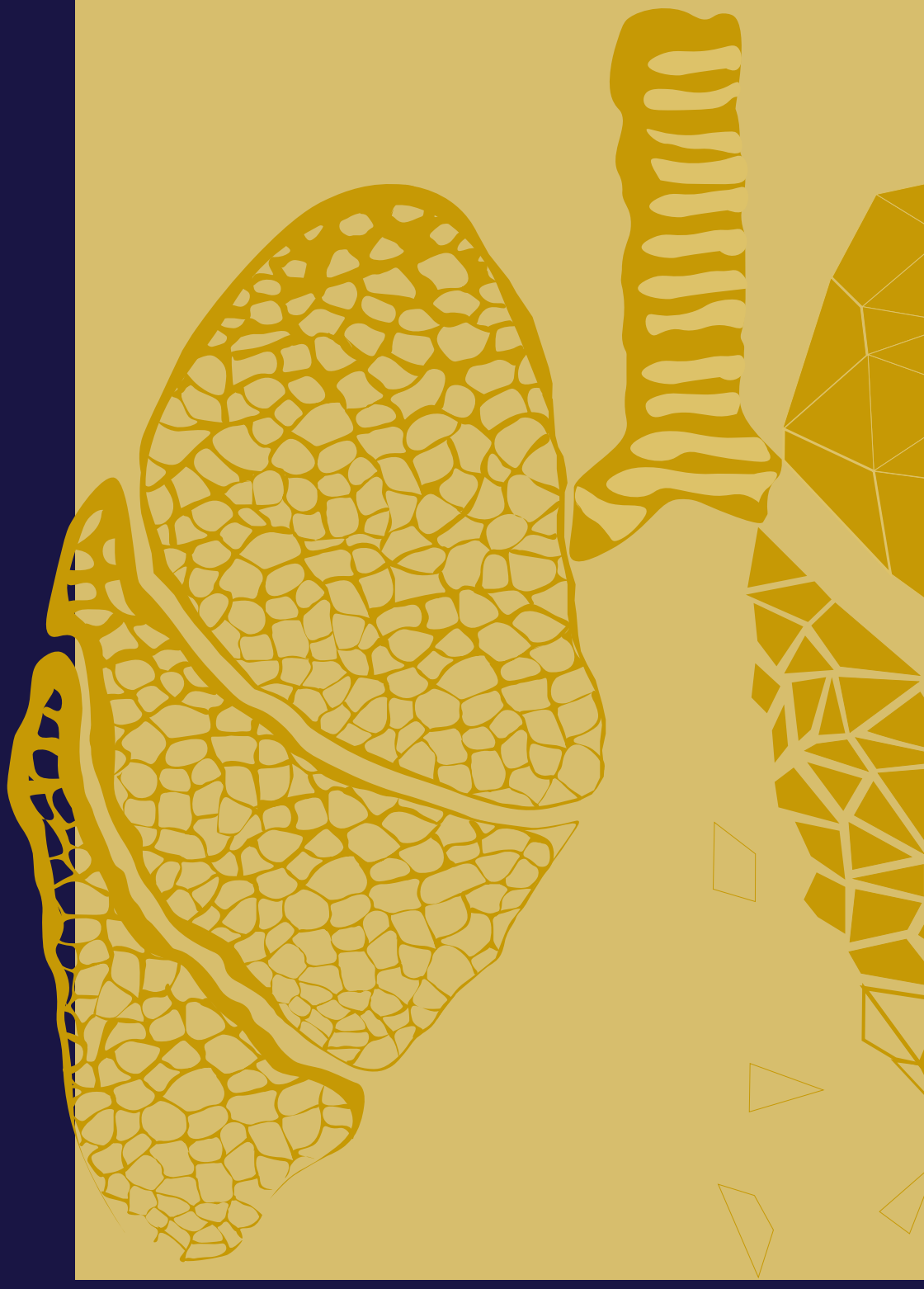




PART IV

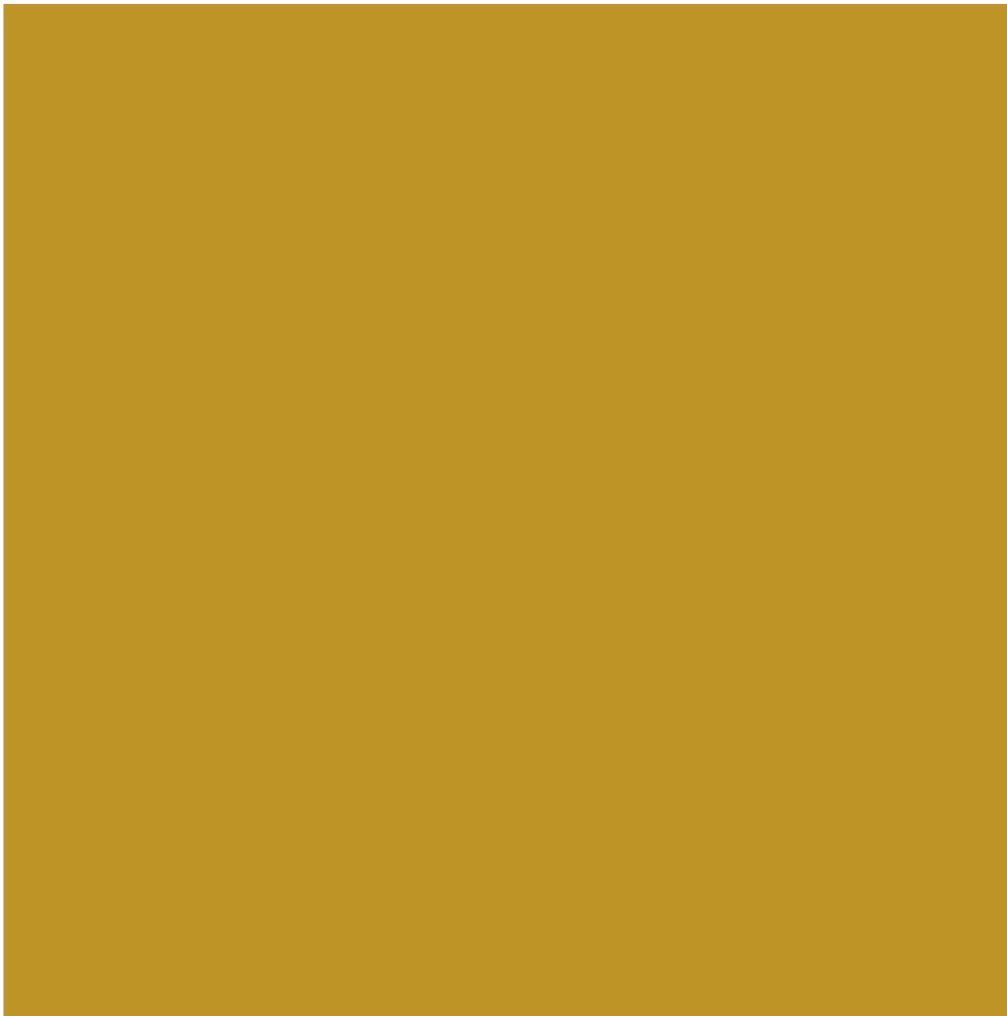
Lessons Learned



Chapter 11

General Discussion & Future Perspective

GENERAL DISCUSSION & FUTURE PERSPECTIVE.



WHERE WE WERE AT THE START

When this thesis started in 2017, platinum-pemetrexed was the only registered systemic treatment option in malignant mesothelioma. Angiogenesis inhibition, by adding bevacizumab, provided a small overall survival befit, but is barely used in daily clinical practice, as this is not registered for malignant mesothelioma.[1,2] Nintedanib, a tyrosine kinase inhibitor which also targets angiogenesis pathways, combined with platinum-pemetrexed was promising in a randomized phase II trial.[3] Hopes were therefore put up for immunotherapy, as promising results were shown in small single arm phase II trials.[4-6]

Milestones during the ride

The landscape of systemic therapy in malignant mesothelioma was finally changing in the last four years, although not as expected. The overall survival benefit of combining nintedanib with platinum- pemetrexed chemotherapy could not be confirmed in a large randomized phase III trial.[7] The promising implementation of immunotherapy was more difficult than expected with randomized studies reporting no (progression) free survival benefit of single agent PD-L1 blockers compared to chemotherapy.[8] However, in a large international phase III study, the combination of nivolumab-ipilimumab was superior to platinum- pemetrexed in the first line setting. As the overall survival is still limited to 18 months, research for this aggressive tumor needs to- and will go on.[9]

GEMCITABINE IN MALIGNANT MESOTHELIOMA

Gemcitabine, although not registered for malignant mesothelioma, has been extensively used for this indication. The use of gemcitabine in daily clinical practice was mainly based on small phase 2 studies, in which gemcitabine was tested as single agent or combined with a platinum compound. The response rates of this combination strategy ranged between 15 to 48 percent.[10-16] However the pemetrexed-containing combination is never compared to a gemcitabine-containing combination, and therefore, pemetrexed-platinum combination became the standard based on the phase III trial by Vogelzang at al.[2]

In this thesis, we showed that gemcitabine is an active treatment in malignant mesothelioma (**chapter 3**). The NVALT19 trial randomized 130 patients 1:1 to either switch maintenance gemcitabine or best supportive care after first line platinum-pemetrexed chemotherapy. We showed a progression free survival benefit of 3 months (hazard ratio of 0.48; 95% CI 0·33–0·71; p=0·0002). Therefore, the NVALT19 was the first randomized trial in malignant mesothelioma which confirmed the activity of gemcitabine in malignant mesothelioma.[17]

Although the effectivity of gemcitabine has never been reported in second line setting, it recently served as a control arm in two randomized studies. The RAMAS trial, in which patients with recurrent malignant mesothelioma were randomized to either gemcitabine or gemcitabine plus ramucirumab, reported an overall survival benefit of 6.3 months in the combination arm (median OS 7.5 months vs. 13.8 months, HR 0.71 (70% CI 0.59-0.85, p = 0.057).[18] In the PROMISE-Meso trial, patients were randomized to either pembrolizumab or chemotherapy (vinorelbine or gemcitabine). Both PFS (7.2 months vs 6.8 months, HR =1.00) and OS (10.7 months vs. 12.4 , HR= 1.12 did not differ between the two arms.[19]

As the landscape of systemic therapy in malignant mesothelioma is rapidly changing with immunotherapy as the new standard therapy, it is hard to determine the place of gemcitabine. The NVALT19 trial was originally designed to find evidence of activity of switch maintenance gemcitabine in malignant mesothelioma, before initiating a large randomized phase III trial which would require possibly over 600 to 700 patients for detecting a realistic overall survival benefit. Taking into account that first line treatment probably will switch to immunotherapy shortly, the intended phase III trial will not be initiated.[17] Interestingly, our study revealed a potential synergetic effect between gemcitabine and immunotherapy. The future will show whether combination of gemcitabine with other agents from this group will be successful.

Biomarkers of gemcitabine

The convincing progression free survival benefit of switch maintenance gemcitabine did not translate in an overall survival benefit. Understanding the lack of a survival benefit and to better predict who will benefit from this treatment is the next step forward.[17]

The ultimate goal in biomarker research is to select the right patients for the right treatment. A prognostic biomarker is a clinical or biological characteristic of the patients that comprehends information about the patient's prognosis, independently of treatment. In contrast to a predictive biomarker which indicates the likely benefit to the patient from a treatment. Conversely, most biomarkers are to some degree both of predictive- and prognostic value. To distinguish between the two types of biomarkers a control arm is needed.

Gemcitabine has been extensively used in solid tumors. Nevertheless robust and va-

lidated predictive biomarkers for response to gemcitabine are lacking. Half of the patient population in the NVALT19 trial did receive best supportive care alone, which gave us the opportunity for translational research for both predictive- and prognostic biomarkers. CYFRA 21-1, a fragment of cytokeratin 19 (CK 19), previously showed to be of prognostic value in malignant mesothelioma.[20,21] Combined with evidence of CYFRA 21-1 as on treatment predictive biomarker in both NSCLC and pancreatic cancer, this provided the rational for our study of its prognostic- and potential predictive value in patients with malignant mesothelioma treated with gemcitabine (**chapter 8**).[22-25] The prognostic value of CYFRA 21-1 was confirmed in a post-hoc analysis of the NVALT19 trial. The overall survival of patients with a CYFRA 21-1 below the reference value (serum levels of 1·9 µg/l) was 19.1 months versus 12.3 months for patient with a CYFRA 21-1 baseline level above the reference value (HR for death 2·28 (95% CI: 1·11- 3·66; stratified for response to first line therapy and pathological subtype). In addition, CYFRA 21-1 might have a predictive value in patients treated with gemcitabine. Patients with a CYFRA 21.1 baseline value <1·9 µg/l tended to have a survival benefit of maintenance gemcitabine in contrast to patients with baseline CYFRA value above 1·9 µg/l, who did not.

One could argue about the explanation how CYFRA 21-1 could have both a prognostic and predictive value in malignant mesothelioma. As CYFRA 21-1 is a protein and part of intermediate filament proteins necessary for stability of epithelial cells, its prognostic value might be mainly a reflection of tumor burden. Correspondingly, the prognostic value of CYFRA 21-1 may be due to cell lysis, releasing cell contents to the blood, by the action of proteases that degrade the cytokeratin filaments.[26] So, the potential predictive value for (progression free) survival in patients with malignant mesothelioma treated with gemcitabine might be a reflection of a subgroup of patients with a tumor type (independently of pathological subtype) of which gemcitabine can inhibit tumor growth. Moreover, it could be that the predictive value of CYFRA 21-1 is not specific for gemcitabine. In other solid tumors, the on treatment reduction of CYFRA 21-1 as early biomarker of response is seen in patients treated with different kinds of cytostatics. Future research in malignant mesothelioma could confirm the predictive value CYFRA 21-1 for revealing a subtype, which is more sensitive to treatment.

Studies showing an immune-modulating effect of gemcitabine from chemotherapy follow in rapid succession. The reduction of myeloid-derived suppressor cells (MDSCs) and T-regulatory (Treg) cells in humans and preclinical tumour models by gemcitabine was described before. The effect of gemcitabine on T- and NK-cell phenotype and proliferation in patients however was limited. More insight in how gemcitabine modulated the immune system might be obtained by (on treatment) biomarker research and might provide a rationale for combination treatment strategies in malignant mesothelioma (**chapter 9**). Gemcitabine treatment was associated with an anti- to pro-inflammatory shift in circulating immune cell phenotype in a pre-defined subgroup of patients of the NVALT19 trial. Gemcitabine significantly depleted MDSC and regulatory T-cell proliferation. The magnitude of MDSC-reduction significantly correlated with CD4+ T-helper and CD8+ T-cell but not NK-cell proliferation. Exploratory analyses revealed several immunological parameters, like in increase in NK-cell and- PD-1 + T-cell proliferation after 3 weeks of treatment, correlating with improved clinical outcome. These pilot data, if validated in larger prospective cohorts, may provide a platform for future development of on-treatment biomarkers that predict improved patient outcome. In addition, it provides a rational to combine gemcitabine with antagonistic and agonistic antibodies. [27]

IMMUNOTHERAPY IN MALIGNANT MESOTHELIOMA

Embarking on malignant mesothelioma research, one should be prepared for deceptions. Where in other solid tumors new (immune) treatment regimens are rapidly succeeding, the treatment of malignant mesothelioma remained the same for more than 15 years. The first large randomized phase III trial with immunotherapy was the DETERMINE trial. Patients were 2:1 randomized the tremelimumab (a CTLA-4 inhibitor) or best supportive care. Neither a PFS- nor a OS benefit was seen of tremelimumab, although the two previous small phase II trials with tremelimumab showed preliminary evidence of activity in malignant mesothelioma.[28-30]

In 2015, the preliminary results of a cohort of patients with malignant mesothelioma in the phase I KEYNOTE-028 were published. This provided the first evidence of activity of single-agent PD-1 blocking in the second-line and beyond. In the following years, small phase II trials with single agent PD-(L) 1 blockade reported response rates of 10-29%, with a median PFS of 2.6-6.1 months.[5,31-33] The real world data of the activity of pembrolizumab in malignant mesothelioma were disappointing with a progression free survival of only 3.1 months, comparable to the placebo arm of the previous DETERMINE trial (2.8 months respectively), as presented in **chapter 5**. However, nivolumab proved to be superior to placebo in the CONFIRM trial in UK.[34] 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). These trials confirm evidence of the potential benefit of the use of PD-1 blocking in the treatment of relapsed mesothelioma.[35] Finally, when pembrolizumab was compared directly to chemotherapy (gemcitabine or vinorelbine) again immunotherapy provided neither a PFS- nor an OS benefit. Remarkably, the number of responses was significantly higher in the pembrolizumab arm compared to the chemotherapy arm (22% vs. 6% respectively, p=0.004). Interestingly, in the phase II- and III studies, a small subgroup of patients had a clinical benefit of single agent PD-1 blocking with responses up to 28.6+ months.[36]

To explore potential biomarkers for clinical benefit of single agent PD-1 blocking we performed a retrospective cohort study of patients with malignant mesothelioma who were treated with nivolumab in the Netherlands, as part of an expanded access program (**chapter 7**). In line with the previous real-world data of pembrolizumab, the response rate in our cohort was 10%, with a median of PFS of 2.3 months (95% CI: 1.6–2.9) and median OS (mOS) of 6.7 months (95% CI: 6.2–10.0). Although PD-L1 status was only available in 33 patients (30%), PD-L1 positivity (≥1%) was associated with an improved ORR (36% vs. 9%, P value 0.05), but not with PFS or OS. Remarkably, the PFS and OS did not differ between patients with an epit-

helioid and a non-epithelioid histology. Out of seventeen clinical candidate predictors, only low albumin was associated with worse OS (P value 0.002).

The first line treatment of patient with malignant mesothelioma will evolve based on the CheckMate 743 trial, in which nivolumab- ipilimumab combination was superior to platinum-pemetrexed (mOS 18·1 months vs 14·1 months; HR 0·74 [96·6% CI 0·60–0·91]; p=0·0020) in 605 patients. More patients in the immunotherapy combination arm had to stop treatment due to side effects (23% of patients) compared to the chemotherapy arm (16%). Any-grade serious treatment-related adverse events were reported in 64 (21%) patients in the immunotherapy combination arm versus 22 (8%) patients treated with chemotherapy. However, after treatment-related adverse events were adjusted for exposure, the overall incidence of treatment-related adverse events was lower with nivolumab plus ipilimumab combination therapy than with chemotherapy.[9]

As stated before, although the response rate of immunotherapy in the later line setting was higher compared to chemotherapy this did not translate in a (progression) free survival benefit.[35] In contrast to CheckMate 743, in which the response rate of chemotherapy was comparable to immunotherapy (43- vs 40% respectively) but with an overall survival benefit of immunotherapy. Also the duration of response in confirmed responders was longer in patients treated with combination immunotherapy compared to chemotherapy (11.0 months vs 6.7 months).[19] This underlines an important problem in patient with malignant mesothelioma: radiological measurement of the tumor is poorly correlated to overall survival. Overall survival might be the most objective and reliable endpoint for trials in malignant mesothelioma. However, (no) cross-over between treatment- arm after progression complicates the interpretation of an overall survival benefit.

In an exploratory subgroup analysis, patients with an epithelial subtype had no significant survival benefit (HR 0.86; 95% CI: 0.69–1.08) of nivolumab-ipilimumab compared to chemotherapy, while in patients with a non-epithelioid subtype survival was vastly prolonged from median 8.8 months to 18.1 months (HR 0.46; 95% CI 0.31-0.68).[9] The value of PD-L1 expression as biomarker for response to immunotherapy in malignant mesothelioma could also not be establish in the CheckMate 743 trial. Overall survival of nivolumab-ipilimumab- arm was similar in the subgroups with less than 1% and with 1% or higher PD-L1. In contrast to the chemotherapy arm, in which survival was better in patients with tumor PD-L1 expression of less than 1% than those with expression of 1% or higher. [9] This indicates PD-L1 that absence of PD-L1 expression might be indicative of better prognosis with chemotherapy.

PROGNOSIS IN MALIGNANT MESOTHELIOMA

As long reliable predictive biomarkers for systemic therapy in malignant mesothelioma have not been identified, the physician and the patient have to discuss when to start a systemic treatment, since the prognosis of individual malignant mesothelioma patients is variable and hard to predict.[37-39] The EORTC model was the most commonly used clinical prediction model (CPM). Its usefulness for individual survival estimation is however limited and only used in studies to stratify risk groups[37,40]. To optimized survival prediction of individual patients with malignant mesothelioma who are about to start a systemic therapy, we developed the MESOPRO score (**Chapter 10**). The score was based on a combination gender, location of the tumour, the pathological subtype, the performance status, CYFRA 21-1, haemoglobin, thrombocytes, alkaline phosphatase and albumin as predictors of survival. The MESOPRO score was developed and narrow validated in which the majority of patients was treated at a dedicated malignant mesothelioma centre in The Netherlands. A large, international independent validation is currently running to confirm the predictive value of MESOPRO score.

FUTURE PERSPECTIVE

Within a year, immunotherapy (nivolumab-ipilimumab) might be the standard first line systemic therapy in malignant pleural mesothelioma. Platinum-pemetrexed will become the preferred second line treatment, though studies are currently lacking to provide a survival benefit in this 2nd line setting.

In the current thesis, we provided evidence of activity of gemcitabine in malignant mesothelioma in the maintenance setting after first line chemotherapy. As immunotherapy will become the standard first line treatment and an overall survival benefit of maintenance gemcitabine was lacking in the NVALT19 trial, the optimal timing and combination strategy of gemcitabine in patients with malignant mesothelioma needs to be reviled. In the current thesis, we made the first step by providing evidence of an immune-modulating effect of gemcitabine in patients with malignant mesothelioma treated with gemcitabine. Studies combining PD-(L)1 blocking and gemcitabine are currently ongoing in other solid tumours (NCT04164082, NCT02807636). Future research is need in malignant mesothelioma to test this combination strategy.

Angiogenesis could be (again) an important target in malignant mesothelioma. Pre-clinical data in malignant mesothelioma and clinical data in other solid tumours provide a good rationale to combine immunotherapy and angiogenesis inhibition.[44] A phase II trial in which patients with malignant mesothelioma were treated with atezolizumab- bevacizumab showed promising results.[45] The additional value of atezolizumab to platinum-pemetrexed- bevacizumab is currently investigated in the BEAT-meso trial (NCT03762018). The activity of lenvatinib, also a TKI targeting angiogenesis, combined with pembrolizumab is currently under investigation in the Dutch PEMMELA trial (NCT04287829). As the combining bevacizumab with gemcitabine-cisplatin in the first line treatment setting did not prided a clinical benefit in malignant mesothelioma, gemcitabine was hypotheses to have a negative interaction gemcitabine and bevacizumab. Now the combination of gemcitabine and ramucirumab tended to provide an overall survival benefit, (pre-clinical) exploring if newer generation angiogenesis inhibitors could have a synergistic effect with gemcitabine might be of value.

Repeatedly small phase II trials, with mostly disease control rate as primary endpoint, were the basis to perform large randomized phase II/III trials with disappointing results. Response rate as primary endpoint in small phase II setting looking for signs of activity would be a step forward. However, ORR is not considered to be the most reliable endpoint in mesothelioma. The response rate of pembrolizumab was higher compared to chemotherapy in the later line setting without a PFS nor an OS benefit. In the first line setting, nivolumab-ipilimumab had a comparable response rate and PFS compared to chemotherapy with an overall survival benefit of immunotherapy. New techniques, by artificial intelligence, might provide a solution by performing three-dimensional response measurements. Currently, a Dutch study is running to developed and validate an algorithm for volume measurements in correlation to survival in more than 1000 malignant mesothelioma patients.

As malignant mesothelioma is a rare disease, (international) collaboration is the best way forward. In this way, new treatment options can be tested faster in larger cohorts, like the PROMISE- meso and the BEAT-meso trial. By centralization of care, more patient might receive treatment, and more knowledge will be gathered. Registration of treatment, and an easy links of registration systems, will provide the opportunity to perform translational research.

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