short review

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Unresectable pleural mesothelioma—hope or still an unmet medical need?

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Summary Malignant pleural mesothelioma (MPM) is a rare tumour that originates from the inner linings of the pleural cavity. The majority of cases are associated with exposure to asbestos for what was banned in the European Union in 1991. Due to the long latency between exposure and onset (20–40 years) the peak of MPM in Western Europe will be reached within the next years. Often diagnosed at an unresectable stage, treatment options remain palliative in the majority of cases. The highly aggressive nature of MPM leads to a dismal prognosis with a median overall survival of approximately one year.
Platinum-based chemotherapy in combination with pemetrexed has been the mainstay of first line treatment in unresectable MPM for many years. Only recently, check point inhibitors have found their way into MPM treatment. The results of the phase III CheckMate 743 trial last year have finally led to a paradigm shift in the treatment of unresectable MPM. This trial showed a significant overall survival benefit for the combination of nivolumab and ipilimumab over standard chemotherapy, especially in nonepithelioid histology. Apart from histology, predictive biomarkers have not been identified for the treatment of MPM so far. Several trials investigating combination therapies with checkpoint inhibitors are currently ongoing and give hope to further improve prognosis for our patients.

Keywords Malignant pleural mesothelioma · Chemotherapy · Checkpoint inhibitor · Ipilimumab · Treatment outcome

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Introduction and current landscape of treatment

MPM is a highly aggressive cancer and has become a world health issue due to its poor prognosis and its increasing incidence. It is highly correlated with the exposure of asbestos with a delay of about 40 years due to the long latency period [1]. The peak of MPM in Western Europe will be reached within the next years [2].

The worst prognosis has been reported for nonepithelioid histology [3]. MPM is generally refractory to local treatment and usually progresses rapidly, resulting in a median overall survival (OS) of 12–36 months for localized disease and 8–14 months for advanced disease [4].

Platinum based chemotherapy with pemetrexed has been the mainstay of systemic treatment for MPM since 2003 [5]. Despite numerous clinical trials, no other cytotoxic treatment options have shown a survival benefit in the first-line or second-line treatment settings.

In 2016 the addition of the monoclonal antivascular endothelial growth factor A (VEGF-A) antibody bevacizumab to platinum-based chemotherapy was the last positive phase III trial in unresectable MPM up to 2020. The combination of cisplatin, pemetrexed and bevacizumab led to a modest OS benefit of 18.8 months compared to 16.1 months with chemotherapy alone [4]. Maintenance with bevacizumab after the six cycles was allowed until disease progression or toxic side effects [4].

In non-small cell lung cancer (NSCLC) maintenance chemotherapy with pemetrexed showed significant OS benefit either as continuation or as switch treatment [6, 7]. However, the CALGB 30901 trial could not translate the benefit of pemetrexed maintenance to MPM [8]. Although the study closed early due to slow accrual, continuation of pemetrexed af-

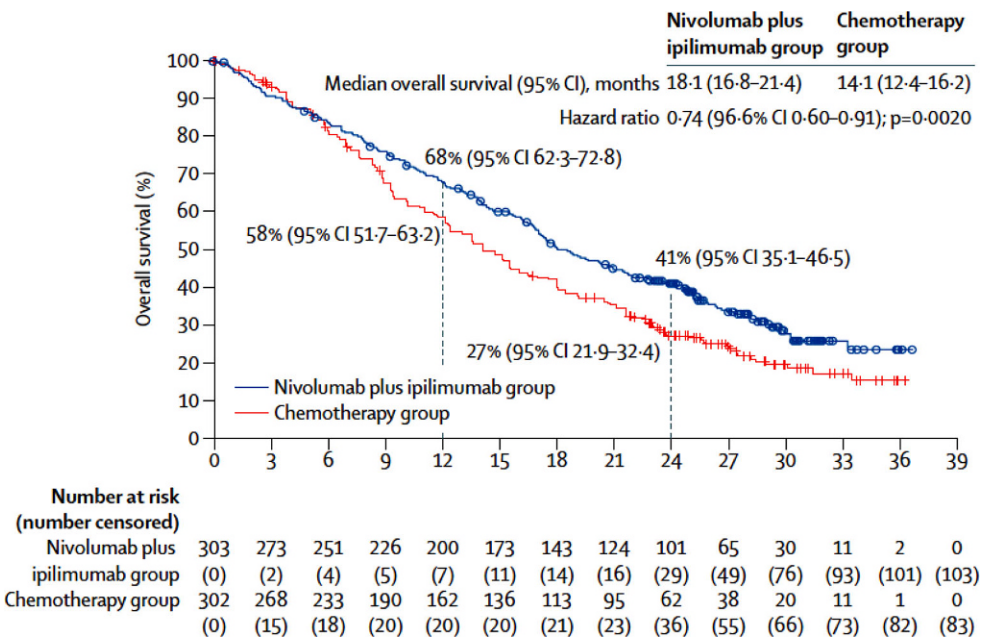

Fig. 1 Median OS of all randomised patients in the CheckMate 743 trial [11]. With permission from Elsevier. This figure is not included under the Creative Commons CC BY license of this publication

ter 4–6 cycles of combination with platinum showed no significant improvement in OS (hazard ratio [HR] 0.86; 95% CI 0.44–1.71; $p=0.6737$) [8]. Switch-maintenance with gemcitabine was recently published in the phase II NVALT19 trial [9]. A total of 130 patients without progression after at least four cycles of platinum and pemetrexed received gemcitabine and supportive care or best supportive care alone. Progression-free survival (PFS) was significantly longer with gemcitabine than with supportive care group (6.2 vs. 3.2 months; HR 0.48; 95% CI 0.33–0.71; $p=0.0002$) [9].

Chemotherapy-based treatment options in the second line setting are rare. At ASCO 2020 the RAMES trial showed promising activity for the combination of gemcitabine and ramucirumab, a human monoclonal antibody against VEGF-receptor 2, in recurrent MPM [10]. In the phase II trial 164 pretreated patients were randomized to gemcitabine and ramucirumab vs. gemcitabine and placebo. OS was significantly longer for the combination with a median 13.8 months vs gemcitabine with 7.5 months (HR 0.71; 70% CI 0.59–0.85; $p=0.057$).

New options: checkpoint inhibitors in MPM

In 2020 treatment options for MPM changed with the results of the CheckMate 743, the first phase III trial showing a benefit for immune checkpoint inhibitors [11].

Dual-agent immunotherapy is meanwhile a main part of treatment in NSCLC [12] and various other malignancies like malignant melanoma [13] and renal cell carcinoma [14]. In the last few years, three phase II trials showed positive signals for single or dual-agent immunotherapy in relapsed MPM. The MAPS-2 trial by the French Cooperative Thoracic Intergroup enrolled 125 patients progressing after first- or second-line pemetrexed and platinum-based treatment. They either received nivolumab ($n=63$) or nivolumab plus ipilimumab ($n=62$). In the intention-to-treat population, 12-week disease control was achieved by 25 patients (40%) in the nivolumab group and 32 patients (52%) in the combination group [15]. Quispel-Janssen J et al. reported results of a single-centre trial in 34 patients who received nivolumab 3 mg/kg every 2 weeks after progression on at least one chemotherapy regimen [16]. In all, 8 patients (24%) had a partial response (PR) at 12 weeks and another 8 had stable disease (SD) resulting in a disease control rate (DCR) at 12 weeks of 47% [16]. The INITIATE study was a prospective single-centre trial treating patients progressing after at least one line of platinum-containing chemotherapy with nivolumab (240 mg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks up to four times). A total of 34 patients were evaluable for response assessment at 12 weeks, 10 patients (29%) had a PR and 13 patients (38%) had SD. DCR was 68% (95% CI 50–83%) [16]. Based on the results of these three trials, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN guidelines) recommend nivolumab with or without ipilimumab as a preferred treatment option (category 2A) in second-line or later MPM setting.

At the virtual World Lung Cancer Conference (WCLC) 2020, which took place virtually in January 2021, first data of the phase III CONFIRM trial were presented. In this trial, patients with previously treated, unresectable, malignant pleural or peritoneal mesothelioma received nivolumab (3 mg/kg) or placebo once every 2 weeks until disease progression or a maximum of 12 months. OS was immature but showed longer survival with nivolumab (median

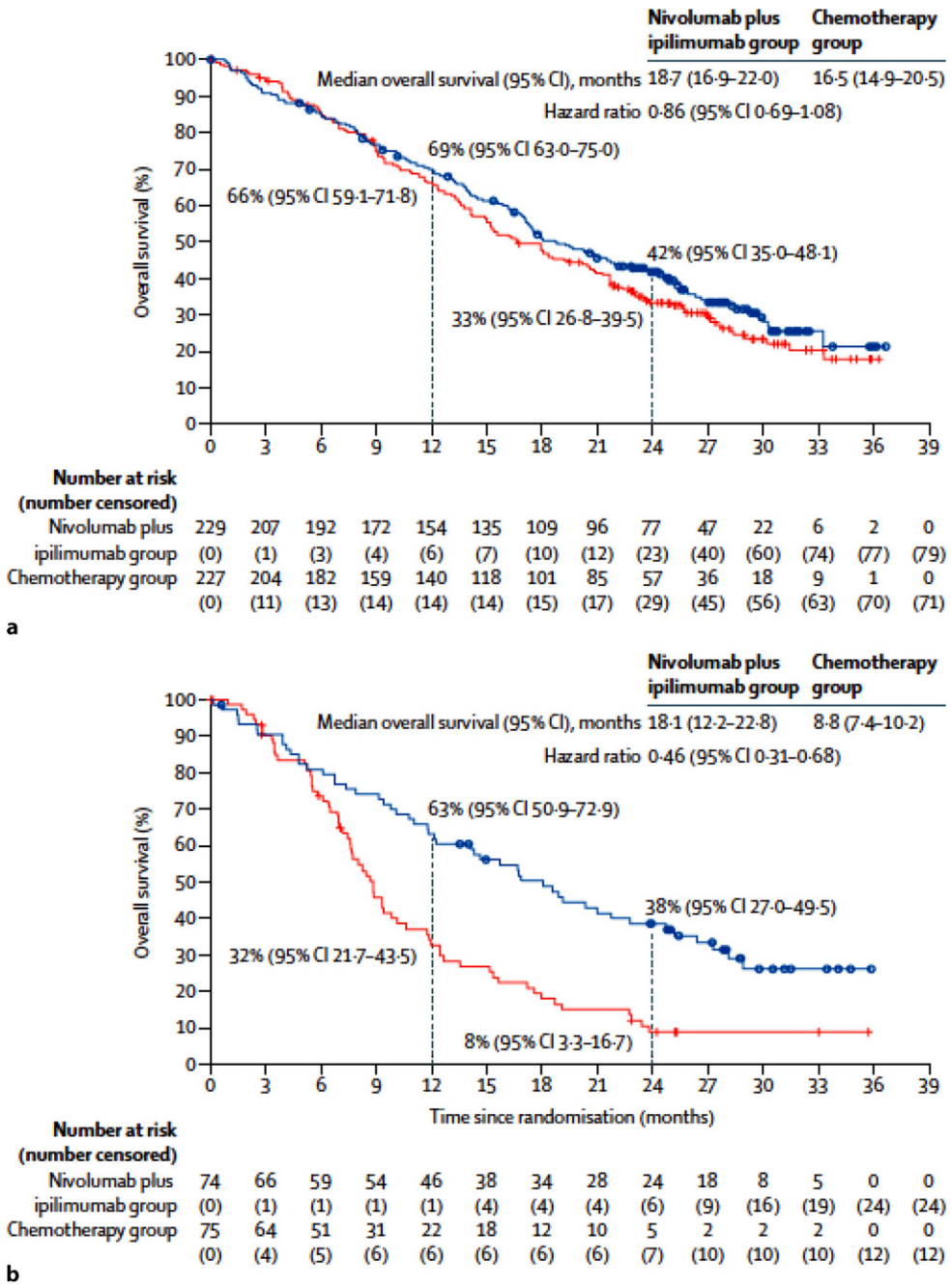

Fig. 2 Median OS of patients with epithelioid tumour histology (**a**) and non-epithelioid tumour histology (**b**) in the CheckMate 743 [11]. With permission from Elsevier. This figure is not included under the Creative Commons CC BY license of this publication

OS 9.2 vs 6.6 months; HR 0.72; 95% CI 0.55–0.94; $p=0.02$). Investigator-assessed PFS was longer for nivolumab vs placebo (3.0 vs 1.8 months; HR 0.62; 95% CI 0.49.0.78; $P<0.001$) [17].

In the front-line setting of MPM, the CheckMate 743 study was the first trial to present an overall survival benefit of checkpoint inhibition [11]. This randomized, phase 3 study investigated first-line nivolumab plus ipilimumab versus standard platinum plus pemetrexed chemotherapy. A total of 605 patients with previously untreated, unresectable MPM were randomly assigned to either nivolumab (3 mg/kg intravenously once every 2 weeks) plus ipilimumab (1 mg/kg intravenously once every 6 weeks) for up to 2 years or platinum plus pemetrexed chemotherapy once every 3 weeks for up to six cycles. At the prespecified interim analysis with a median follow-up of 29.7 months immunotherapy significantly improved OS, with a median of 18.1 months (95% CI 16.8–21.4) in the nivolumab plus ipilimumab group versus 14.1 months (12.4–16.2) in the chemotherapy group (HR 0.74; 96.6% CI 0.60–0.91; Fig. 1). The 2-year overall survival rates were 41% (95% CI 35.1–46.5) versus 27% (21.9–32.4) [11].

A benefit for the dual-agent immune checkpoint blockade was assessed in most subgroups with the exception of patients aged 75 years or older. The largest difference in OS gain was seen between patients with

nonepithelioid (HR 0.46; 95% CI 0.31–0.68) and epithelioid histology (HR 0.86; 95% CI 0.69–1.08; Fig. 2). The benefit in the nonepithelioid subgroup was primarily driven by the inferior effect of chemotherapy in these patients. The median OS was similar in both groups with 18.7 months in epithelioid histology and 18.2 months in nonepithelioid histology.

Interestingly, median progression-free survival (PFS) did not differ significantly between treatment groups. Median PFS was 6.8 months (95% CI 5.6–7.4) with dual-agent immunotherapy and 7.2 months (95% CI 6.9–8.0) with chemotherapy (HR 1.00; 95% CI 0.82–1.21). However, PFS rates at 2 years were numerically greater in the immunotherapy group that in the chemotherapy group (16 vs 7%).

Predictive biomarkers for checkpoint inhibition in MPM have not been identified yet. Although PD-L1 is established for single agent immunotherapy in NSCLC [18], the predictive value of PD-L1 as biomarker in MPM is limited. In the CheckMate 743 trial, median OS was similar with nivolumab plus ipilimumab in the subgroups with less than 1% (17.3 months), 1% or higher (18.0 months) PD-L1 expression. Notably, survival with chemotherapy was better in patients with PD-L1 expression of less than 1% than those with expression of ≥1%, defining a negative prognostic role of PD-L1 for chemotherapy in MPM. These findings are descriptive and exploratory and need to be interpreted with caution. PD-L1 was not a stratification factor in the CheckMate 743 and the sample size of the PD-L1 less than 1% group was small.

Ongoing trials in MPM first-line setting

A very tempting treatment approach for MPM is the combination of checkpoint inhibition and chemotherapy as it is already used in daily practice for other tumour entities like NSCLC and even small-cell lung cancer (SCLC) [19]. Various clinical trials investigating this concept are currently ongoing. The phase III DREAM3R trial combines standard cisplatin-based chemotherapy and pemetrexed with or without the PDL-1 inhibitor durvalumab and is currently recruiting (NCT04334759). Another interesting, ongoing, phase III trial is the BEAT-meso trial as it uses the combination of carboplatin, pemetrexed and bevacizumab as treatment for the standard group. The experimental arm combines this regimen with atezolizumab as quadruple treatment (NCT03762018). The third phase III trial is conducted by the Intergroupe Francophone de Cancerologie Thoracique (IFCT) and investigates cisplatin and pemetrexed with or without pembrolizumab (NCT02784171). Recruitment has already finished and we are awaiting results in 2022.

Take Home Message

The prognosis of unresectable malignant pleural mesothelioma (MPM) is poor and its rising incidence represents a highly unmet medical need. However, the arrival of checkpoint inhibition in MPM offers new treatment options and gives hope for future combination therapies to improve survival and life quality for patients.

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Conflict of interest G. Absenger and A. Terbuch declare that they have no competing interests.

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