Systemic therapy in malignant mesothelioma: treat it or leave it

Gooijer, C.J. de

Chapter 6

Treat it or Leave it: Immuno-Oncology in Mesothelioma Observed by the Eyes of Argus

Cornedine J. de Gooijer and Paul Baas

J Thorac Oncol. 2018 Nov;13(11):1619-1622.

EDITORIAL.

Comment on

Pembrolizumab as Palliative Immunotherapy in Malignant Pleural Mesothelioma. 10.1016/j.jtho.2018.08.007

Despite the fact that there is still no registered secondline treatment in patients with malignant pleural mesothelioma (MPM), several drugs have been tested in this patient group in a single-arm phase II setting. A variety of results have been published, but most of these studies suffered from the fact that they included a small number of patients and/or a highly selected group. Only one randomized phase III study with chemotherapy has been reported which included 243 pretreated patients. An improved progression-free survival (PFS) was seen in the arm with pemetrexed arm (3.6 versus 1.5 months, p¼0.0148) compared to best supportive care (BSC). This, however, did not translate in a median overall survival (mOS) benefit (8.4 versus 9.7 months in the BSC arm, p¼0.7434).[1] For the use of immunotherapy, one large phase IIb study compared placebo with a CTL4 inhibitor and reported a disease control rate (DCR) of 11.6% at 6 months, a PFS of 2.7 months and an overall survival (OS) of 7.3 months in the placebo arm.[2] These data can therefore be used as the natural history of patients with MPM when untreated in second- or third-line setting.

In this issue of the Journal,Metaxas et al.[3] presented a real-world analysis of pembrolizumab as palliative immunotherapy in patients with MPM. In this brief report, they retrospectively report the overall response rate of 18.3%, a PFS of 3.1 months, and OS of 7.2 months in 93 patients who were

treated with pembrolizumab in first-line or beyond. They correlated the outcome to pathologic subtype and programmed death ligand 1 (PD-L1) status (SP253 in Switzerland and E1L3N in Australia). In this editorial, we will put these results in a broader perspective.

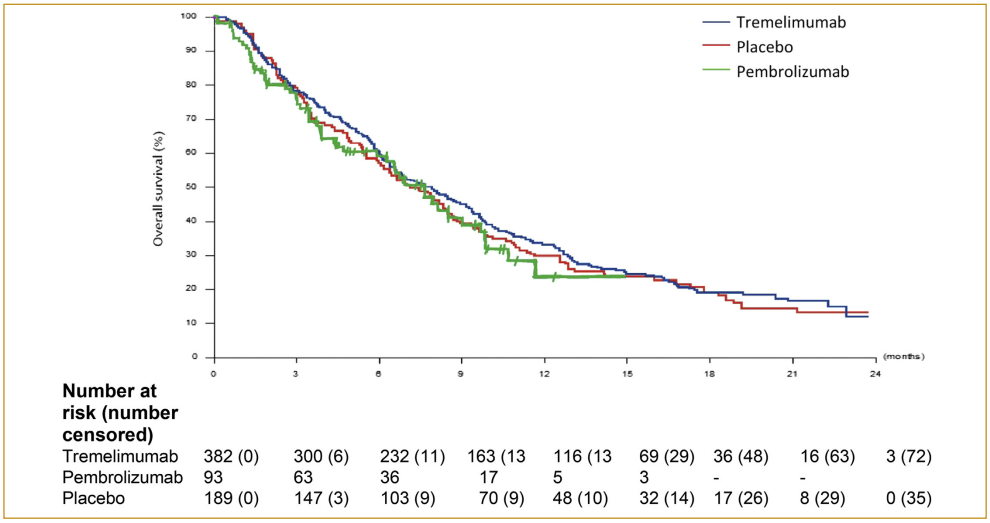
Immunotherapy has shown consistent improvement in mOS in several solid tumors.[4] The growing knowledge about the complex microenvironment of MPM and involvement of immune cells gives high hopes on immunotherapy.[5] In 2015, the preliminary results of a cohort of patients with MPM in the phase I (KEYNOTE-028 trial) were published. This provided the first evidence of activity of single-agent pembrolizumab in the second-line and beyond. These promising results, a median PFS (mPFS) of 5.4 months and an mOS of 18 months, lead to more clinical research of immune-oncology (IO) treatment in MPM (Table 1).[6] Similar results were obtained in single-arm phase II studies with pembrolizumab or nivolumab with or without ipilimumab (Table 1).[7-10] Currently, the additional value of ipilimumab to nivolumab in MPM is still not clear. Scherpereel et al.[9] initiated a randomized phase II study of nivolumab ±ipilimumab. However, this study was not powered to detect a difference between the two arms, making it difficult to make sound conclusions on superiority. Despite the promising results of the initial single-arm phase II trials, tremelimumab (an anti–CTLA-4 antibody) failed to show any superiority in second- or third-line in a large randomized phase IIb trial.1[1-13] Tremelimumab combined with durvalumab (anti–PD-L1 antibody) in 40 patients with MPM resulted in similar results as the two previous single-arm phase II studies with single-agent tremelimumab (Table 1).[11]

Table 1: Overview clinical outcomes of studies with immunotherapy in malignant mesothelioma.

	Phase II trials Pembro-lizumab [5, 13]	Retrospective analyses pembrolizumab [14]	Phase II trial avelumab [15]	Phase II trials Nivolumab [6, 9]	Phase II trial Nivolumab + Ipilimumab [6-8]	Phase II trials Tremelimumab [11, 12]	Randomized phase IIb tremelimu-mab vs placebo [2]	Phase II trial Tremelimumab + durvalumab [10]
Pt analysed	90	139	53	102	79	58	571	40
ORR (%)	20-21	15-18	9.4	15-29	26-28	7-14	5 vs 2	25
DCR (%)	63-72	44-48	56.6	43-67	52-72	31-38	28 vs 22	63
mPFS (months)	4.5-5.4	3.1-Not reported	3.9	2.6-6.1	5.6-not reported	6.2	2.8 vs 2.7	5.7
mOS (months	11.5-18.0	7.2-8.0	Not reported	10.4-11.8	Not reported	10.7-11.3	7.7. vs 7.3	16.6

Abbreviations: DCR; disease control rate, mOS; median overall survival, mPFS, median progression free survival, ORR; overall response rate, Pt; patient.

To correctly place into perspective the real-world study of Metaxas et al.[3] a control arm is required. Therefore, we do not know what the possible additional value of pembrolizumab is and how bad the outcome would be when no treatment was given at all. Although comparison of trials has significant limitations, it shows us that we must be cautious with acceptance of a new treatment. Similar to tremelimumab, pembrolizumab was promising in small phase I-II studies, but in the realworld survival, the data were close to the data of placebo arm of the DETERMINE trial (mPFS 3.1 months versus 2.7 months and mOS 7.2 months versus 7.3 months, respectively (Fig. 1). Selecting the fittest patients in studies by using strict inclusion criteria could therefore be a reason for the lack success in the real-world data. Examples of selection are the criteria to be amenable for repeated biopsies and having a performance score (PS) of 0-1. In the study by Mataxas et al.[3], 29% of the patients had a PS of 2. Unfortunately, Mataxas et al.[3] did not present the survival curves by PS score alone. Another limitation of the study is the variation of used dosages, ranging from 2 mg/kg every 21 days up to 10mg/kg every 14 days. Although DCR is a common primary endpoint in these studies, radiological response assessment in this study was based neither on immunerelated Response Evaluation Criteria in Solid Tumors nor consistent with those modified for MPM. There was no central radiological reviewing and the times of response measurement were not standardized. Therefore, comparison of response rates is unreliable. With respect to an improved outcome based on PD-L1 expression, the data results are controversial. Desai et al.[14] examined the effect of pembrolizumab but could not establish a PD-L1 threshold in a cohort of 35 patients of a phase II study. The patients were not selected for PD-L1 status and the results were comparable to those of the KEYNOTE-028 study. In other phase II studies in unselected populations, good results were also reported irrespective of the



Number at risk (number censored)									
Tremelimumab	382 (0)	300 (6)	232 (11)	163 (13	116 (13	69 (29)	36 (48)	16 (63)	3 (72)
Pembrolizumab	93	63	36	17	5	3	-	-	
Placebo	189 (0)	147 (3)	103 (9)	70 (9)	48 (10)	32 (14)	17 (26)	8 (29)	0 (35)

Figure 1: Reconstruction of overall survival curve of the two arms of Determine study (tremelelimumab and placebo) and the overall survival curve of the real world data of pembrolizumab by Mataxas et al.[2,3]

PD-L1 status. In subanalyses of Mataxas et al.[3], a higher PD-L1 expression was associated with response and the mPFS was longer in the group with high expression. In the multivariate analysis, however, neither histology nor PD-L1 expression remained significantly associated with outcome at any cutoff level. Another explanation for the disappointing results could be the differences in biology of MPM. In a series of 329 mesothelioma cases, combining several immune checkpoints (PD-L2, LAG3, and TIM3), tumor-infiltrating lymphocytes with PD-L1 expression, CD4þ, and CD8þinfiltration revealed that the microenvironment of MPM is highly heterogeneous. Therefore, combination therapy could be more effective than single-agent strategies given the relatively low rates of strong PD-L1 expression and low mutational burden in MPM.[5]

Because the real-world data of pembrolizumab are close to the historic placebo arm, the use of immunotherapy outside of trials should be limited. Studies that are currently ongoing or recently closed are: (1) the phase 3 Checkmate 743 study (NCT02899299) in which 600 patients have been randomized between cisplatin-pemetrexed or nivolumab-ipilimumab in first-line treatment; and (2) the CONFIRM trial (NCT03063450), which is a double-blind, placebo-controlled phase III clinical trial that investigates the effect of nivolumab in patients with relapsed mesothelioma in third-line or beyond. These phase III clinical trials with a control arm are crucial to evaluate the real impact of IO therapies in this population. Translation of the treatments in trial settings to general practice in mesothelioma will remain a challenge. Although our enthusiasm for IO treatment is high, a critical appraisal of the data is necessary before accepting a new treatment in patients with mesothelioma.

1. Jassem J. et al. 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: 1698-1704

2. Maio M. et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol. 2017; 18: 1261-1273

3. Metaxas Y. et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. J Thorac Oncol. 2018; 13: 1784-1791

4. Muller M. et al. Pembrolizumab for the treatment of non–small cell lung cancer. Expert Rev Anticancer Ther. 2017; 17: 399-409

5. Thapa B. et al. The immune microenvironment, genome-wide copy number aberrations, and survival in mesothelioma. J Thorac Oncol. 2017; 12: 850-859

6. Alley E.W. et al. 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: 623-630

7. Goto Y. et al. MA 19.01 A phase II study of nivolumab: a Multicenter, Open-Label, Single Arm Study in Malignant Pleural Mesothelioma (MERIT). J Thorac Oncol. 2017; 12: S1883

8. Disselhorst M. et al.OA 02.02 ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma: a phase II study. J Thorac Oncol. 2017; 12: S1746

9. Scherpereel A. et al. Second- or third-line nivolumab (Nivo)

versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: results of the IFCT-1501 MAPS2 randomized phase II trial. J Clin Oncol. 2017; 35 (LBA8507-LBA)

10. Quispel-Janssen J. et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. J Thorac Oncol. 2018; 13: 1569-1576

11. Calabro L. et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Lancet Respir Med. 2018; 6: 451-460

12. Calabrò L. et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2013; 14: 1104-1111

13. Calabrò L. et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med. 2015; 3: 301-309

14. Desai A. et al. Phase II trial of pembrolizumab (P) in patients (pts) with previously-treated mesothelioma (MM). J Clin Oncol. 2018; 36: 8565

15. Rivalland G. et al. Outcomes of anti–PD-1 therapy in mesothelioma and correlation with PD-L1 expression. J Clin Oncol. 2017; 35: 8514

16. Hassan R. et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase Ib trial: safety, clinical activity, and PD-L1 expression. J Clin Oncol. 2016; 34: 8503