Malignant pleural mesothelioma (MPM), which is linked to asbestos exposure and is a rare, lethal disease of the serosal membrane in the chest, has an incidence which continues to increase worldwide (1,2). MPM is histologically classified into three major subtypes: epithelioid, biphasic (or mixed) and sarcomatoid. Notwithstanding these well-defined MPM histological subtypes, there are tremendous differences in clinical outcomes including long-term survival in patients whose tumor histology is indistinguishable from conventional, highly aggressive MPM.

MPM is generally diagnosed in the late stage where chemotherapy remains the only therapeutic option. Unfortunately, the efficacy of chemotherapy is modest, with a median overall survival of about 12 months (3). This limited efficacy has been associated with MPM’s ability to evade the immune system clearance and to establish an immune-suppressive environment (4,5). Consequently, it is not surprising that patients enrolled in the MAPS phase 3 trial and in the LUME-Meso phase 2 trial benefited from the addition of bevacizumab and nintedanib to the standard cisplatin and pemetrexed backbone, respectively. In a small phase 1b non-randomized open-label study, the treatment with the anti-PD-1 monoclonal antibody pembrolizumab, was well tolerated, leading to a 20% response rate (RR) and a median duration of response of 12 months (95% CI: 6.8–40.7) in previously treated MPM patients (6). A phase 2 study of the same agent in previously treated MPM patients, unselected for PD-L1 expression, led to comparable results, showing an overall RR (ORR) of 22% and a disease-control rate (DCR) of 61% (7). Interestingly, the objective response was correlated to the PD-L1 expression. Moreover, data with nivolumab in 27 MPM patients treated in the American Nivolumab Expanded Access Program showed an ORR of 24% while the DCR and the 6-month survival rate were 60% and 52%, respectively (8).

Similarly, phase 1 data on avelumab, which is another checkpoint inhibitor directed against PD-L1, demonstrated a lower RR (9.4%) but comparable median OS (10.9 months), which was even higher in PD-L1 positive cases (≥5% assessed by DAKO 73-10 antibody, 22.0 months) (9).

To improve the efficacy of immune modulators and to counteract phenomena of resistance, the combination of immune checkpoint blocking antibodies has been investigated in other tumor types. In metastatic melanoma, for instance, the association of nivolumab with ipilimumab, whose combined use has been approved by the US Food and Drug Administration, has improved the overall survival (10). This pivotal clinical study has shed light on the fundamentals for using combinations of immune checkpoint blocking antibodies in different tumor types (11). In line with this, an NIBIT-MESO-1 trial (12), has recently investigated the activity of tremelimumab (anti-CTLA-4 monoclonal antibody) in combination with durvalumab (anti-PD-L1 monoclonal antibody), in first- or second-
line treatment for MPM patients. The clinical activity of
CTLA-4 blockade in monotherapy was previously reported
in second-line treatment for MPM patients, although the
efficacy was not confirmed in the randomized, placebo-
controlled phase 2 DETERMINE study (13,14).

NIBIT-MESO-1 (12) is a single-arm, single-centre,
open-label phase 2 study which included adult patients
with histologically confirmed, unresectable pleural or
peritoneal MM. Patient inclusions encompassed cases that
had refused first-line chemotherapy, cases with disease
progression during or after standard chemotherapy
treatment, and patients with lesions measurable and suitable
for repeated assessments according to standard evaluation
criteria for both pleural and peritoneal MM. Patients
excluded were those previously treated with monoclonal
antibodies against CTLA-4, PD-1, or PD-L1 or those
with active immune diseases or brain metastases. The
pharmacokinetic was based on a previous, phase 1b trial in
non-small-cell lung cancer. Specifically, the induction phase
consisted of 4 cycles of tremelimumab (at the dosage of
1 mg/kg) in association with durvalumab (at the dosage of
20 mg/kg), both administered intravenously every 4 weeks.
The maintenance phase consisted of durvalumab at the same
dosage and schedules as in the induction, but administered
for up to 9 cycles. Follow-up is still ongoing. The primary
endpoint was the proportion of patients with an immune-
related objective response (complete response or partial
response) according to immune-related criteria for patients
with pleural and peritoneal mesothelioma. Secondary
epipoint endpoints included safety, proportion of patients with
immune-related disease control (complete response, partial
response, or stable disease), immune-related progression-
free survival, progression-free survival, and overall survival.
The association between individual efficacy endpoints
and baseline PD-L1 levels was also included among the
secondary endpoints. Safety was assessed monthly after each
dose administration both during induction and maintenance
phases. After the last administration of tremelimumab and
durvalumab, safety was assessed every 30 days for up to
90 days, while patients with severe adverse effects were
monitored for one year.

Since fewer than 30% of all treatment-related adverse
events (grade 3–4) were observed in the first 10 patients, all
the originally planned patients (40 in total) were enrolled.
Immune-related objective response was observed in 11
patients and confirmed in 10 patients by CT scan. The
median duration of immune-related partial response in
these patients was 16.1 months and thus the study reached
its primary endpoint. Immune-related disease control,
with a median duration of 10.6 months, was observed in 26
patients, while the median immune-related progression-free
survival was 8 months, and immune-related progression-
free survival was 55% at 6 months and 28% at 12 months.
Median progression-free survival and median overall
survival were 5.7 and 16.6 months, respectively, with 25
patients still being alive at 1 year. Sixty-eight percent of
patients experienced grade 1 or 2 treatment-related adverse
events (most dermatological), while grade 3 and 4 occurred
in 18% of patients. No treatment-related deaths were
reported. Overall, this study describes a tolerable safety
profile for the combination and hints at its potentially
clinical benefit.

A recent French randomized phase 2 non-comparative
study assessed the efficacy of nivolumab alone or in
combination with ipilimumab in pre-treated advanced MPM
patients. In the 62 patients treated in the combination arm,
the median PFS was 5.6 and 4.0 months for those treated
with nivolumab alone (n=63) (15). Although data are still
not mature, at a median follow-up of 15 months, median
OS was 13.6 months in the single-agent arm, while it was
not even reached with the combination of drugs.

Unfortunately, it is difficult make comparisons between
the above studies due to the profound differences in the trial
design, the enrolled populations (e.g., histological subtypes,
percentage of peritoneal mesotheliomas, adopted response
evaluation criteria) and the agents used (single-agent vs.
combination therapies). However, in spite of such intrinsic
limitations, the median progression-free survival and the
median overall survival of the NIBIT-MESO-1 trial were
comparable with those observed in the KEYNOTE-028
study, in which patients were selected according to
PD-L1 levels. Notably, in the NIBIT-MESO-1 trial,
the level of PD-L1 at the baseline was not significantly
associated to any clinical response (immune-related
objective response, immune-related disease control,
immune-related progression-free survival or 1-year overall
survival). This observation is particularly relevant, since in
many studies with immune modulators, the level of PD-L1
is still considered a relevant parameter for effectiveness
(16,17). However, the findings here reported suggest
that additional criteria are urgently needed. A detailed
molecular analysis at the genomic and transcriptional level
of the tumor and the relative microenvironment, could
be extremely informative in identifying novel critical
biomarkers to improve patient stratification and selection.
In other tumor types, the mutational burden (TMB) seems
to be a useful parameter in identifying good responders to immune modulators (18).

Compared to other malignancies, MPM is characterized by fewer recurrent genetic alterations (19). At the same time, MPM is reported to be associated with very low TMB, as recently reported by Ladanyi and colleagues who analyzed The Cancer Genome Atlas (20). Yet, in the same study, the authors found that another negative immune checkpoint, VISTA, was highly expressed in this tumor as compared to the others, a fact which begs further research from future studies.

Unfortunately, these single-arm studies suggest hints of anti-cancer activity but do not allow us to draw any decisive conclusion in the absence of an internal comparative arm. Although there are no officially accepted second lines in MPM, non-approved agents such as gemcitabine vinorelbine are commonly used in this setting.

Overall, the NIBIT-MESO-1 study (12), despite its limitations, suggests that the combination of tremelimumab and durvalumab has an acceptable tolerability and leads to some clinical benefit in MM patients. The trade-offs between activity and toxicity do still need to be carefully assessed, and consequently, further well-designed studies are needed to extend and consolidate these findings. As pointed out by Calabrò et al., within this innovative context of combination therapies, the use of two-immune checkpoint blocking antibodies in association with other drugs might further improve clinical benefits in the near future. While ongoing clinical trials are mainly focusing on adding immune checkpoint inhibitors to chemotherapy in the first-line treatment, early preclinical data indicate that bromodomain inhibitors (BBIs) can be used as effective agents in restoring an immune-active environment in MPM (21). Nevertheless, caution should be applied before combining many drugs in a clinical trial, since the resulting toxicity may be intolerably exponential.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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