Immune checkpoint inhibitors in mesothelioma

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Chapter 4

ESMO handbook of Immuno-Oncology – chapter Mesothelioma

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Chapter 2.3.3 Mesothelioma
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Definition

Malignant Pleural Mesothelioma (MPM) has been known for its resistance to a variety of therapies, and has therefore been the focus for new treatment approaches such as immuno-oncology treatment. Although mesothelioma is not a typical immunogenic tumour, in the past it has been observed that some patients with MPM responded well on the instillation of BCG (Bacillus Calmette-Guérin) or after the development of an empyema (1). In the 20th century, some groups observed that immune infiltration in biopsies predicted for a better survival. Mesothelioma is also infiltrated by immune effector cells, cytokines and regulatory T-cells (2,3). This led to the idea that the immune system could play an important role in the biology of MPM.

Predictive and /or prognostic biomarkers of clinical relevance

Mesothelioma has a moderate expression of PD-L1, 20%-40% of patients have an expression of >1%. Non-epithelioid histological subtype has a significant higher number of PD-L1-positive (PD-L1+) patients. The PD-L1-negative (PD-L1-) patients have a significantly better prognosis than the PD-L1+ patients, with a median survival of 16.3 versus 4.8 months respectively. The effect of PD-L1 status on prognosis does not depend on the histology (4,5). Mesotheliomas have a low protein-altering mutation rate. Compared with other cancers it is in the lowest third of the tumour mutational burden landscape (6). There is no significant difference in mutational burden between the histological subtypes of mesothelioma (7). Despite this low mutational burden, in a subgroup of patients with mesothelioma immune-oncologic therapy is beneficial, possibly due to the presence of immune cells in the tumour-microenvironment.

The prognostic significance of immune cells infiltrating the tumour has been investigated in several studies. With more CD4-expressing cells or CD8+ lymphocytes in the mesothelioma there is a tendency to longer survival. High levels of IL-7R are associated with an increased risk of death. CD163+ cells and their ratio to tumour-infiltrating lymphocytes (TILs) [CD8+ T cells and CD20+ B cells] are an independent marker of prognosis in mesothelioma (8).

Clinical results

Unlike the turbulent development in melanoma and lung cancer, the number of studies in MPM has developed at a slow pace. The studies reported in peer-reviewed journals or presented at major meetings are listed in Table 1. Most of these studies focus on the

anti-programmed cell death protein 1 (PD-1) monoclonal antibodies nivolumab and pembrolizumab.

Data emerging from these studies indicate that the overall response rate (ORR) is comparable with the results obtained in lung cancer and other tumours, but there seems to be no clear correlation between PD-L1 expression level and response. In general, the primary endpoint of the second line studies is the disease control rate (DCR) at 12 weeks. Long-term survivors have not yet been reported due to the recent initiation of these studies.

Table 1: Completed studies of immuno-oncology therapy for mesothelioma

Study	Drug(s)a	Phase	# Pts	Outcome
Determine (13)	Tremelimumab vs placebo 2:1	IIB	571	DCR: 28 vs 22% OS: 7.7 vs 7.3 months
NivoMes (11)	Nivolumab	II	33	DCR: 50% ORR: 15%
Javelin (12)	Avelumab	IB	53	DCR: 57% ORR: 9.4% mPFS: 17 weeks
Keynote 028 (9)	Pembrolizumab 10mg/kg 2qw For PD-L1 > 1%	IB	25	DCR: 72% ORR: 20% mPFS: 5.4 months mOS: 18 months
Pembro (10) NCT02399371	Pembrolizumab	II	34	DCR 76% ORR 21% mPFS: 6.2 months mOS: not reached
MAPS 2 (14)	Nivolumab vs Nivolumab + ipilimumab (1:1)	II	125	DCR: 43 vs 52% ORR: 17 vs 26%
INITIATE NCT03048474	Ipilimumab + nivolumab	II	38	DCR: 72% ORR: 28%
DC vaccine (15)	DC-based immunotherapy + cyclophosphamide	I	10	DCR: 80% Reduces regulatory T cells Safe
Antimesothelin immunotoxin (16)	Cisplatinum + pemetrexed + SS1P	I	24	Safe Well tolerated PR: 77%

The number between brackets stands for references
DC, dendritic cell; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death 1; PR, partial response; Pts, patients; qXw, every X weeks.
[a] Standard dosages of therapy, unless otherwise specified

PD-1 blockade.

One phase Ib study, Keynote 028, examined pembrolizumab in a variety of tumour types. This is the only study that included patients who expressed PD-L1 (defined as > 1%), including a subset of 25 patients with MPM. The ORR for mesothelioma was 20% and DCR was 72%. The clinical benefit (complete response [CR] + partial response [PR] + stable disease [SD]) at 6 months was 40%. Median overall survival was 18 months. Historical data on median overall survival with second-line therapy ranges from 5.7 to 10.9 months.

Five patients (20%) presented treatment-related adverse events (trAEs) of grade ≥ 3, including thrombocytopaenia, dyspnoea, increase in alanine aminotransferase, neutropaenia, decrease in appetite and pyrexia (9).

An interim analysis of a phase II study with single agent pembrolizumab confirmed the DCR and limited toxicity profile (10). In Switzerland, data collected from patients who received pembrolizumab for relapsed MPM were reviewed retrospectively. Response rates and survival outcomes were promising in the unselected population and comparable with clinical trials for patients with Eastern Cooperative Oncology Group (ECOG) 0-1 and 2nd line treatment (as were inclusion criteria for Keynote 028).

Comparable results were reported when nivolumab was used (11).

PD-L1 blockade

Limited studies have been performed with PD-L1 blockers. The JAVELIN solid tumour study, a phase IB trial, tested the use of avelumab in 53 patients. ORR was 9.4% and DCR was 57%. Median PFS was 17 weeks. The toxicity profile was acceptable, four patients (7.5%) had trAEs of grade ≥ 3 (colitis, lymphopenia, increased gammaglutamil transferase (GGT) or creatine phosphokinase (CPK)) (12).

CTLA-4 blockade

One of the largest studies performed in MPM is the use of tremelimumab in second and third line. A total of 571 patients were randomised to receive tremelimumab or placebo (2:1). The preliminary safety profile of tremelimumab was acceptable. This was a negative study, since no difference in the primary end point, overall survival, was noted (13).

Combination checkpoint inhibitors

In the MAPS2 trial 125 patients were included that received either nivolumab or nivolumab plus ipilimumab. Interim analysis for the first 108 patients showed a DCR of 43% at 12 weeks with nivolumab and 52% with nivolumab plus ipilimumab. ORR was 17% with nivolumab alone and 26% with nivolumab plus ipilimumab (14).

An interim analysis of 26 patients in the Dutch INITIATE trial (NCT03048474), a phase II trial in which patients receive nivolumab plus ipilimumab showed comparable results with a DCR of 69% and ORR of 27% at 12 weeks. Toxicity was relatively low.

Potential future developments

In table 2, ongoing studies are reported. For checkpoint inhibitors, two trials explore the toxicity and changes in immunologic micro-environment with immunotherapy as neoadjuvant treatment for surgery. One study investigates the toxicity of pembrolizumab when given after radiotherapy.

A few studies investigate the difference in efficacy for chemotherapy (ChT) versus immunotherapy, some in first line and some in further lines.

Adoptive cell therapy

A few phase I studies are investigating the safety and feasibility of intrapleural or intravenously administered human chimeric antigen receptor (CAR) modified T cells in patients with mesothelin (MSLN)-expressing cancers. No results have been published for mesothelioma.

Anticancer vaccines

Dendritic cells (DCs) have been used in tumour cell vaccinations for mesothelioma. Cornelissen et al described 10 patients in whom dendritic cell vaccination was given after immune modulation of the body with cyclophosphamide. This resulted in radiographic disease control in 8 out of 10 patients. Seven of these 10 patients survived 24 months or more and 2 patients were alive at 50 and 66 months after treatment (15).

This approach is now being investigated in two other trials (see table 2). The European DENIM phase III trial will test DC-based immunotherapy with allogeneic tumour lysate as maintenance treatment after chemotherapy.

Table 2: Ongoing studies of immuno-oncology therapy for mesothelioma

Study	Drug(s)	Phase	# Pts	Primary endpoint	Remarks
Neoadjuvant pembrolizumab NCT02707666	Pembrolizumab before surgery	I	15	Toxicity γ gene expression	University of Chicago
Adjuvant pembrolizumab NCT02959463	RT + adjuvant pembro (+/- surgery or ChT)	I	24	Toxicity	MD Anderson
Durvalumab Tremelimumab + surgery NCT02592551	-Durva + surgery -Durva + tremelimumab + surgery -Control arm + surgery	II	-8 -8 -4	CD8/Treg ratio and ICOS	Single center Houston
Pembrolizumab vs chemo NCT02784171	-Cisplatin + pemetrexed -Cisplatin + pemetrexed + pembro -Pembro alone	II	126	PFS	Canada
Promise NCT02991482	Pembro vs standard of care	III	142	PFS	ETOP study
Durvalumab and tremelimumab NCT03075527	Durva q4w + tremelimumab q4w	II	40	ORR	Dana-Farber Institute
PrE0505 NCT02899195	Durva q4w + ChT	II 1L	55	OS	ECOG study
Checkmate 743 NCT02899299	Nivo + ipi vs Platinum+ pemetrexed	III 1L	600	OS and PFS	Multinational
NIBIT-MESO-1 NCT02588131	Durva + tremelimumab	II 1L,2L	40	ORR	Italian study
Keynote 158 Pembrolizumab NCT02628067	Pembro	II	1350	ORR	Multinational
MesoDec NCT02649829	Autologous DC vaccination	I/II	20	Feasibility and safety	Single centre Antwerp
MesoCancerVac NCT02395679	DCs loaded with allogeneous cell lysate	I	9	Tolerability	Single centre Rotterdam
Oncolytic virus NCT02714374	Neoadjuvant GL-ONC1 vaccinia +/- eculizumab	IB	36	Treatment-related AE	Single centre San Diego
NCT01503177	Intrapleural measles virus	I	36	AE	Mayo clinic

1L, first line; 2L, second line; AE, adverse event; ChT, chemotherapy; DC, dendritic cell; Durva, durvalumab; ECOG, Eastern Cooperative Oncology Group; ETOP, European Thoracic Oncology Platform; ICOS, inducible T cell co-stimulator cells; Ipi, ipilimumab; OS, overall survival; ORR, objective response rate; Nivo, nivolumab; Pembro, pembrolizumab; PFS, progression-free survival; Pts, patients; qXw, every X weeks; RT, radiotherapy; trAE, treatment-related adverse event; Treg, regulatory T cell.

Immunotoxin immunotherapy

Mesothelin (MSLN) is overexpressed in mesothelioma. SS1P is an immunotoxin consisting of an anti-MSLN antibody fragment fused to pseudomonas exotoxin. Hassan showed that SS1P can be administered safely and had an impressive tumour response in mesothelioma. Thirteen out of 24 patients received the maximum tolerated dose, and 77% demonstrated a partial response in combination with ChT (16).

Another MSLN-targeted immunotoxin that is currently being investigated is LMB-100.

Oncolytic viral therapy

For vaccinia immunotherapy, there is still only preclinical research. Two phase I studies are investigating the toxicity of oncolytic viral therapy for mesothelioma (see Table 2, NCT02714374 and NCT01503177).

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