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Editorial

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Dual Immune Checkpoint Inhibitors in the Treatment of Malignant Pleural Mesothelioma

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Editorial

Malignant pleural mesothelioma (MPM) is a highly aggressive and incurable cancer that originates from the mesothelial cells of the pleural cavity [1]. It is associated with a long latency period of inhalation of asbestos fibers of 20-40 years [2]. There are three subtypes of MPM, such as epithelioid (60%), sarcomatoid (10%), and biphasic (30%), which comprise both epithelioid and sarcomatoid histological features. The sarcomatoid type has the poorest prognosis with a median overall survival (OS) of 3 months, whereas the epithelioid and biphasic have median survival of only 7% at 3 years [2]. The non-epithelioid subtypes (sarcomatoid and biphasic) have very poor response to the standard of care (SoC) chemotherapy [2].

Most patients with MPM are diagnosed very late with diffuse, unresectable disease. The standard first-line chemotherapy for MPM consists of the doublet cisplatin plus pemetrexed. The regimen has a low response rate ranging from 26.3% [3] to 41% [4], and extends the OS by 2-3 months. Addition of bevacizumab a vascular endothelial growth factor (VEGF) inhibitor to cisplatin plus pemetrexed has been shown to extend the median overall survival up to 19 months (16-22 months), versus 16 months (14-18 months) with cisplatin plus pemetrexed [5]. Although the extension to the OS is not substantial, it is, however, worthwhile in improving the health-related quality of life (HLQoL) of patients with this dreaded incurable cancer.

Several other pan-VEGFR1/2/3 inhibitors, such as cediranib [6], and nintedanib [7], and multi-targeted growth factor blockers, including sorafenib [8], sunitinib [9], and vatalanib [10] did not meet the endpoint in clinical trials, and were associated with a high rate of grade 3-4 treatment-related adverse events. There is unmet need for the investigation of biomarkers of different MPM subtypes, and in the development of novel targeted biotherapeutics for the treatment of MPM, such as immune checkpoint inhibitors.

The innovative idea that the immune system had the ability to suppress several carcinomas, and thus plays an important role in the body's defence against tumour development and growth was propositioned by Paul Ehrlich in 1909 [11,12]. This is a unique characteristic feature of cancers in immune evasion, whereby the immune system does not mount an effective anti-tumour response [13,14]. Tumour cells express immune suppressive receptors known as immune-checkpoints (IC), which inhibits T cell immune response, such as cytotoxic T-lymphocyte-associated antigen-4 CTLA-4 [15], programmed cell death-1, and its ligands PD-1/PD-L1/1 [16], and lymphocyte activation gene-2 [17]. CTLA-4 signaling limits the initiation of the T cell in lymph nodes early in the immune response, whereas PD-1 restricts T cell activity later in the tumour microenvirnment [18]. The CTLA-4, and PD-1/PD-L1/2 checkpoints are used by tumours to evade and suppress the immune system, which result in tumour growth, spread, and resistance to chemotherapy. Currently, there are several monoclonal antibodies which have been developed to block the immune checkpoints, involved in downregulating the immune responses [19-21], such as nivolumab, ipilimumab, pembrolizumab, and tremelimumab [22-25]. Table 1 lists the angiogenesis inhibitors, and immune checkpoint inhibitors approved by the Food and Drug Administration (FDA), and in development.

Biologic	Target	Stage of development
Bevacizumab	VDFR-1/2	Marketed 2004
Nintedanib	VEGFR1-3,PDGFRa, PDGFRb	Phase III
Cediranib	VEGFR1-3, PDGFR	Phase II
Sorafenib	VEGFR1-3,PDGFRb, FGFR1, FGFR1, c-Kit	Phase II
Sunitanib	VEGFR, PDGFR, Flt3, c-Kit	Phase II
Vandetanib	VEGFR1,VEGFR2, PDGFRb	Phase II
Durvalumab	Anti-PD-1	Phase III
Pembrolizumab	Anti-PD-1	Phase II/III
Nivolumab	Anti-PD-1	Marked 2020
Ipilizumab	Anti-CTLA-4	Marketed 2020
Tremelimumab	Anti-CTLA-4	Phase IIb

Table 1: Angiogenesis inhibitors and immune checkpoint inhibitors approved and in development for the treatment of malignant pleural mesothelioma. Bevicizumab is included in the National Comprehensive Cancer Network guidelines, 2016 as an option for front-line therapy in patients with MPM

Several immune checkpoint inhibitors have been shown to be effective in prolonging the median OS, and progression-free survival (PFS), and some have been approved by the FDA for the treatment of several solid cancers, including MPM [22-25]. Single agent ICI immunotherapy is not as effective as dual IC blockade [22]. CTLA-4, and PD-(L1) im-

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mune checkpoint inhibitors (ICI) have an additive and synergistic effects in the treatment of malignant pleural mesothelioma (MPM). The combination of nivolumab a CTLA-4 inhibitor and ipilimumab a PD-1 inhibitor has been shown to be significantly superior compared with nivolumab alone in the treatment of MPM. The dual ICI have been shown to significantly improve the disease control rate (DCR) to 52% vs 40% compared with nivolumab alone, and to prolong the objective response rate (ORR) to 28% vs 19%, and the median progression free survival (PFS) to 5.6 months vs 4 months compared with nivolumab alone [26]. However, dual ICI treatment was associated with higher treatment-related adverse effects (93% vs 89%) [26]. Updated results of the IFCT-1501 MAPS2 results revealed median survival of 15.9 months (10.7-22.2) in patients treated with nivolumab plus ipilimumab compared with 11.9 months (6.7-17.4) in patients treated with nivolumab alone [27]. Disselhorst et al. [28] have also reported the efficacy of nivolumab plus ipilimumab combination. Treatment with nivolumab plus ipilimumab resulted in a response rate of 38%, and a disease control rate of 68% at 3 months of treatment. Another combination of ICIs was investigated for the treatment of MPM consisting of tremelimumab a CTLA-4 inhibitor, and durvalumab a PD-L1 blocker in 40 patients in the NIBIT-MESO-1 clinical trial [24]. Treatment with dual ICIs resulted in an ORR of 28%, a DCR of 65%, a median PFS of 8.0 months, and an overall survival of 16.6 months [29].

Different ICIs doublet have almost similar efficacy and safety profile, however, the nivolumab plus ipilimumab combination is the most preferred combination, because it has been proved to be effective in all the histological subtypes of MPM, and to be superior to SoC chemotherapy. In phase 3 CheckMate 743 multicentre trial involving 605 patients with unresectable MPM, treatment with nivolumab plus ipilumab resulted in a significant and meaningful improvement in the median OS of 18.1 months versus 14.1 months (p=0.0020) in the cisplatin and pemetrexed treated patients [30]. Dual ICI immunotherapy also significantly extended the 2-year survival up to 41% versus 27% in the chemotherapy group. Furthermore, the median duration of response (DOR) for the doublet ICI was 11.0 months versus 6.7 months with chemotherapy. Thirty-two percent of the responders to the immunotherapy experienced response up to 2 years versus only 8% of the patients who received chemotherapy. Noteworthy, the median OS achieved with dual ICIs was almost similar in the epithelioid, and non-epithelioid histopathological subtypes (18.7 months versus 18.1 months, respectively). There was significant benefit observed in the non-epithelioid subgroup for the checkpoint inhibitor combination versus the standard of care chemotherapy (18.7 month vs 8.8 months, respectively). Treatment with cisplatin plus pemetrexed resulted in an expected substantial difference in the efficacy of the chemotherapy between the epithelioid and non-epithelioid histotypes. SoC chemotherapy resulted in significant increase in the median OS of 63% in the epithelioid subtype versus 32% in the non-epithelioid histotype at one year, and 38% versus 8% at two years, respectively. Furthermore, the overall survival benefit of treatment with dual ICIs in the non-epithelioid subtype was remarkable. The OS benefit observed in the non-epithelioid histotype was 18.7 months compared with 8.8 months in the chemotherapy group [30]. This might have been contributed to established poor prognosis, and inferior efficacy of chemotherapy in the non-epithelioid subtype [30].

Recently, analysis of the CheckMate 743 trial has resulted in the Food and Drug Administration (FDA) approval of the combination therapy of nivolumab plus ipilimumab as a first-line treatment for unresectable MPM [30,31].

Malignant pleural mesothelioma is a highly aggressive and incurable cancer that originates from the mesothelial cells of the pleural cavity. The SoC chemotherapy comprising of cisplatin plus pemetrexed with or without bevacizumab has low overall response rate and is not curative. Dual immune checkpoint inhibitors, such as nivolumab plus ipilimumab significantly improve the ORR, DCR, median OS, and PFS, and are effective in both the epithelioid and non-epithelioid histology subtypes of MPM. Dual ICI therapy is superior to SoC chemotherapy, particularly in the non-epithelioid histotype, which has a poor response to chemotherapy. Currently, nivolumab plus ipilimumab immunotherapy is recommended as first-line therapy for MPM.

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Conflict of Interest

Authors have declared that no Conflict of Interest

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