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What can independent research for mesothelioma achieve to treat this orphan disease?

Guazzelli A[1], Meysami P[1], Bakker E[2], Bonanni E[3], Demonacos C[4], Krstic-Demonacos M[1], Mutti L[5]

1 School of Environment and Life Sciences, University of Salford, Salford, UK.
2 School of Medicine, University of Central Lancashire, Preston, UK.
3 National Asbestos Observatory, Rome, Italy.
4 Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, UK.
5 Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, PA, USA.

Correspondence: chariman@gime.it

Abstract

Introduction: Malignant pleural mesothelioma (MPM) is a rare neoplasm with a poor prognosis, as current therapies are ineffective. Despite the increased understanding of the molecular biology of mesothelioma, there is still a lack of drugs that dramatically enhance patient survival.

Area Covered: This review discusses recent and complete clinical trials supported by the NIH, other U.S. Federal agencies, universities and organizations found on clinicaltrials.gov. Firstly, chemotherapy-based trials are described, followed by immunotherapy and multitargeted therapy. Then we introduce drug repositing and the use of drug docking as tools to find new interesting molecules. Finally, we highlight potential molecular pathways that may play a role in mesothelioma biology and therapy.

Expert Commentary: Numerous biases are present in the clinical trials due to a restricted number of cases, inappropriate endpoints and inaccurate stratification of patients which delay the finding of a treatment for MPM. The most crucial issue of independent research for MPM is the lack of more substantive funding to translate these findings to the clinical setting. However, this approach is not necessarily scientific given the low mutational load of mesothelioma relative to other cancers, and therefore patients need a more solid rationale to have a good chance of successful treatment.

Highlights box
• Mesothelioma clinical trials rarely met the principal parameters for the design of high-quality trials mainly due to the size of the population investigated.
• Although targeted therapy and immunotherapy, in particular immune checkpoint inhibitors, has been approved by the FDA for the treatment of cancers such as melanoma, these therapies have shown low clinical benefit for MPM patients
• The approach of drug repositioning is based on a solid scientific rationale, combined with a good clinical trial design and effective endpoints may increase the chance to identify promising treatments for MPM.
• MPM is a heterogenous tumor, many molecular mechanisms including hypoxia, metabolism, microRNAs and gene-environment interaction should be the main areas for designing new promising therapeutic agents.
• The lack of appropriate interest and funding for research into MPM has most certainly affected the opportunity to achieve dramatic progress in the treatment of this neoplasm.

1. Introduction

Malignant mesothelioma is a highly lethal and rare malignant neoplasm with poor prognosis [1]. Mesothelioma mainly arises from mesothelial cells lining the pleura (approximately 80% of cases; malignant pleural mesothelioma (MPM)) and peritoneum (approximately 20% of cases) whilst very rare mesothelioma cases have been reported to originate from the pericardium and tunica vaginalis [2]. Between the critical factors leading to mesothelioma, exposure to asbestos is considered the primary cause, as asbestos exposure results in of chronic inflammation in the mesothelium promoting the carcinogenic processes [3]. Radiation and simian virus 40 (SV40) are additional agents suspected to cause MPM [4]. Recently, it has been reported that individuals bearing *BRCA1 associated protein-1 (BAP1*) mutations could be genetically predisposed to MPM since families with germline *BAP1* mutations develop MPM without any exposure to asbestos [5]. In addition, Nasu et al. reported that the high percentage of *BAP1* mutations were found in sporadic MPM (>60%) suggesting that *BAP1* is the most mutated gene in MPM and a potential "driver" in MPM pathogenesis [6]. Other relevant genes found highly altered in MPM patients are *NF2* (75% of the cases) and *CDKN2A* (60% of the cases). MPM is characterized by three different histological subtypes: the most frequent is epithelioid, which has a better prognosis than the sarcomatoid and biphasic (mixed of epithelioid and sarcomatoid subtypes) histologies. MPM occurs most frequently in adult males, with a sex ratio of approximately 3.6:1. The disease is usually diagnosed 30 to 40 years after occupational asbestos exposure and the mean age at the diagnosis is usually at 70 years [7]. The lack of accurate and reliable biomarkers for detecting early stage of MPM makes this cancer very difficult to diagnose and treat leading to poor prognosis as the survival rate after diagnosis is around 9-14 months [8]. Recently, studies have shown that BAP1 immunohistochemistry (IHC) and p16 fluorescence in situ hybridization (FISH) are reliable markers of malignancy in biopsies of mesothelioma [9]. Analysis based on 2008 data reported an average of 14200 new cases registered each year worldwide [10]. The worldwide incidence of MPM has increased and it is estimated that a peak will be reached between 2015 to 2030. High incidence rates have been recorded in the USA, the UK, Australia and Italy [11] and it has been predicted to increase further in the future, in particular in developing countries where asbestos has not been banned yet [12].

Once MPM is diagnosed, clinical staging is used to assess a prognostic score and decide the best treatment option. The most used staging classification system is the American Joint Committee on Cancer (AJCC) staging system, that is based on TNM (tumour, node, metastasis) classification [13]. Treatment options vary according to the TNM stage of cancer. Surgery is recommended only for selected patients with early-stage disease and stable health conditions [12]. Other options are a multimodality regimen, which consists of a combination of chemotherapy, surgery, and radiotherapy. The current standard first-line systemic treatment is combination chemotherapy of cisplatin and antifolate [12]. Nevertheless, the clinical benefit of this combination treatment over other therapeutic approaches is not clear [7]. The reasons for the disappointing effects of current therapies are not clear, therefore there is an increased need to understand why some patients respond to immunotherapy and others do not. This review focusses on independent preclinical and clinical research related to mesothelioma selected by only the clinical trials funded by Universities, National Institutes of Health (NIH) and charitable organisations from https://clinicaltrials.gov/, closing with an expert opinion from a translational research team.

1. Body

1.1. The failure of the current treatments

The current clinical trials for patients with MPM are mainly based on combination of standard chemotherapy plus one or more emerging agents (**Table 1**). In 2003, Vogelzang et al. published a clinical study which has been established as standard first line treatment using pemetrexed in combination with cisplatin for MPM patients in advanced stage disease but this combination confers a median progression-free survival (PFS) of 5.7 months [14]. Many other studies have been initiated to investigate the effect of combinatory treatments as first line treatment for MPM. For instance, Van Meerbeck et al. set a phase III trial which provided confirmatory evidence that a combination of cisplatin with an antifolate is superior to cisplatin alone [15]. Other phase II studies have employed cisplatin and gemcitabine [16,17], pemetrexed and carboplatin [18,19], bortezomib and cisplatin [20] but all have shown lack of improvement in overall survival (OS) and PFS. Most recently current standard chemotherapy is combined with additional drugs, for example, cisplatin and pemetrexed were combined with bevacizumab [21,22], or Imatinib Mesylate [23] with Amatuximab [24]. The most successful clinical trial is the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) where the OS is significantly improved by two months compared to chemotherapy only.

Several biases are met in the clinical trials for MPM patients, which could be the cause of the ineffective current experimental therapies. The principal hallmarks for the design of high quality trials are randomisation, blinding, adequate power, and a clinically relevant patient population [25]. Mesothelioma clinical trials rarely met all these parameters mainly due to the size of the population investigated. MPM is an orphan disease because it is rare compared to other cancers and once it has been diagnosed the survival is very poor (less than one year), which poses difficulties in the investigation of the long-term effects of a studied drug. Moreover, this cancer has high genetic and phenotypic intra-tumoral heterogeneity with additional differences of the spatial and temporal evolution of MPM, during the treatment, which increases the complications on treatment decisions [26].

Table 1. Summary of complete clinical trials using chemotherapy with or without other treatments for MPM patients. The selected studies were funded by Universities, National Institutes of Health (NIH) and charitable organisations from https://clinicaltrials.gov/.

Title	# pts	Phases	Sponsor/Collaborators	NCT Number
Intrapleural Photodynamic Therapy in a Multimodal Treatment for Patients With Malignant Pleural Mesothelioma	6	Phase II	University Hospital, Lille|Institut National de la SantÃ© Et de la Recherche MÃ©dicale, France|University of Pennsylvania|RÃ©gion Nord-Pas de Calais, France	NCT02662504
Vascularity Impact on the Treatment Outcome in Malignant Pleural Mesothelioma(VITMPM)	50		Ain Shams University	NCT02603315
Active Symptom Control With or Without Chemotherapy in Treating Patients With Malignant Pleural Mesothelioma	840	Phase III	Medical Research Council|National Cancer Institute (NCI)	NCT00075699
Isolated Thoracic Perfusion (ITP-F) for MPM	23		Medias Klinikum for Surgical Oncology	NCT02467426
Pemetrexed Disodium and Cisplatin Followed By Surgery and Radiation Therapy in Treating Patients With Malignant Pleural Mesothelioma	59	Phase II	European Organisation for Research and Treatment of Cancer – EORTC	NCT00227630
Pemetrexed Disodium and Cisplatin Followed by Surgery With or Without Radiation Therapy in Treating Patients With Malignant Pleural Mesothelioma	153	Phase II	Swiss Group for Clinical Cancer Research	NCT00334594
Mesothelioma Avastin Plus Pemetrexed-cisplatin Study	448	Phase II|Phase III	Intergroupe Francophone de Cancerologie Thoracique|University Hospital, Caen|Groupe Francais De Pneumo-Cancerologie	NCT00651456
Effect of FAS and FAS Ligand Polymorphisms on Patients With Platinum-Based -Treated Malignant Pleural Mesothelioma	68		Ain Shams University	NCT02269878
Study of Carboplatin and Vinorelbine in Malignant Pleural Mesothelioma	40	Phase II	Rigshospitalet, Denmark	NCT00272558
Gemcitabine in Long Infusion and Cisplatin for Malignant Pleural Mesothelioma Treatment	78	Phase II	Institute of Oncology Ljubljana|Ministry of Higher Education, Science and Technology, Solvenia	NCT01243632
Phase II Study of IMC-A12 in Patients With Mesothelioma Who Have Been Previously Treated With Chemotherapy	20	Phase II	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	NCT01160458
Extrapleural Pneumonectomy /Pleurectomy Decortication, IHOC Cisplatin and Gemcitabine With Amifostine and Sodium Thiosulfate Cytoprotection for Resectable Malignant Pleural Mesothelioma	141	Phase I	Brigham and Women's Hospital|Dana-Farber Cancer Institute	NCT00571298
Pilot Study of Allogeneic Tumor Cell Vaccine With Metronomic Oral Cyclophosphamide and Celecoxib in Patients Undergoing Resection of Lung and Esophageal Cancers, Thymic Neoplasms, and Malignant Pleural Mesotheliomas	10	Phase I	National Cancer Institute (NCI)|National Institutes of Health Clinical Center (CC)	NCT01143545

A Phase II Study of PF-03446962 in Patients With Advanced Malignant Pleural Mesothelioma	17	Phase II	NCIC Clinical Trials Group|Canadian Cancer Trials Group	NCT01486368
Pleurectomy/Decortication Followed by Intrathoracic/Intraperitoneal Heated Cisplatin for Malignant Pleural Mesothelioma	70	Phase I	Dana-Farber Cancer Institute|Brigham and Women's Hospital	NCT00165555
Phase II Study of Bevacizumab, Pemetrexed and Carboplatin as First-Line Therapy in Malignant Pleural Mesothelioma	77	Phase II	Armando Santoro, MD|Istituto Clinico Humanitas	NCT00407459
Cisplatin With or Without Raltitrexed in Treating Patients With Malignant Mesothelioma of the Pleura	256	Phase III	European Organisation for Research and Treatment of Cancer – EORTC	NCT00004920
Cisplatin With or Without Pemetrexed Disodium in Treating Patients With Malignant Mesothelioma of the Pleura That Cannot be Removed by Surgery	Null	Phase III	Memorial Sloan Kettering Cancer Center|National Cancer Institute (NCI)	NCT00005636
Cisplatin, Interferon Alfa, Surgery, and Radiation Therapy in Treating Patients With Malignant Pleural Mesothelioma	6	Phase I	Fox Chase Cancer Center|National Cancer Institute (NCI)	NCT00003263
Pemetrexed Plus Gemcitabine or Carboplatin for Patients With Advanced Malignant Pleural Mesothelioma	32	Phase II	Eastern Cooperative Oncology Group|National Cancer Institute (NCI)|North Central Cancer Treatment Group	NCT00101283
Pemetrexed, Cisplatin, and Vitamin B12 in Treating Patients With Mesothelioma of the Chest That Cannot Be Removed by Surgery	60	Phase II	Centre Oscar Lambret|National Cancer Institute (NCI)	NCT00541073
Decitabine in Treating Patients With Unresectable Lung or Esophageal Cancer or Malignant Mesothelioma of the Pleura	Null	Phase I	National Cancer Institute (NCI)	NCT00019825
S9810: Gemcitabine Plus Cisplatin in Treating Patients With Malignant Mesothelioma of the Pleura That Cannot Be Removed by Surgery	57	Phase II	Southwest Oncology Group|National Cancer Institute (NCI)	NCT00003723
Combination Chemotherapy Before Surgery in Treating Patients With Mesothelioma of the Lung	61	Phase II	Swiss Group for Clinical Cancer Research	NCT00030745
Dendritic Cell-based Immunotherapy Combined With Low-dose Cyclophosphamide in Patients With Malignant Mesothelioma	10	Phase I	Erasmus Medical Center	NCT01241682

1.2. New potential targets in MPM

2.2.1 Immunotherapy

One of the “hot” topics regarding cancer treatment is immunotherapy which aims to educate immune system components to trigger an effective immune response to kill cancer cells. Several immunotherapeutic strategies have been developed and investigated [27]. Immunotherapy consists of multiple strategies including the engineering of antibodies or immune cells to enhance their anti-tumour effect or stimulating the immune system to induce an effective immune response [28]. This strategy has been investigated in several tumours and the FDA has approved immunotherapy for treating melanoma, lung cancer, kidney cancer, and other cancers [29-31]. Several clinical trials assessed the effect, safety and tolerance of

immunotherapy in mesothelioma and here we reported only clinical trials that have been supported by NIH, Universities and no-profit organisations (**Table 2**) (**Figure 1**).

An example of immunotherapy applied to mesothelioma is the use of immunotoxic antibodies against mesothelin. Mesothelin is a 40 kDa glycoprotein with low expression in normal human tissues and high expression in many cancers, therefore this protein is an attractive antigen for antibody-based immunotherapy [32]. SS1(dsFv)PE38 (SS1P) is a recombinant immunotoxin against mesothelin that consists of a murine antimesothelin variable antibody fragment (Fv) bound to PE38, a truncated portion of Pseudomonas exotoxin A [32]. Two clinical trials have been assessed and supported by NIH, one (NCT01362790) investigated the effect of SS1P in combination with standard chemotherapy combination. The results showed that SS1P is well tolerated when given in combination with standard chemotherapy and 10 (77%) had a partial response, 1 had stable disease, and 2 had progressive disease [32]. The other study assessed how effective SS1P is when it is given with pentostatin and cyclophosphamide (NCT01445392). The results have not been published yet.

Gene therapy in combination with immunotherapeutic option has been investigated in a phase I study using an adenoviral vector expressing interferon-β (Ad.IFN-β) in 17 patients with malignant pleural mesothelioma or malignant pleural effusions (NCT00066404)[33]. After 2 months, modified (Response Evaluation Criteria in Solid Tumors) RECIST responses were as follows: one partial response, two stable diseases, nine progressive diseases, and two non-measurable diseases. One patient died after 1 month.

One of the most adopted immunotherapy strategies for cancer treatment is use of antibodies that block immune checkpoints. These monoclonal antibodies inhibit the immune checkpoints by preventing the receptors and ligands from binding to each other, thereby blocking the signalling that promotes cancer survival by evading T-cell-mediated death [34]. The immune checkpoint receptors cytotoxic T lymphocyte-associated 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are expressed on the surface of cytotoxic T-cells and interact with their ligands binding of B7-1 (cluster CD80) and programmed death ligand-1 (PDL-1) on antigen presenting cells to promote cancer survival [35]. Several immune checkpoint inhibitors have been approved including ipilimumab (an anti-CTLA-4 agent), nivolumab and pembrolizumab against anti-PD-1, nivolumab, and pembrolizumab as PDL-1 inhibitor, atezolizumab against PDL-1 for treating cancers such multiple melanomas, lung and ovarian cancer [36]. Pembrolizumab has been investigated alone (NCT02399371) in MPM patients previously treated in a phase II study. 35 patients were enrolled and the median PFS was 6.2 months and median OS has not been reached with a high level of toxicity (grade 3/4 and 1/2). Nivolumab (Nivo) and ipilimumab (Ipi) have been assessed as $2^{nd}/3^{rd}$ line treatment in 125 patients. Generally, disease control rate (DCR) is <30% with the current drugs tested in 2^{nd}-line but the results from the phase II clinical trials reported that twelve weeks-DCR was 42.6% with Nivo, and 51.9% with Nivo+Ipi. In the combo arm, grade/G3-4 toxicities were slightly increased compared to Nivo alone (86.9%/16.4%) vs (77.8%/9.5%) and 3 treatment-related deaths were observed [37].

Dendritic cell-based immunotherapy includes vaccinations based on the use of dendritic cells (DCs). DCs are the most potent APCs and induce the activation and proliferation of cytotoxic CD8+ and helper CD4+ T lymphocytes to eliminate cancer cells [38]. DCs vaccines are developed *ex vivo* and injected as tumour antigen pulsed dendritic cells [39]. This therapeutic

approach has been investigated in mesothelioma. The administration of tumour lysate-pulsed dendritic cells was assessed in a clinical trial with 9 patients with mesothelioma. The aim of the study was to evaluate the safety and immunological response induced by the treatment. The results showed that the vaccination was safe with no grade 3 or 4 toxic effects, only moderate fever and after three vaccinations, cytotoxic activity against autologous tumour cells were detected in a subgroup of patients. Median survival was 19 months but nine patients died of disease; one patient is alive with disease (NCT02395679)[40]. Although immunotherapy has some beneficial effects on some solid tumours, in MPM the response has been disappointing so far and there are many concerns with regard to its true impact [8]. Since the role of the immune system in MPM is multifaceted, research should focus on the tumour microenvironment characteristics such hypoxia and the chronic inflammatory state, tumour-associated macrophages (TAMs), T regulatory cells and cancer-associated fibroblasts. In addition, the interaction of genetic instability and the environment promote even further the development and progression of this cancer. Therefore, targeting one of these pathways or a combination could provide promising outcomes when combined to immunotherapy and the only way to achieve these results is funding basic research not directly aimed at the translation of what already known for other tumours but paving new MPM-tailored immunotherapies[41-43].

2.2.2 Multi-targeted therapy

2.2.2.1 Tyrosine-kinase inhibitors (TKI)

For the past decades, the knowledge about cancer biology has increased exponentially, therefore to overcome the low clinical benefit of chemotherapeutic approaches, clinical and experimental research was focussed on developing and investigating the role of small molecule inhibitors to target several molecular pathways involved in carcinogenesis. The first molecules that were targeted are growth factors, which promote uncontrolled tumour growth and tumour angiogenesis. These molecules are part of a big family of transmembrane tyrosine kinase receptors (TKRs), including epidermal growth factor receptor (EGFR), insulin-like growth factor (IGF) and vascular endothelial growth factor receptors (VEGFRs) [2]. Several studies showed that EGFR protein is overexpressed in more than 50% of MPM cases. From five clinical trials enrolling mesothelioma patients treated with erlotinib, four were sponsored by NIH or other sponsors (Table 2). A phase II study enrolled 63 previously untreated MPM patients to investigate the effect of erlotinib. Immunohistochemical analysis of EGFR has shown that 75 % of patients tumours highly expressed EGFR, but nonetheless, there was no response for 33 patients with measurable disease, median OS was 10 months and PFS was only 2 months. Therefore, single-agent erlotinib was not effective in MPM (NCT00039182) [44]. Another phase II study investigated the response rate, progression, survival, and toxicity of erlotinib with bevacizumab in 24 patients previously treated with one chemotherapy regimen. Complete or partial response was not achieved and OS was 5.8 months and PSF 2.2 months (NCT00137826)[45]. Another drug inhibiting EGFR is gefitinib that has been assessed in a phase II study in previously untreated malignant mesothelioma patients. 43 patients were enrolled and one1 (2%) had a complete response, one (2%) had a partial response and 5 (12%) had an early death. Although the majority of mesothelioma patients had EGFR overexpression, gefitinib was not effective in malignant mesothelioma. Another class of small inhibitors has been studied in mesothelioma patients that target vascular endothelial growth factor (VEGF) and its receptor VEGFR. Studies have shown high levels of both molecules in MPM tissue specimens (NCT00025207)[46]. Numerous anti-VEGF/VEFGR inhibitors have been independently assessed in malignant mesothelioma including cediranib[47], sunitinib[48], and

vatalanib[49] demonstrating no effect or poor activity, with no clinical benefits. SV40-dependent Akt pathway has been found upregulated in malignant mesothelioma, which protects against cell death in HMC and malignant mesothelioma cells after amosite (a particular kind of asbestos) exposure, therefore targeting this pathway may make MPM patients sensitive to chemotherapy. Therefore, TKR activating mutations are not the main responsible for MPM resistance rather SV40-positive human mesothelial cell and exposure to amosite fibers for long term promotes cell survival via Akt Activation[50].

2.2.2.2 Antibodies based therapy

Antibodies have been developed against growth factors such as IFG-1 and VEGF. Cixutumumab, a monoclonal antibody that selectively inhibits ligand binding to IGF-1R, was tested in mesothelioma patients since *in vitro* and preclinical studies demonstrated tumour reduction after cixutumumab treatment. A phase II study has been conducted for previously treated MPM patients but the results are not available. Bevacizumab (Avastin) is the most encouraging drug that targets VEGF signalling which is a humanized monoclonal antibody against VEGFA. Bevacizumab was approved in the EU in 2005 for the treatment of many solid cancers such as non-small cell lung cancer (NSCLC), colorectal carcinoma and renal cell cancer [51-53] (**Figure 1**). From seven clinical trials for bevacizumab, five have been accomplished and sponsored by NIH or other sponsors. Bevacizumab has been investigated in combination with standard chemotherapy. Bevacizumab was evaluated in combination with gemcitabine and cisplatin in a randomized, double-blind, placebo controlled study in 115 MPM patients (NCT00027703). There were differences in response between bevacizumab and placebo arms (PFS; 6.9 vs 6.0 months) and OS (15.6 vs 14.7 months) [54]. Bevacizumab was also tested in combination with carboplatin and pemetrexed in a Phase II study in patients with unresectable MPM. The median PFS was 6.9 months and the median OS was 15.3 months and the study failed to achieve the primary endpoint of 50 % improvement in PFS compared to standard chemotherapy [54]. Another phase II study investigated the combination of bevacizumab with pemetrexed and cisplatin in 53 patients with previously untreated and unresectable mesothelioma (NCT00295503). Although the treatment was well tolerated, it failed to achieve its primary endpoint of 33% improvement in PFS at 6 months [21].

Novel anticancer agents including histone deacetylase (HDAC) inhibitors, nuclear factor-κB (NF-κB) pathway inhibitor, anti-TGFβ monoclonal antibody, and anti-Met small inhibitors are all currently under investigation. Belinostat targets HDAC which regulates epigenetic mechanisms of tumour suppressor genes through chromatin remodelling with tumourigenic effects [55]. A phase II trial was designed to analyse the effect of belinostat as second-line treatment in patients with MPM (NCT00365053). 13 patients were enrolled but belinostat was not effective as a single second-line therapy in MPM patients [56]. Bortezomib is a specific proteasome inhibitor that promotes downregulation of NF-κB and stimulates apoptosis. Although preclinical results were encouraging, the results showed low clinical activity and high toxicity in a Phase II study in pre-treated patients with MPM [57]. GC1008 is a neutralizing anti-TGFβ antibody and its clinical safety and median survival were the main aims of this Phase 2 study [58] (**Figure 1**). 13 pre-treated MPM patients participated to the study and the results reported that GC1008 is well tolerated; however, there was an indication that the treatment might promote the malignant cell growth in a few patients.

Ultimately in hindsight, the front-line treatment for MPM is based on pemetrexed, cisplatin, and bevacizumab, as these are the treatments shown to significantly improve patient survival. Notably, for bevacizumab, this treatment was based on solid preclinical experiments that proved VEGF to be an autocrine growth factor for mesothelioma [59]. Furthermore, it was also shown that high serum VEGF levels are linked with poorer patient prognosis and therefore represents a clear example of the kind of independent research that promoted pharmaceutical organisations to invest.

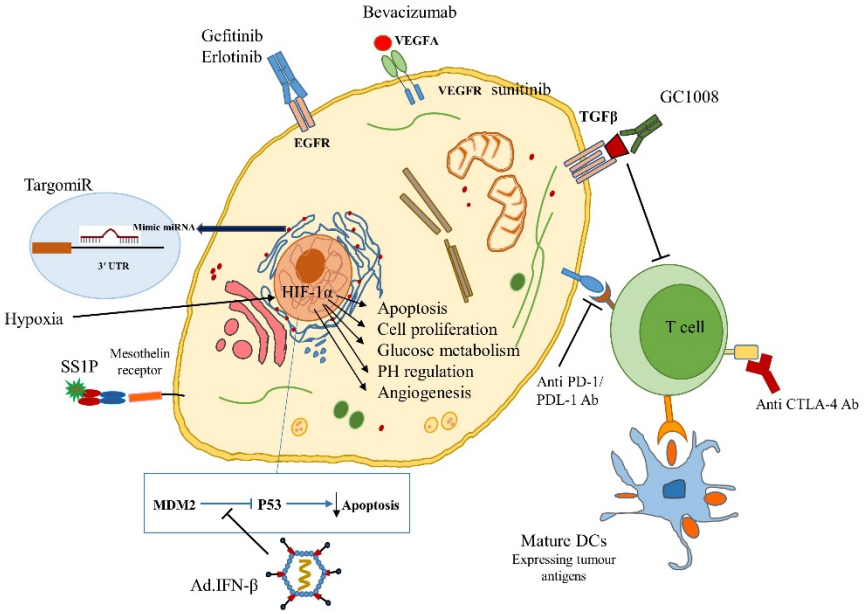

Figure 1 Summary of recent therapeutic agents tested in mesothelioma and potential targets.
Immunotherapy includes; antibody (Ab) targeting immune checkpoints (programmed cell death-1 and programmed cell death ligand 1; PD-1/PDL-1, cytotoxic T-lymphocyte–associated antigen 4; CTLA4) and immunotoxin Ab targeting mesothelin (SS1P). An example of gene therapy is an adenoviral vector expressing interferon-β (Ad.IFN-β) and vaccines have been tested with mature dendritic cells (DCs) engineered to express a tumour antigen. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor A (VEGFA). GC1008 is a neutralizing anti-TGFβ (Transforming growth factor β) antibody. Small inhibitors include anti-EGFR (epidermal growth factor receptor) and anti-VEGFR (vascular endothelial growth factor receptor). HIF-α, Hypoxia-inducible factor 1-α, miR (microRNA) TargomiR is a strategy that uses minicells carrying mimic miR-16 function.

2.3 How repositioning drugs can help mesothelioma therapy

Drug repositioning is a potential approach for the identification of new therapeutic use for already approved drugs. The majority of biochemistry and clinical proprieties such as bioavailability and safety profiles, proven formulation and manufacturing routes, and reasonably characterized pharmacology, are known for most approved molecules which favour the inclusion of these repositioned drugs in clinical phases more rapidly and at a lower cost than novel therapeutic agents [60]. For rare diseases such as mesothelioma that are understudied at the preclinical and clinical levels, the development of new compounds is problematic and needs worldwide collaboration from numerous clinical trial centres in order to achieve successful outcome from innovative drugs. Drug repositioning may be an attractive

strategy for diseases such as mesothelioma, by offering a reduced timeframe from preclinical research to the bedside [61]. Furthermore, with the expected increase of incidence of MPM in developing countries, drug repositioning could offer solutions for patients living in these countries. Repositioning may apply to a wide variety of drugs (see subsequent sections) and be performed in a variety of ways. Recent research used the DRUGSURV database [62] to target individual genes/proteins that were identified as important for mesothelioma based on computational modelling of TP53 and stratified patient data [63](**Figure 2**).

Other approaches include drug/molecular docking; this is one of the most powerful approaches for structure-based discovery [64], as it predicts the interaction between small molecule ligands and targets (such as proteins that are targeted for inhibition or modulation). There are numerous softwares available to conduct this, including PyRx which, in conjunction with other software and resources, has been applied in the past to identify small molecule inhibitors that break the interaction between TP53 (obviously highly important for cancer) and its inhibitors [65]. Applied to mesothelioma, drug docking could utilise databases such as the ZINC database (which offers structures for approved drugs as well as experimental drugs [66]) to obtain drug structures and perform an *in silico* screen of these drugs against proteins that are believed to be important for mesothelioma development. This approach could, therefore, identify repositioned drugs in a molecular structure-based approach. The below sections will cover a variety of repositioned drugs and how they may apply to mesothelioma.

2.3.1 Antiemetic drugs

One of the first repositioned drugs is thalidomide, an antiemetic drug, used in the past for morning sickness in pregnant women with detrimental consequences because of its teratogenic effects [67]. Later, it has been demonstrated that thalidomide has anticancer proprieties and therefore it has been assessed in several human cancers in clinical trials, which led to its approval for the treatment of multiple myeloma [68]. In MPM, thalidomide has been evaluated in clinical trials without prior investigations in preclinical models. A phase II clinical study investigated the efficacy and toxicity of thalidomide in patients with MPM. The promising results showed that 27.5% of previously treated patients and treated with thalidomide as a single agent had disease stabilization for >6 months and the median survival was 230 days. These results warrant phase III studies in MPM [69]. Unfortunately, in a randomised phase III study thalidomide failed to improve OS, 10.6 months in the thalidomide group versus 12.9 months in the active supportive care group in patients with MPM after first-line therapy in chemotherapy [70].

2.3.2 Histone deacetylase inhibitors

Valproate is another drug widely used as an antiepileptic drug and found to have several anticancer effects through its HDAC inhibiting activity [71]. In addition, it has been shown that valproate induced tumour differentiation, reduced tumour growth and metastasis formation and promoted apoptotic cell death [72]. Therefore, valproate has been assessed in clinical trials for treating several cancers including glioblastoma and cervical cancer [73,74]. Valproate has also been evaluated in preclinical and clinical research in patients with MPM. The synergistic activity of valproate in combination with chemotherapy contributed to the design of a phase II trial to investigate valproate in combination with doxorubicin in patients with refractory or recurrent MPM after standard first-line chemotherapy [75,76]. Among 45 patients, seven

(16%) obtained a partial response. The median PFS was 2.5 months and the median OS was 6.7 months [76].

2.3.3 Statins

Another class of compounds frequently used for drug repositioning is statins. Generally, statins are used for the treatment of hypercholesterolemia and related atherosclerotic diseases, such as coronary artery disease. Statins also have anticancer proprieties [77] and have been intensely examined *in vitro* in human MPM cells. Rubins et al. demonstrated that Lovastatin decreased cell viability in a dose-dependent manner in human MPM cell lines, through apoptosis induction [78]. Another study showed that the combination of lovastatin and valproate reduced cell invasion of Acc-Meso-1 cells [79]. A synergistic effect of pemetrexed in combination with simvastatin induced apoptosis in MSTO-211 MPM cells by reactive oxygen species-dependent mitochondrial dysfunction and Bim induction as reported by Hwang et al. [80]. It has also been shown that statins have a role in the reversal of doxorubicin resistance by accumulating nitric oxide species in human MPM cells**.** Furthermore, statins have been shown synergistic antiproliferative effects with γ-tocotrienol (an isoform of vitamin E) on human MPM cells, via inhibition of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activations [81]. The potential to reposition lovastatin has also been demonstrated *in vivo*. The drug reduced primary tumour and metastasis in a NOD/SCID/ γ-null (NOG) mouse model of human MPM [82]. However, the role of statins in MPM has not yet been investigated in clinical trials.

2.3.4 Antifungal drugs

Itraconazole is generally administrated as broad-spectrum anti-fungal agent but it has been demonstrated *in vivo, in vitro,* and through clinical research that it has several antineoplastic properties [83]. Itraconazole decreased the viability in a dose-dependent manner by decreasing Gli1 expression, which is a key factor of the hedgehog pathway in various human MPM cell lines of epithelioid, sarcomatoid and biphasic subtypes [84]. However, itraconazole is yet to be assessed *in vivo* or in a clinical trial in MPM.

Arsenic trioxide (ATO), a traditional Chinese medicine, has also been used for cancer treatment. Nonetheless, it has a high grade of toxicity, it was repositioned in western medicine and ATO was approved for the treatment of relapsed or refractory acute promyelocytic leukemia by the U.S. Food and Drug Administration in September 2000 [85]. ATO treatment has been also evaluated on human MPM cells, in the NCI-H2052 MPM cell line ATO cause apoptosis by activating c-JunNH2-terminal kinase (JNK)1/2, and the extracellular signal-regulated kinase (ERK) pathway [86]. An antiproliferative effect and cytotoxic effect of ATO [62] was also reported *in vitro* and *in vivo* in MPM by apoptosis induction mediated through downregulation of E2F1 and downregulation of thymidylate synthase, which is involved in pemetrexed resistance when overexpressed [87].

2.3.5 DNA methyltransferase inhibitors

Disulfiram (DSF) is a drug of the dithiocarbamate family and is an irreversible inhibitor of aldehyde dehydrogenase approved by the FDA to treat alcoholism [88]. It has also demonstrated to inhibit tumour growth since DSF has epigenetic properties as a DNA methyltransferase inhibitor [89].

In human MPM DSF has been studied *in vitro* together with copper to induce cytotoxicity, demonstrating that DSF–copper (DSF-Cu) complex inhibited proliferation of MPM cell lines

and induced apoptosis [90]. Moreover, the inhibition of tumour growth was confirmed *in vivo* model, showing a 71% decrease of tumour growth when compared to control tumours [90].

2.3.6 Nonsteroidal anti-inflammatory drugs

Acetylsalicylic acid or aspirin prevents the function of cyclooxygenase (COX)-1 and COX-2 and is mainly used as a nonsteroidal anti-inflammatory drug but has been shown to promote apoptosis and suppresses the acquisition of chemoresistance [91]. Aspirin has been investigated in human MPM cell lines showing the inhibitory effect on colony formation by secreting high amounts of high-mobility group box (HMGB)1, a protein that regulates nucleosome assembly and chromatin structure [92]. The antiproliferative effect of aspirin on MPM cells was confirmed *in vivo* [92]. However, Aspirin has not yet been tested in clinical trials in MPM patients.

Celecoxib is a selective COX-2 inhibitor [66] approved by the FDA since December 1999 in familial adenomatous polyposis [93]. In MPM, celecoxib decreased prostaglandin E2 levels in AB1, a murine MPM cell line [94]. The effect of celecoxib has also been evaluated *in vivo* in BALB/c mice xenografted using AB1 cells, however clinical assessment of the role of COX-2 in MPM is still missing.

2.3.7 Oral antidiabetics

Metformin is a biguanide derivative, which is prescribed for type 2 diabetes. Metformin may act as an anticancer drug that promotes apoptosis, cell cycle arrest and invasion [95]. In MPM, the influence of metformin on the intercellular transfer of cellular contents has been assessed in cell lines of the biphasic, sarcomatoid and epithelioid types. Metformin suppressed tunnelling nanotube formation *in vitro* [96]. Regardless of this effect, metformin did not significantly reduce cell proliferation. So far, metformin has not been investigated *in vivo* or in clinical trials in MPM.

2.3.8 Vitamin E isoform

It is known that vitamin E has a role in cancer acting as an antioxidant adjuvant. Tocotrienol (T3) is an isoform of vitamin E which has an effect on NF-κB, signal transducer and activator of transcription (STAT) 3, apoptosis, nuclear factor (erythroid-derived 2)-like 2, hypoxia-inducible factor 1 (HIF-1), growth factor receptor kinases, and angiogenic pathways [97]. Tocotrienol-rich fraction extracted from rice and source of γ-T3 synergizes with cisplatin reducing the chemoresistance in H28, a human cisplatin-resistant MPM cell line [98]. In addition, the combination of γ-T3 with statins promoted an antigrowth effect on human MPM cells through reduction of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activations [81]. γ-T3 has not been investigated *in vivo* or in clinical trials in MPM.

α-tocotrienol is another isoform of tocotrienol with pro-apoptotic anticancer properties, its redox-silent analogue, 6-O-carboxypropyl-α-tocotrienol (T3E), has been tested *in vitro* in human MPM cells which inhibited the cell proliferation of human MPM H28 cells [99]. α-T3 has not been investigated *in vivo* or in clinical trials in MPM.

2.3.9 Antibiotics

Anisomycin is an antibiotic produced by Streptomyces griseolus and acts as a protein synthesis inhibitor, low dose of anisomycin enhanced the sensitivity to TNF-related apoptosis-inducing ligand (TRAIL) in mesothelioma cells [100]. This sensitisation enhanced the activity of Bim by post-translational modifications which primes the cells for apoptosis via the death receptor pathway. These data have not been confirmed *in vivo* or in clinical trials.

2.3.10 Bisphosphonates

Bisphosphonates are approved for treatment of bone lesions such as osteoporosis, cancer-induced osteolytic bone disease and hypercalcaemia [101]. Moreover, nitrogen-containing bisphosphonates such as zoledronic acid (Zol) have anticancer effects [102]. *In vivo* and in vitro experiments in mesothelioma showed that Zol induced apoptosis and S-phase arrest in a p53-independent manner[103]. Several clinical trials have been assessed the effect of Zol in mesothelioma patients. A study by Jamil et al. [104] examined the effect of single agent Zol in a small group of patients with MPM who had progressed after one or more prior systemic therapies. Among eight pretreated patients, the median PFS was 2 months and the median OS was 7 months without significant toxicity. Another study by Clive et al. [105], looking at the role of Zol in malignant pleural effusions, showing that two patients with MPM had a reduction in tumour bulk on radiology after receiving two doses of ZA intravenously. A recent multicentre double-blind randomised controlled feasibility study aims to assess the recruitment and acceptability of Zol/placebo alongside chemotherapy in MPM[106].

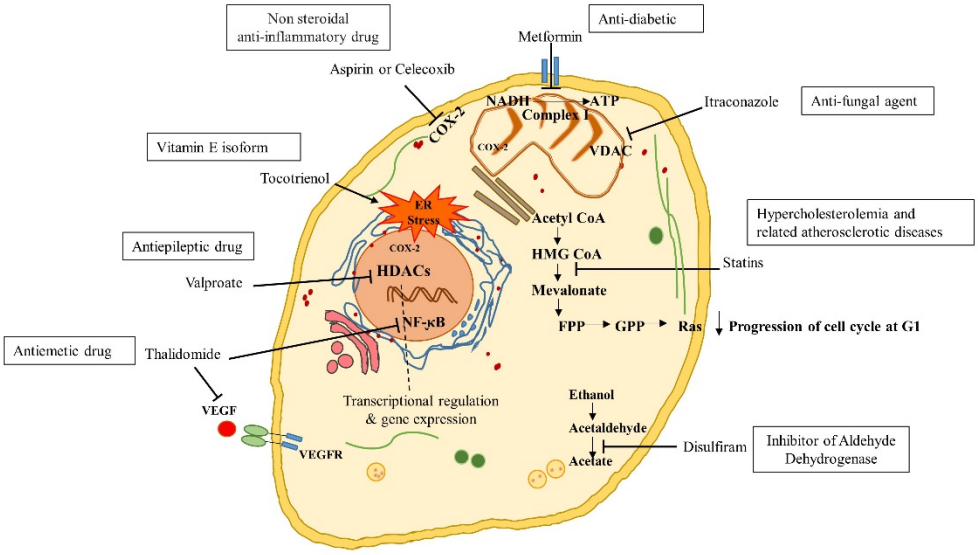

Figure 2 Examples of drugs repositioning in mesothelioma.
Abbreviations: NADH; nicotinamide adenine dinucleotide, ATP; Adenosine triphosphate, COX-2; Cyclooxygenase-2, VDAC; Voltage-dependent anion channel, CoA; coenzyme A reductase, HMG; 3-hydroxy-3-methylglutaryl, FPP; farnesyl pyrophosphate, GPP; geranyl pyrophosphate, ER; endoplasmic reticulum, HDAC; histone deacetylases, NF-κB; nuclear factor kappa-light-chain-enhancer of activated B cells, VEGFR; vascular endothelial growth factor receptors, VEGF; vascular endothelial growth factor.

2.4 Discovery of new small molecules

Basic research has led to the discovery of new pathways relevant to the development of MPM, and the latest studies focussed on mechanisms involved mainly in tumour microenvironment such as hypoxia, caused by the lack of oxygen and formation of the abnormal tumour blood vessels. In 2006, Klabatsa et al described that mesothelioma and not mesothelial cells overexpressed HIF-1α corresponding with the presence of hypoxia [107]. Later, it has been demonstrated with [F-18] fluoromisonidazole (FMISO) PET-CT that there are significant areas

of hypoxia, particularly in dominant tumour masses, in mesothelioma patients, therefore mesothelioma may be considered a hypoxic tumour [108]. One study investigated which pathways are induced by hypoxia to promote aggressive phenotypic changes in human mesothelioma cell lines. The high CD44 cell population of mesothelioma cells was significantly increased in hypoxia when compared with normoxia. In addition, hypoxia significantly increased the resistance of mesothelioma cells to cisplatin. While cisplatin treatment decreased in normoxic condition and hypoxia also increased the ratio of Bcl-2 to Bax in mesothelioma cells treated with cisplatin. Hypoxia promoted the mobility, invasiveness and epithelial to mesenchymal transition of HMM cells [109]. Although targeting hypoxia seems promising and topotecan, YC-1, PX-478 are compounds targeting directly hypoxia through the inhibition of HIF-1, they have not been tested in clinical trials in mesothelioma [110]. MicroRNAs (miRNAs or miRs) are other small regulatory molecules widely investigated in cancer since their deregulation influences tumorigenesis. Since they are small circulating molecules, they are mainly studied as biomarkers for diagnostic and prognostic aims. A study reported that MiR-185, miR-197, and miR-299 were differentially expressed in MPM samples compared to healthy pleura. Two-miRNA prognostic signatures were identified Let-7c-5p and miR-151a-5p which are linked to hypoxia and energy metabolism respectively [111]. It has been found that miRNA-31 induced chemoresistance though an ABCB9-independent mechanism in MPM[112]. The only current clinical trial that assesses the role of miRNAs as a therapeutic tool in mesothelioma is based on testing a miR-16 mimic (Table 2). In an *in vivo* study, miR-16-loaded minicells called EDV^{TM}nanocells (EDVs) were able to control tumour growth in a dose- and frequency-dependent manner, with the highest dose (administered four times per week), completely inhibiting tumours [113]. Following these data, a phase I study in MPM and NSCLC patients ('MesomiR 1') is currently assessing the safety and dose-escalation of TargomiRs (NCT03531840). Authors found that the maximum tolerated dose was 5×10^9 TargomiRs once weekly. One (5%) had a partial response, 15 (68%) had stable disease, and six (27%) had progressive disease and 21 (78%) deaths occurred, of which 20 were related to tumour progression and one was due to bowel perforation [114](**Figure 1**). Another innovative field is tumour metabolism that is acquiring more importance in mesothelioma. Mesothelioma cells are mainly glycolytic dependent even in the presence of oxygen (Warburg effect), therefore targeting glycolytic pathway may be a successful strategy to target cancer cells. Citrate, an inhibitor of phosphofructokinase (PFK) has been tested in chemoresistant mesothelioma cell line and the results showed that the inhibition of PFK by citrate in addition to depletion of ATP, diminution of the expression of the anti-apoptotic proteins and inhibition of hexokinase may promote the cytotoxic and synergistic effect with cisplatin [115]. Another study found that the secreted frizzled-related protein 4 (sFRP4), a Wnt inhibitor may reduce and alter cancer cell metabolism, leading to sensitisation of cancer cells to chemotherapeutics and cell death [116]. Other potential therapeutic targets are excitatory amino acid transporters, a glutamate carrier, Dishevelled3, an activator of the Wnt pathway and glutamine synthetase [117]. Recent findings indicate that the *BAP1* gene has a crucial function in mesothelioma. *In vitro* studies demonstrated that BAP1 regulates Ca^{2+} flux by stabilization of inositol-1,4,5-trisphosphate receptor expression promoting apoptosis [118]. In addition, it has been demonstrated that *BAP1*+/− fibroblasts enhanced aerobic glycolysis and lactate secretion, in contrast, they decreased mitochondrial respiration and ATP production in comparison with *BAP1* wild type (WT) [118]. However, a phase II clinical trial is recruiting patients with WT and mutant *BAP1* to investigate whether patients with BAP1 mutations are more responsive to

olaparib, a Poly (ADP-ribose) polymerases inhibitor that has been approved for treating germline and somatic BRCA1-mutant ovarian cancer. Since BAP1 is associated with BRCA1 activity, this trial may provide promising results (NCT03531840) (Table 2).

Table 2. ***Summary of clinical trials of new potential drugs in MPM***

	Target	**Drugs**	**Combinations**	**Phases**	**Sponsor/ Collaborators**	**NCT Number**
Immunotherapy	**Mesothelin**	SS1P	CDDP-PEM	Phase I	National Cancer Institute (NCI)	NCT01445392
		SS1P	Pentostatin/Cyclop	Phase I/II	National Cancer Institute (NCI)	NCT01362790
	PD-1	Pembrolizumab	Alone	Phase II	University of Chicago **Collaborator:** National Cancer Institute (NCI)	NCT02399371
	Gene therapy	Adenoviral-mediated IFN-β BG00001		Phase I	Abramson Cancer Centre of the University of Pennsylvania **Collaborator:** National Cancer Institute (NCI)	NCT00066404
Tyrosine-kinase inhibitors (TKI)	**Dendritic Cell-based vaccine**	Tumour lysate-loaded autologous dendritic cells		Phase I	Erasmus Medical Centre	NCT02395679
	EGFR	Erlotinib	Alone	Phase II	National Cancer Institute (NCI)	NCT00039182
		Erlotinib	Bevacizumab	Phase II	National Cancer Institute (NCI)	NCT00137826
		Gefinitib (ZD1839, Iressa)		Phase II	National Cancer Institute (NCI)	NCT00025207
Antibodies based therapy	**Anti-angiogenesis inhbitors**	Bevacizumab		Phase II	University of Texas Southwestern Medical Centre **Collaborators:** University of Chicago Columbia University Duke University **Information provided by (Responsible Party):** Jonathan E. Dowell, University of Texas Southwestern Medical Centre	NCT00295503 NCT00027703

					National Cancer Institute (NCI)	
	Histone deacetylase inhibitors	Belinostat		Phase II	National Cancer Institute (NCI)	NCT00365053
Discovery of new small molecules	**A miR-16-based microRNA mimic**	TargomiRs		Phase I	Asbestos Disease Research Foundation	NCT02369198
	PARP inhibitor	Olaparib		Phase II	National Cancer Institute (NCI)	NCT03531840

Add conclusions

2. Expert Opinion

The lack of appropriate interest and funding for research into MPM has most certainly affected the opportunity to achieve dramatic progress in the treatment of this neoplasm. As has become clear throughout this manuscript, a recurring issue that has been seen is that there is an insufficient bedrock of preclinical research to support translation to the clinic. Unfortunately, what has often been done is to attempt to reapply existing drugs that have shown success in other cancer types to treat mesothelioma. Whilst faster, this approach demonstrates its frailty through for example the use of tyrosine kinase inhibitors and, despite high hopes, immunotherapy, both of which have shown limited benefit for MPM. Should we desire to significantly improve MPM patient survival, it must first be acknowledged that there is still a long way to go.

Recent findings regarding MPM gene-driven metabolism provide new opportunities to stratify patients on the specific biological characteristics of this tumour. These studies also allow identification of a broad range of newly identified specific targets for MPM that may represent a significant improvement for patients in the near future. To achieve these results, specific independent investments are necessary. As stated, the approach of adopting drugs that have shown benefit in other tumours is of low clinical benefit, and therefore investment into new ideas leading to new therapies for this “niche” tumour would be beneficial, particularly with targeted drug repositioning that is based on a solid scientific rationale, complemented by good clinical trial design and effective endpoints such as overall survival.

Our hope is that over the next few years the research groups currently investigating MPM will find a way to integrate their knowledge and that grant submission systems will allow for the submission of team-oriented multidisciplinary project/programmes to cope with this upcoming demand of solid translational research for MPM. MPM is characterised by a low mutational

load which complicates finding tailored therapy for this illness. However, as quoted above, there has been a recent surging flow of data to unravel how gene-driven metabolism[118] affects MPM cell growth and hinders response to standard treatments. These achievements, together with the pathway through which these effects are exerted, are of potential huge interest and many efforts being aimed at their validation is currently underway. Such validated results will provide solid data for patients to reasonably rely on to continue to hope. Therefore, we also believe that independent research should be imbued by pure passion and dedication, which will help in coping with patient demands.

It has recently been shown via a retrospective study of precision medicine from 2006 to 2018 that the portion of patients who can benefit of precision treatments increased very little when compared with all the resources deployed in this direction: from 0.70 % in 2006 to 4.90 % in 2018 [119]. It seems reasonable to figure out that we need better multi-disciplinary integration to accelerate our achievements in this field.

Conflict of Interest Statement

All authors have nothing to disclose.

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** Useful study for understing the direction of future personalized medicine by Massard and colleagues.