Drug repurposing in malignant pleural mesothelioma: a breath of fresh air?

Arnaud Boyer1,2, Eddy Pasquier3, Pascale Tomasini1,2, Joseph Ciccolini2, Laurent Greillier1,2, Nicolas Andre2, Fabrice Barlesi1,2 and Celine Mascaux1,2

Affiliations: 1Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Multidisciplinary Oncology and Therapeutic Innovations Dept, Marseille, France. 2Centre de Recherche en Cancérologie de Marseille (CRCM, Marseille Cancer Research Centre), Inserm UMR1068, CNRS UMR7258 and Aix-Marseille University UM105, Marseille, France. 3Aix Marseille University, Assistance Publique des Hôpitaux de Marseille, Dept of Haematology and Paediatric Oncology, Marseille, France.

Correspondence: Céline Mascaux, Service d’Oncologie Multidisciplinaire et Innovations Therapeutiques, Hopital Nord, Chemin des Bourrely, 13915 Marseille cedex, France. E-mail: celine.mascaux@ap-hm.fr

@ERSpublications

Drug repurposing is an interesting research area for mesothelioma, which has a very poor outcome and few drugs approved http://ow.ly/igTq30hSloC

Cite this article as: Boyer A, Pasquier E, Tomasini P, et al. Drug repurposing in malignant pleural mesothelioma: a breath of fresh air?. Eur Respir Rev 2018; 27: 170098 [https://doi.org/10.1183/16000617.0098-2017].

ABSTRACT Drug repurposing is the use of known drugs for new indications. Malignant pleural mesothelioma (MPM) is a rare cancer with a poor prognosis. So far, few treatments have been approved in this disease. However, its incidence is expected to increase significantly, particularly in developing countries. Consequently, drug repurposing appears as an attractive strategy for drug development in MPM, since the known pharmacology and safety profile based on previous approvals of repurposed drugs allows for faster time-to-market for patients and lower treatment cost. This is critical in low- and middle-income countries where access to expensive drugs is limited. This review assesses the published preclinical and clinical data about drug repurposing in MPM.

In this review, we identified 11 therapeutic classes that could be repositioned in mesothelioma. Most of these treatments have been evaluated in vitro, half have been evaluated in vivo in animal models of MPM and only three (i.e. valproate, thalidomide and zoledronic acid) have been investigated in clinical trials, with limited benefits so far. Efforts could be coordinated to pursue further investigations and test promising drugs identified in preclinical experiments in appropriately designed clinical trials.

Conflict of interest: E. Pasquier reports personal fees for consultancy from Pierre Fabre Oncology, outside the submitted work. J. Ciccolini reports personal fees from Pierre Fabre (who commercialised a drug used in mesothelioma patients), outside the submitted work. L. Greillier reports grants, personal fees and non-financial support from Roche and Novartis. He also reports personal fees and non-financial support from Lilly, Boehringer Ingelheim, AstraZeneca and Pfizer, and personal fees from Bristol-Myers Squibb and Pierre Fabre for drug trials. F. Barlesi reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer, outside the submitted work. C. Mascaux reports board member and speakers fees from Roche and Kephren, and speakers fees from Bristol-Myers Squibb, Lilly, Roche, AstraZeneca and Boehringer Ingelheim, outside the submitted work.

Copyright ©ERS 2018. ERR articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.
The concept of drug repurposing

The aim of drug repurposing is to identify and develop new indications for approved drugs [1, 2]. In oncology, drug repositioning consists of demonstrating the anticancer properties of marketed drugs approved for nonmalignant diseases [3]. Because repositioned drugs have well-known safety and pharmacokinetic profiles, faster development can be expected. Indeed, clinical development can start directly with phase II trials to assess the efficacy of the drug. Furthermore, this strategy is economically attractive, particularly in low- and middle-income countries (LMIC) where accessing new cancer treatments is difficult [4]. Because it is based on old and inexpensive drugs and because most of these treatments have oral formulations, this strategy limits the need for extended hospital stays and long journeys to care centres. In addition, these drugs are known to have tolerable side-effects as compared to classical anticancer agents, so the need for supportive care is limited.

Drug repurposing relies on two main approaches: 1) activity-based repurposing, where candidate drugs are evaluated in cancer models in vitro and/or in vivo and 2) in silico drug repurposing, where interactions between drugs and their potential molecular targets are modelled in silico by using public databases and bioinformatics tools [5]. By using either or both of these approaches, several drugs approved for nonmalignant diseases have been shown to exert potent anticancer effects and have been successfully repurposed to target specific pathways. For instance, anti-angiogenic activity can be obtained with β-blockers [6] or celecoxib [7], and inhibition of the sonic hedgehog pathway can be obtained with itraconazole [8].

Potential of drug repurposing in malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is a rare cancer with a dismal prognosis [9], mainly caused by exposure to asbestos with an aetiological fraction of ≥80% [10]. MPM is classified into three major histological subtypes: epithelioid (50% of cases), sarcomatoid (15% of cases) and biphasic or mixed (35% of cases). MPM has a strong male predominance and is usually diagnosed 30–40 years after the occupational exposure [11]. The World Health Organization (WHO) has recognised that asbestos is one of the most important occupational carcinogens and has declared that asbestos-related diseases should be eliminated throughout the world [12]. DRISCOLL et al. [13] estimated that 43 000 people worldwide die of MPM each year, with 17 062 deaths in United States between 1994 and 2008 and 49 779 deaths in the same period in Europe [14]. The number of MPM deaths reported and the number of countries reporting MPM deaths increased between 1994 and 2008, mainly in developed countries, probably due to better disease recognition and an increase in incidence. In Europe, LA VECCHIA et al. [15] predicted that peak mortality from MPM will occur between 2010 and 2020 when the generation born between 1940 and 1950 will reach the peak age for MPM incidence and mortality. Currently, the number of MPM deaths is lower in developing countries, because developing countries began their asbestos use later [16], and because MPM is underdiagnosed as it requires expertise and immunohistochemical staining. Although asbestos production has decreased worldwide since the early 1990s because it has been banned in several countries, its use has increased in many countries as China, India, Kazakhstan, Russia, Ukraine and Uzbekistan [17]. The WHO estimates that 125 million people worldwide are still exposed to asbestos in their workplace [18]. Nowadays, asbestos exposure is high in developing countries. For example, it is reported that in India in 1994 [19], levels of fibres per cubic centimetre were found to be 100- to 1000-fold higher in textile factories or cement mills than the current permissible exposure limit in the United States. Consequently, developing countries should expect a significant rise in MPM incidence in the coming decades.

Most patients diagnosed with MPM have unresectable disease and are usually treated with chemotherapy. The standard first-line treatment for patients with advanced MPM consists in a combination of pemetrexed and cisplatin, which increases median overall survival (OS) from 9.3 to 12.1 months compared with treatment with cisplatin alone (p=0.020) [20]. Recently, the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial showed that the addition of bevacizumab to cisplatin and pemetrexed significantly increased OS (median 18.8 versus 16.1 months, hazard ratio (HR) 0.77 (95% CI 0.62–0.95); p=0.0167) in MPM with expected and manageable toxic effects [21]. Thereby, the cisplatin/pemetrexed/bevacizumab regimen could become a treatment option in the future for patients who are eligible to receive bevacizumab [22]. For subsequent therapy lines, no standard salvage therapy exists [23]. In a phase III trial comparing pemetrexed to palliative care alone, SORENSEN et al. [24] demonstrated that pemetrexed improved progression-free survival (PFS) and time to progression without impact on OS. Other chemotherapeutic agents, such as gemcitabine or vinorelbine show only marginal response rates [25, 26]. Other research strategies are currently being investigated, with promising results for immune checkpoint inhibitors or antimesothelin antibodies [27, 28]. However, their high cost could limit their use in developing countries once approved.

Thus, the prognosis of patients with MPM is very poor, with an average OS of 18 months from diagnosis. Moreover, there are only few treatment options available with only one chemotherapy regimen approved.
for first-line treatment of MPM and no standard treatment for second-line treatment. Thus, new treatment strategies are urgently needed. Because MPM is a rare cancer, clinical development of new drugs is difficult and requires worldwide collaboration from clinical trial centres in order to recruit more quickly and allow faster access to innovative molecules. Drug repositioning may be an attractive strategy in this pathology because it offers the possibility of faster drug development and consequently shorter paths to clinical approval. Furthermore, with the expected increase of incidence of MPM in LMIC, drug repositioning could offer solutions for patients living in these countries. Herein, we review the reported preclinical and clinical reported data of drug repurposing strategies in MPM.

Methods
We searched and extracted eligible studies about drug repurposing in MPM by an electronic search from the PubMed database. The keywords applied in the search were as follows: “mesothelioma” with “drug repositioning” or “[name of the molecule known to have an anticancer effect]”. In the latter case, the molecules were selected on the basis of previous articles on drug repurposing in oncology. We selected only publications written in the English language. The manual selection of relevant trials was first based on abstract analysis. The search ended in November 2016. The bibliographies noted in all the identified studies were used to complete this search.

Antiemetic drugs
Thalidomide is a historical example of drug repositioning. The drug was first developed in the 1950s to treat morning sickness in pregnant women. This was one of the biggest man-made medical disasters: >10000 children were born with a range of severe and debilitating malformations [29]. Thalidomide was withdrawn from the market as an antiemetic drug in the 1960s. It has since evolved to treat the cutaneous manifestations of erythema nodosum leprosum [30] and has shown antineoplastic properties by the inhibition of tumour angiogenesis [31] and cell proliferation [32], and through immunomodulatory effects [33]. Thalidomide has been evaluated in a variety of human cancers in clinical trials, which has led to its approval for the treatment of multiple myeloma [34]. In France, thalidomide is approved for previously untreated elderly patients with multiple myeloma in combination with melphalan and prednisone [35].

In MPM, thalidomide has been assessed in clinical trials without prior investigations in preclinical models. Despite encouraging results in a phase II trial with 28% disease stabilisation at 6 months observed with thalidomide as single agent in previously treated MPM patients [36], thalidomide failed to improve OS or PFS versus active supportive care in patients with MPM after first-line therapy in a randomised phase III study [37]. Median overall survival was 10.6 months in the thalidomide group and 12.9 months in the active supportive care group (HR 1.2, p=0.21). Similar disappointing results were observed in stage 3 nonsmall cell lung cancer (NSCLC) [38]. Table 1 provides a summary of the repurposed drugs.

Histone deacetylase inhibitors
Histone deacetylase (HDAC) inhibitors have antitumor effects by epigenetic induction of gene transcription resulting in tumour cell growth inhibition and apoptosis [39]. The first HDAC inhibitor tested in MPM was vorinostat, a HDAC inhibitor currently approved for the treatment of relapsed and refractory cutaneous T-cell lymphoma [97]. Despite encouraging in vitro and in vivo data, results in patients with MPM were disappointing, as vorinostat did not improve OS when compared to placebo in second-line or third-line therapy: median OS was 30.7 weeks in the vorinostat group and 27.1 weeks in the placebo group (HR 0.98, p=0.86) [23].

Valproate is a widely prescribed antiepileptic drug that has anticancer effect by its HDAC inhibiting properties. Among its multifaceted anticancer effects, valproate can induce tumour differentiation, reduce tumour growth and metastasis formation [98], induce apoptotic cell death [99], and increase tumour cell sensitivity to radiation [100]. Valproate showed anticancer activity in several tumour sites including glioblastoma, neuroblastoma, retinoblastoma and cervical cancer [101–103]. However, results are disappointing in myelodysplastic syndrome and acute myeloid leukaemia [104]. Valproate has shown preclinical and clinical activity in MPM. The association of valproate with pemetrexed and cisplatin increases caspase-dependent apoptosis in M14K, M38K and ZL34 human MPM cell lines, belonging to the epithelioid, biphasic and sarcomatoid subtypes, respectively and its efficacy was superior to suberoylanilide hydroxamic acid, a well-known HDAC inhibitor [105]. The synergistic activity of valproate in combination with chemotherapy was confirmed in vivo in mouse models of epithelioid MPM [105]. Subsequently, valproate was tested in combination with doxorubicin in patients with refractory or recurrent MPM after standard first-line chemotherapy in a phase II trial. Among 45 heavily pretreated patients, seven (16%) obtained a partial response. The median PFS was 2.5 months and the median OS was 6.7 months [40].
**Statins**

Statins are a class of drugs with lipid-lowering effect through inhibition of the mevalonate pathway [106]. Statins have antineoplastic properties [107] such as cell cycle arrest [41], apoptosis induction [42], sensitisation to cytotoxic drugs [43], angiogenesis inhibition [44], invasion and metastasis inhibition [45] and tumour differentiation [46]. In a recent retrospective study in small cell lung cancer, a statistically significant increase in median OS was observed in statin-treated patients when compared to those not receiving statins (median OS 8.4 versus 6.1 months, p<0.05) [105]. Results from a phase III comparing etoposide and cisplatin or carboplatin as first-line chemotherapy with or without pravastatin in pretreated patients with small cell lung cancer are expected [50]. In a phase III clinical trial, statins failed to improve OS in gastric cancer patients in combination with capecitabine [48] or in colorectal cancer patients in combination with Xeliri/Folfiri [49].

Statins have been extensively investigated in vitro in human MPM cells. Lovastatin [109] was shown to decrease cell viability in a dose-dependent manner in human MPM cell lines, through apoptosis induction. In addition, the combination of lovastatin and valproate was shown to reduce cell invasion of Acc-Meso-1, a human-derived MPM cell line [110]. HWANG et al. [51] reported a synergistic effect of the combination of pemetrexed and simvastatin on apoptosis induction in MSTO-211 MPM cells by reactive oxygen species.

| TABLE 1 | Drugs repurposed in malignant pleural mesothelioma (MPM) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Valproate**   | Epilepsy         | HDAC [39]       | Phase II ongoing in different types of cancer | Phase II [40]   |
| **Statin**      | Dyslipidaemia [38] | Induction of cell cycle arrest [41] | Phase III: gastric cancer [48], colorectal cancer [49] | Preclinical [47, 51–53] |
|                 |                  | Induction of apoptosis [42] | Phase III: ongoing in SCLC [50] |
|                 |                  | Sensitises cells to chemotherapy [43] | |
|                 |                  | Inhibition of angiogenesis [44] | |
|                 |                  | Inhibition of invasion and metastasis [45] | |
|                 |                  | Induction of tumour differentiation [46] | |
|                 |                  | Reversion of multidrug resistance [47] | |
| **Itraconazole**| Antifungal       | Induction of angiogenesis [54] | Phase II: NSCLC [55] | Preclinical [58] |
|                 |                  | Inhibition of hedgehog pathway [8] | Prostate cancer [56] |
| **Arsenic trioxide** | Traditional Chinese medicine | Induction of apoptosis [59] | FDA approved: promyelocytic leukaemia [60] | Preclinical [58, 61, 62] |
| **Disulfiram**  | Addiction to alcohol [63] | DNA N-methyl transferase inhibition | Phase II: NSCLC [64] | Preclinical [65] |
| **Celecoxib**   | NSAIDs [66]      | Inhibition of cell cycle progression [67] | Phase II: breast cancer [70], glioblastoma [71], ovarian cancer [72] | Preclinical [73] |
| **Metformin**   | Diabetes type 2  | Inhibition of mTor [74] | Phase III: pancreatic cancer [77] | Preclinical [80] |
| **Tocotrienol** | Antioxidant [81, 82] | Inhibition of cell cycle [75] | Phase III ongoing: breast cancer [78], endometrial cancer [79] | Preclinical [52, 85, 88] |
| **Thalidomide** | Sickness in pregnant females (withdrawn) [29] | Inhibition of angiogenesis [83] | Phase II: breast cancer [86] | Preclinical [37] |
| **Anisomycin**  | Antibiotic [89]  | Inhibition of PI3K/AKT pathway [84] | Phase II ongoing: ovarian cancer [87] |
| **Zoledronic acid** | Osteoporosis, hypercalcaemia [91] | Inhibition of cell proliferation [85] | | |
|                 |                  | Immunomodulatory function [32] | | |
|                 |                  | Inhibition of angiogenesis [31] | FDA approved: multiple myeloma [34] |
|                 |                  | Inhibition of cell proliferation [32] | Phase III [37] |
|                 |                  | Immunomodulatory function [33] | |
|                 |                  | Inhibition of angiogenesis [31] | |
|                 |                  | Inhibition of cell proliferation [32] | |
| **HDAC**: histone deacetylase inhibitor; **SCLC**: small cell lung cancer; **NSCLC**: nonsmall cell lung cancer; **FDA**: United States Food and Drug Administration; **NSAIDs**: nonsteroidal anti-inflammatory drugs; **EMT**: epithelial–mesenchymal transition. |
species-dependent mitochondrial dysfunction and Bim induction. RIGANTI et al. [47] showed that statins revert doxorubicin resistance by increasing nitric oxide production in human MPM cells MM98, OC99 and GF99. Additionally, statins have been shown to exert synergistic antiproliferative effects with γ-tocotrienol (isoform of vitamin E) on human MPM cells H2052 (sarcomatoid), H28 (epithelioid), H2452 (biphasic) and MSTO-211H (biphasic; MSTO) via inhibition of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activation [52]. The potential of lovastatin alone has also been demonstrated in vivo as it significantly reduced primary tumour and metastasis in a NOD/SCID/γ-null (NOG) mouse model of human MPM [53]. The role of statins in MPM has not yet been investigated in clinical trials.

**Antifungal drugs**

Itraconazole is an antifungal drug with several proven antiproliferative properties. Itraconazole acts as an anti-angiogenic agent [54] by direct inhibition of vascular endothelial growth factor receptor (VEGFR)2 glycosylation and consequently inhibits VEGFR2 autophosphorylation after VEGF stimulation [111]. It also inhibits the hedgehog signalling [8] pathway by acting on the smoothened protein (an essential hedgehog pathway component) and consequently suppressing the tumour growth. Of note, hedgehog signalling is involved in MPM cell growth [112]. Itraconazole has shown encouraging results in phase II trials in several tumour types. In previously treated NSCLC, itraconazole combined with pemetrexed was superior compared to pemetrexed alone (median OS 32 months versus 8 months, p=0.012) [55]. In addition, itraconazole showed activity in castration-resistant metastatic prostate cancer [56] and in basal cell carcinoma [57]. Furthermore, itraconazole [58] suppresses the viability of various human MPM cell lines of epithelioid, sarcomatoid and biphasic subtypes, in a dose-dependent manner, at least in part by reducing Gli1 expression, which is a key actor of the hedgehog pathway. However, itraconazole is yet to be evaluated in vivo or in a clinical trial in MPM.

**Traditional Chinese medicine**

Traditional Chinese medicine relies in part on the concept of using a controlled dose of poison to treat patients [113]. Arsenic trioxide (ATO) is an inorganic compound, which has been used in traditional Chinese medicine [61] to treat a wide variety of illnesses including syphilis and parasite infections. ATO has been repositioned successfully in oncology. It exerts its anticancer effects through the induction of apoptosis [59], and the inhibition of angiogenesis by inhibiting VEGF-A expression [114]. ATO has been approved by the United States Food and Drug Administration (FDA) since 2000 for patients with relapsed promyelocytic leukaemia [60]. In addition, ATO has been evaluated in solid tumours with encouraging results in hepatocellular carcinoma [115] when combined to locoregional therapy (overall response rate 81.96% (95% CI 72.32–91.62%) versus 59.37% (95% CI 47.34–71.41%) for patients treated by locoregional therapy alone; p<0.05). Although ATO was approved by the FDA when administered intravenously, oral formulations have been developed and have shown activity equal to the intravenous formulation, and a more favourable toxicity profile [60].

The effects of ATO on human MPM cells have been assessed in vitro. Like itraconazole, ATO suppresses cell viability of various MPM cell lines by reducing [58] Gli1 expression. In addition, ATO was shown to induce apoptosis in the NCI-H2052 MPM cell line [61] by activating two mitogen-activated protein kinase pathways: the c-Jun NH2-terminal kinase pathway and the response and extracellular signal-regulated kinase (ERK) pathway. The ERK pathway mediates cell proliferation and apoptosis [116]. An antiproliferative effect and cytotoxic effect of ATO [62] was also reported in multiple MPM cell lines (sarcomatoid, epithelioid and biphasic) by apoptosis induction mediated through downregulation of E2F1, a transcription factor involved in proliferation, apoptosis, cell cycle, tumour growth and senescence [117], and downregulation of thymidylate synthase, which is involved in pemetrexed resistance when overexpressed [118].

The role of ATO on human MPM was confirmed in vivo [62] using a nude mouse xenograft model of epithelioid MPM. The relative tumour size after 23 days of ATO treatment was statistically lower comparing to control group (p<0.05) with suppression of E2F1 expression and caspase-3 cleavage. ATO has not been tested in MPM patients yet.

**DNA methyltransferase inhibitors**

Disulfiram (DSF), a member of the dithiocarbamate family, is an irreversible inhibitor of aldehyde dehydrogenase approved by the FDA to treat alcoholism [63]. DSF inhibits tumour growth by its epigenetic properties as a DNA methyltransferase inhibitor [119]. In addition, DSF can potentiate the effects of anticancer drugs [120, 121]. In a recent phase II trial, the addition of DSF to cisplatin and
vinorelbine [64] was found to increase OS in NSCLC patients as compared with chemotherapy alone (10 versus 7.1 months, p=0.041). Moreover, there were two long-term survivors in the DSF group.

DSF has been assessed in vitro in human MPM via a DSF–copper (DSF-Cu) complex, as copper is required in DSF-induced toxicity and radio sensitisation of cancer cells [122]. The complex DSF-Cu inhibits proliferation of MPM cell lines via promotion of apoptosis, in part by inhibiting nuclear factor-κB in a dose-dependent manner [65]. The inhibition growth tumour by stimulating apoptosis was confirmed in vivo [65]. DSF-Cu-treated Balb/c mice xenografted with MPM AB12 murine cells showed a 71% inhibition of tumour growth compared to control tumours. As previously seen in vitro, DSF-Cu inhibited murine MPM tumour growth by promoting apoptosis.

Nonsteroidal anti-inflammatory drugs
Acetylsalicylic acid or aspirin inhibits cyclooxygenase (COX)-1 and COX-2 and is the most widely used nonsteroidal anti-inflammatory drug worldwide [123]. Aspirin has been shown to induce apoptosis in both COX-dependent and COX-independent mechanisms [124], and suppresses the acquisition of chemoresistance [125]. The use of aspirin has demonstrated improved outcomes in colorectal cancer [126, 127].

Aspirin [115] was shown to inhibit colony formation in REN, HMESO and PHI, three MPM cell lines secreting high amounts of high-mobility group box (HMGB)1, a protein that regulates nucleosome assembly and chromatin structure. In contrast, aspirin does not inhibit colony formation in the PPM-MILL cell line, which secretes low-to-undetectable amounts of HMGB1. Moreover, motility, migration, invasion and epithelial–mesenchymal transition (EMT) of REN cells was inhibited by aspirin in a HMGB1-dependent manner. The anticancer and HMGB1-inhibiting activity of aspirin on MPM cells was confirmed in vivo [123]. Severe combined immunodeficient mice (SCID) were xenografted with HMGB1-secreting REN cells (derived from an explant of an epithelial MPM) and aspirin significantly reduced tumour growth compared with control (p<0.0001). 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 [128]. Among its anticancer effects, celecoxib inhibits cell cycle progression [67], induces apoptosis [68], inhibits angiogenesis and metastasis [69], and increases tumour cell lysis induced by immune cells [129]. The efficacy of COX-2 inhibition by celecoxib has been assessed in phase II clinical trials of different tumours with conflicting results [70–72]. In a recent meta-analysis [130], we noted an improvement of response rate for advanced NSCLC patients when chemotherapy was associated with celecoxib compared to chemotherapy alone (odds ratio (OR) 1.34, 95% CI 1.08–1.67; p=0.009) without improvement of 1-year survival rate (OR 1.08, 95% CI 0.8–1.35; p=0.512). Several phase III trials are ongoing in different cancers. In MPM, celecoxib was shown to reduce prostaglandin E2 levels in AB1, a murine MPM cell line [73]. The impact of COX-2 inhibition by celecoxib has been evaluated in vivo in BALB/c mice xenografted with AB1 cells. Celecoxib reduced the number of myeloid-derived suppressor cells, which play a critical role in tumour immune escape by suppressing T-cell and natural killer cell function. Consequently, combining dendritic cells (DC)-based immunotherapy with celecoxib in MPM improved survival (p=0.027), compared to a single treatment with celecoxib (p=0.305) or DC-based immunotherapy (p=0.456). Clinical assessment of the role of COX-2 in MPM is missing.

Oral antidiabetics
Metformin is a biguanide derivative, which is prescribed for type 2 diabetes. Metformin may act as an anticancer drug through inhibition of the mTor pathway [74], cell cycle arrest leading cells to apoptosis [75] and inhibition of EMT [76]. Retrospective analyses of medical records of diabetic patients treated by metformin have suggested an improved cancer prognosis [131]. In a phase II clinical trial, there was no advantage for the addition of metformin to erlotinib and gemcitabine in the treatment of advanced pancreatic cancer, but we noted that a subgroup of patients with high plasma concentrations of metformin (>1 mg·L<sup>−1</sup>) seemed to have an improved survival (HR 0.37, 95% CI 0.14–0.98; p=0.049) [77]. Several phase III trials are currently ongoing, especially in breast and endometrial cancers [78, 79].

The tunnelling nanotubes are thought to be an alternative means for intercellular communication in cancer and it is possible that they propagate chemotherapy resistance via intercellular transfer of proteins [80]. Tunnelling nanotube formation occurs during mesothelioma cell invasion in vitro. 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 [132], as did everolimus, an mTor inhibitor. Despite this effect, metformin did not significantly affect cell proliferation. To our knowledge, metformin has not been investigated in vivo or in clinical trials in MPM. However, a retrospective analysis [133] of 300 patients with type 2 diabetes and MPM showed no
Evidence that metformin could improve survival: median OS was 8.8 months for metformin users versus 6.5 months for nonusers (p=0.37).

Vitamin E isofrom
Tocotrienol (T3) is one of the isofoms of vitamin E which acts as an antioxidant, anti-inflammatory agent and is implicated in curing age-associated disease [81, 82]. γ-T3 and δ-T3 have the most extensively described anticancer properties [134, 135]. γ-T3 inhibits tumour angiogenesis [83] and cancer cell proliferation by acting on the PI3K/Akt pathway [84]. Tocotrienol-rich fraction (TRF) extracted from rice bran is an abundant source of γ-T3. A monocentric study has been undertaken [86] to test the effectiveness of adjuvant TRF therapy in combination with tamoxifen in women with early oestrogen receptor-positive breast cancer. However, this combination failed to improve outcome compared to tamoxifen alone. A phase II trial is ongoing in previously treated ovarian cancer patients comparing tocotrienol with cabazitaxel [87].

In vitro, Nakashima et al. [85] showed that the TRF extracted from rice attenuates the chemoresistance to cisplatin by inactivating the PI3K/Akt pathway in H28, a human cisplatin-resistant MPM cell line. In combination with statins, γ-T3 exerts antiproliferative effects [52] on human sarcomatoid, epithelioid and biphasic MPM cells through inhibition of the mevalonate pathway, induction of endoplasmic reticulum stress and caspase 3 activation. γ-T3 has not been investigated in vivo or in clinical trials in MPM.

α-tocotrienol is another isofrom of tocotrienol with pro-apoptotic anticancer properties [136]. 6-O-carboxypropyl-α-tocotrienol (T3E), a redox-silent analogue of α-tocotrienol has been evaluated in vivo in human MPM cell lines. T3E inhibits the growth of human MPM H28 cells [88], while sparing the growth of nontumorigenic mesothelial cells (Met-5A). The inhibition of MPM cell growth was mediated by the inactivation of Stat3 and the Src family of protein tyrosine kinases (SFK). SFK is activated in MPM growth of nontumorigenic mesothelial cells (Met-5A). The inhibition of MPM cell growth was mediated by the inactivation of Stat3 and the Src family of protein tyrosine kinases (SFK). SFK is activated in MPM

Antibiotics
Anisomycin is an antibiotic produced by Streptomyces griseolus, inhibiting protein synthesis [139]. It also acts as a protein translation inhibitor known to sensitize tumour cells to apoptosis induced by TNF-related apoptosis-inducing ligand (TRAIL) [89]. In H28 and REN MPM cell lines [90], anisomycin delivered at low subtoxic concentrations (25 ng·mL−1) was a potent sensitizer of apoptosis induced by TRAIL. In contrast, anisomycin did not sensitize nonmalignant human mesothelial cells to TRAIL-induced apoptosis. This sensitisation was shown to require Bim, indicating that anisomycin sensitises MPM cells to TRAIL-induced apoptosis at the level of the mitochondria. These data have not been confirmed in vivo or in clinical trials in MPM.

Bisphosphonates
Bisphosphonates are currently used in clinical for decades for bone lesions such as osteoporosis, cancer-induced osteolytic bone disease and hypercalcaemia [91]. In addition to these properties, nitrogen-containing bisphosphonates such as zoledronic acid (Zol) have anticancer effects [92, 93] such as inhibition of tumour cell proliferation, inhibition of tumour cell adhesion and invasion, inhibition of angiogenesis, inhibition of bone metastases and immunomodulatory effects. The administration of Zol (and clodronate) could be an option as adjuvant therapy for postmenopausal patients with breast cancer, because the EBCTCG meta-analysis found a little benefit in postmenopausal patients by reducing the rate of breast cancer recurrence in the bone and improving breast cancer survival [95, 140]. In advanced NSCLC with bone metastases, adding Zol to chemotherapy improves OS as compared with chemotherapy alone (578 days versus 384 days, p<0.0001) [141]. In castration-resistant prostate cancer, Zol reduces skeletal-related events, especially when combined with docetaxel [143]. In addition, Zol has been shown to reduce skeletal-related events in multiple myeloma patients [143]. Zol has shown preclinical and clinical activity in MPM. In human mesothelioma cells 211H, H28, H226, H2052, H2452 and Met-5A, Zol suppresses the growth of mesothelioma cells through apoptosis induction and cell cycle arrest in a p53-independent manner [144]. Moreover, Wackhöfer et al. [145] have shown that Zol inhibited the growth of AB12 and AC29 mouse mesothelioma cells by inhibiting the mevalonate pathway. Moreover, Zol was shown to decrease the Ras/ERK1/2 activity which is responsible for chemosensitising human mesothelioma cells to P-glycoprotein substrates (doxorubicin, vinblastine and etoposide) and to decrease indoleamine 1,2-dioxygenase-mediated immunosuppression [94]. The activity of Zol on mesothelioma cells was confirmed in vivo with inhibition of tumour growth when Zol was
administered intrapleurally in a dose-dependent manner [144]. Zol was subsequently tested in a
prospective single-arm clinical trial in patients with unresectable 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. In this study, a decrease of VEGF level was
predictive of favourable response [96].

Conclusions
Because the prognosis of patients with MPM remains poor, and with its incidence on the rise, particularly
in LMIC, new and innovative research perspectives are required. This review highlights the potential of
using drugs approved for nonmalignant disease, which could be investigated. Although other important
research avenues are currently being investigated in MPM, such as immune checkpoint inhibitors, vaccine
or antimesothelin monoclonal antibody [27, 28], drug repurposing could provide cheaper and more
accessible treatment options for patients in developing countries.

Mesothelioma is a tumour with known molecular alterations [146] in different signalling pathways, for
which there is not necessarily an available treatment. In this review, we attempted to draw up a
comprehensive list of the various repurposed drugs that have been evaluated in mesothelioma in
preclinical or clinical studies. We have tried to understand the mechanisms involved in the antitumor
activity of each of them.

So far, only three repurposed drugs have been investigated in clinical trials in MPM: valproate and
thalidomide showed good results in phase II trials. However, in a phase III trial thalidomide failed to
improve outcomes, and valproate has not yet been tested. Two drugs with promising results in preclinical
assessments failed to be confirmed as being useful in patients. This highlights that high failure rates in
patient evaluations in clinical trials often occur, despite promising data at the preclinical level, and
consequently, preclinical data may never be translated to patients. Thus, preclinical data should be assessed
in early-phase clinical trials.

Even if drug repositioning is an attractive approach, investigators should keep in mind its limitations. The
first is that the repurposed drugs are rarely effective in monotherapy, with antitumour activity more
frequently seen in association with other repurposed drugs or known cytotoxic drugs. Moreover, although
the low cost of these treatments may be an advantage in being able to treat a large number of patients in
developing countries, this could be a barrier for pharmaceutical companies to push their indication into
oncology. In addition, these molecules are currently no longer patentable and substitutes are often
available, making their commercial interest very low. Finally, their use could be limited by their possible
side-effects and their contraindications. Although these drugs are known to have tolerable side-effects,
their toxicity in cancer patients treated with other cytotoxic drugs is not known. For example, there were
two toxic deaths in 16 patients treated with valproate–doxorubicin [40].

Drug repurposing is an innovative and interesting research area, particularly in MPM where few
treatments are approved and where research may be time-consuming due to a lower incidence than other
types of thoracic cancer. In addition, if drug repurposing was found to be effective in clinical trials, this
strategy could potentially treat a large number of patients with MPM around the world, as its incidence
will mostly increase in the poorer countries, where access to innovative molecules is limited.

Thus, clinical trials evaluating this therapeutic strategy in MPM are needed. These must be conducted after
selecting the most relevant drugs or drug associations in preclinical models. To fast-track selection of

in silico

approaches can be used to model the interactions between drugs and their
molecular targets and thus test a large number of combinations. Indeed, many signalling pathways
involved in MPM are known, as are many potential targets of known drugs.

However, many questions arise about how best to conduct a clinical trial of drug repurposing in MPM.
Because there is no treatment currently approved, second-line therapy appears to be the most appropriate
setting. The association with pre-existing cancer treatments or the combination of multiple repurposed
drugs acting on complementary signalling pathways may be more active than the monotherapy approach.

In conclusion, drug repurposing is an important research area in mesothelioma, with many questions
remaining unresolved on the different modalities, but a promising avenue for medical advances.

References
1  Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug

Discov 2004; 3: 673–683.
2  Pantziarka P, Hutchinson L, André N, et al. Next generation metronomic chemotherapy—report from the Fifth

Biennial International Metronomic and Anti-angiogenic Therapy Meeting. May 6–8, 2016, Mumbai. Ecancermedicalscience

2016; 10.
Andrée N, Banavali S, Snihur Y, et al. Has the time come for metronomics in low-income and middle-income countries? *Lancet Oncol* 2013; 14: e239–e248.

LeBaron VT. Global cancer disparities and the need for new initiatives. *Oncol Nurs Forum* 2016; 43: 118–120.

Shim JS, Liu JO. Recent advances in drug repositioning for the discovery of new anticancer drugs. *Int J Biol Sci* 2014; 10: 654–663.

Pasquier E, Ciccolini J, Carre M, et al. Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. *Oncotarget* 2011; 2: 797–806.

Khan Z, Khan N, P Tiwari R, et al. Biology of Cox-2: an application in cancer therapeutics. *Curr Drug Targets* 2011; 12: 1082–1093.

Kim J, Tang JY, Gong R, et al. Traconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell* 2010; 17: 388–399.

Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960; 17: 260–271.

McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. *Eur Respir J* 1996; 9: 1932–1942.

Bianchi C, Giarelli L, Grandi G, et al. Latency periods in asbestos-related mesothelioma of the pleura. *Eur J Cancer Prev* 1997; 6: 162–166.

World Health Organization. Asbestos: Elimination of Asbestos-Related Diseases. 2006. www.who.int/medicentre/factsheets/fs634/en/ Date last updated: August 2017.

Dave SK, Beckett WS. Occupational asbestos exposure and predictable asbestos-related diseases in India. *Am J Ind Med* 2005; 48: 137–143.

Delgermaa V, Takahashi K, Park EK, et al. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. *Bull World Health Organ* 2011; 89: 716–724.

La Vecchia C, Decarli A, Peto J, et al. An age, period and cohort analysis of pleural cancer mortality in Europe. *Eur J Cancer Prev* 2000; 9: 179–184.

Takahashi K, Kang SK. Towards elimination of asbestos-related diseases: a theoretical basis for international cooperation. *SAfH Health Work* 2010; 1: 103–106.

Virta RL. Worldwide Asbestos Supply and Consumption Trends from 1900 through 2003. US Department of the Interior, US Geological Survey. 2006. https://pubs.usgs.gov/circ/2006/1298/c1298.pdf

Stayner L, Welch LS, Lemen R. The worldwide pandemic of asbestos-related diseases. *Ann Rev Public Health* 2013; 34: 205–216.

Davie SK, Beckett WS. Occupational asbestos exposure and predictable asbestos-related diseases in India. *Am J Ind Med* 2005; 48: 137–143.

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; 21: 2636–2644.

Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; 387: 1405–1414.

Zauderer MG. A new standard for malignant pleural mesothelioma. *Lancet* 2016; 387: 1352–1354.

Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Oncol* 2015; 16: 447–456.

Sørensen JB, Sundstrom S, Perrell K, et al. Pemetrexed as second-line treatment in malignant pleural mesothelioma after platinum-based first-line treatment. *J Thorac Oncol* 2007; 2: 147–152.

Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer* 2009; 63: 94–97.

Van Meerbeek JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. *Cancer* 1999; 85: 2577–2582.

Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): interim results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017; 18: 623–630.

Hassan R, Kindler HL, Jahan T, et al. Phase II clinical trial of amatuximab, a chimeric antimesothelin antibody with pemtettrex and cisplatin in advanced unresectable pleural mesothelioma. *Clin Cancer Res* 2014; 20: 5927–5936.

Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today* 2015; 105: 140–156.

Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. *Clin Ther* 2003; 25: 342–385.

D’Amato RJ, Loughnan MS, Flynn E, et al. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; 91: 4082–4085.

Sherbet GV. Therapeutic potential of thalidomide and its analogues in the treatment of cancer. *Anticancer Res* 2015; 35: 5767–5772.

De Keersmaecker B, Fostier K, Corthals J, et al. Immunomodulatory drugs improve the immune environment for dendritic cell-based immunotherapy in multiple myeloma patients after autologous stem cell transplantation. *Cancer Immunol Immunother* 2014; 63: 1023–1036.

Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. *New Engl J Med* 1999; 341: 1565–1571.

Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 2007; 370: 1209–1218.

Baas P, Boogerd W, Daleos O, et al. Thalidomide in patients with malignant pleural mesothelioma. *Lung Cancer* 2005; 48: 291–296.

Buikhuizen WA, Burgers JA, Vincent AD, et al. Thalidomide versus active supportive care for maintenance in patients with malignant mesothelioma after first-line chemotherapy (NVALT 5); an open-label, multicentre, randomised phase 3 study. *Lancet Oncol* 2013; 14: 543–551.

https://doi.org/10.1183/16000617.0098-2017
Rudin CM, Brahmer JR, Juergens RA, You M, Varona-Santos J, Singh S, Kim DJ, Kim J, Spaunhurst K, Asakura K, Izumi Y, Yamamoto M, Riganti C, Orecchia S, Pescarmona G, Arnold DE, Gagne C, Niknejad N, Vincent L, Soria C, Mirshahi F, Lim SH, Kim TW, Hong YS, Tuerdi G, Ichinomiya S, Sato H, Hwang KE, Kim YS, Hwang YR, NCT00433498. Etoposide and Cisplatin or Carboplatin as First-Line Chemotherapy with or Without Pravastatin

Feleszko W, M et al. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Oncologist 2011; 170: e197–201.

Hoang T, Dahlberg SE, Schiller JH, et al. Randomized phase III study of thoracic radiation in combination with paclitaxel and carboplatin with or without thalidomide in patients with stage III non-small-cell lung cancer: the ECOG 3598 study. J Clin Oncol 2012; 30: 616–622.

Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Nat Rev Drug Discov 2002; 1: 287–299.

Scherpereel A, Berghmans T, Lafitte JJ, et al. Valproate–doxorubicin: promising therapy for progressing mesothelioma. A phase II study. Eur Respir J 2011; 37: 129–135.

Cooper S. Reappraisal of G1-phase arrest and synchronization by lovastatin. Blood 1999; 93: 1308–1318.

Vincent L, Soria C, Mirshahi F, et al. Cerivastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, inhibits endothelial cell proliferation induced by angiogenic factors in vitro and angiogenesis in vivo models. Arterioscler Thromb Vasc Biol 2002; 22: 623–629.

Denoyelle C, Vasse M, Körner M, et al. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. Carcinogenesis 2001; 22: 1139–1148.

Arnold DE, Gagne C, Niknejad N, et al. Lovastatin induces neuronal differentiation and apoptosis of embryonal carcinoma and neuroblastoma cells: enhanced differentiation and apoptosis in combination with dbcAMP. Mol Cell Biochem 2010; 345: 1–11.

Riganti C, Orecchia S, Pescarmona G, et al. Statins revert doxorubicin resistance via nitric oxide in malignant mesothelioma. Int J Cancer 2006; 119: 17–27.

Kim ST, Kang JH, Lee J, et al. Simvastatin plus capcitabine–cisplatin versus placebo plus capcitabine–cisplatin in patients with previously untreated advanced gastric cancer: a double-blind randomised phase 3 study. Eur J Cancer 2014; 50: 2822–2830.

Lim SH, Kim TW, Hong YS, et al. A randomised, double-blind, placebo-controlled multi-centre phase III trial of XELIRI/FOLFIRI plus simvastatin for patients with metastatic colorectal cancer. Br J Cancer 2015; 113: 1421–1426.

NCT00433498. Etoposide and Cisplatin or Carboplatin as First-Line Chemotherapy with or Without Pravastatin in Treating Patients With Small Cell Lung Cancer. https://clinicaltrials.gov/ct2/show/NCT00433498 Date last updated: December 3, 2014.

Hwang KE, Kim YS, Hwang YR, et al. Enhanced apoptosis by pemetrexed and simvastatin in malignant mesothelioma and lung cancer cells by reactive oxygen species-dependent mitochondrial dysfunction and Bim induction. Int J Oncol 2014; 45: 1769–1777.

Tuerdi G, Ichinomiya S, Sato H, et al. Synergistic effect of combined treatment with gamma-tocotrienol and statin on human malignant mesothelioma cells. Cancer Lett 2013; 339: 116–127.

Asakura K, Irumi Y, Yamamoto M, et al. The cytostatic effects of lovastatin on ACC-MESO-1 cells. J Surg Res 2011; 170: e197–e209.

Chong CR, Xu J, Lu J, et al. Inhibition of angiogenesis by the antifungal drug itraconazole. ACS Chem Biol 2007; 2: 263–270.

Rudin CM, Brahmer JR, Juergens RA, et al. Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer. J Thorac Oncol 2013; 8: 619–623.

Antonarakis ES, Heath EI, Smith DC, et al. Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. Oncologist 2013; 18: 163–173.

Kim DJ, Kim J, Spaunhurst K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. J Clin Oncol 2014; 32: 745–751.

You M, Varona-Santos J, Singh S, et al. Targeting of the Hedgehog signal transduction pathway suppresses survival of malignant pleural mesothelioma cells in vitro. J Thorac Cardiovasc Surg 2014; 147: 508–516.

Shao W, Fanelli M, Ferrara PE, et al. Arsenic trioxide as an inducer of apoptosis and loss of PML/RARα protein in acute promyelocytic leukemia cells. J Natl Cancer Inst 1998; 90: 124–133.

Falchi L, Verstosvsek S, Ravandi-Khashi F, et al. The evolution of arsenic in the treatment of acute promyelocytic leukemia and other myeloid neoplasms: moving toward an effective oral, outpatient therapy. Cancer 2016; 122: 1160–1168.

Eguchi R, Fujimori Y, Takeda H, et al. Arsenic trioxide induces apoptosis through JNK and ERK in human mesothelioma cells. J Cell Physiol 2011; 226: 762–768.

Lam SK, Li YY, Zheng CY, et al. Downregulation of thymidylate synthase and E2F1 by arsenic trioxide in mesothelioma. Int J Oncol 2015; 46: 113–122.

Testino G, Leone S, Borro P. Treatment of alcohol dependence: recent progress and reduction of consumption. Minerva Med 2014; 105: 447–466.

Nechushitan H, Hamamreh Y, Nidal S, et al. A phase IIb trial assessing the addition of disulfiram to chemotherapy for the treatment of metastatic non-small cell lung cancer. Oncologist 2015; 20: 366–377.

Cheryian VT, Wang Y, Muthu M, et al. Disulfiram suppresses growth of the malignant pleuropulmonary mesothelioma cells in part by inducing apoptosis. PLoS One 2014; 9: e93711.

Mcdam BF, Catella-Lawson F, Mardini IA, et al. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA 1999; 96: 272–277.

Han C, Leng J, Demetris AJ, et al. Cyclooxygenase-2 promotes human cholangiocarcinoma growth: evidence for cyclooxygenase-2-independent mechanism in celecoxib-mediated induction of p21WAF1/CIP1 and p27KIP1 and cell cycle arrest. Cancer Res 2004; 64: 1369–1376.

Liu X, Yue P, Zhou Z, et al. Death receptor regulation and celecoxib-induced apoptosis in human lung cancer cells. J Natl Cancer Inst 2004; 96: 1769–1780.
Wei D, Wang L, He Y, et al. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res 2004; 64: 2030–2038.

Perroud HA, Rico MJ, Alasino CM, et al. Safety and therapeutic effect of metronomic chemotherapy with cyclophosphamide and celecoxib in advanced breast cancer patients. Future Oncol 2013; 9: 451–462.

Penas-Prado M, Hess KR, Fisch MJ, et al. Randomized phase II adjuvant factorial study of dose-dense temozolomide alone and in combination with isotretinoin, celecoxib, and/or thalidomide for glioblastoma. Neuro Oncol 2015; 17: 266–273.

Legge F, Paglia A, D’Asta M, et al. Phase II study of the combination carboplatin plus celecoxib in heavily pre-treated recurrent ovarian cancer patients. BMC Cancer 2011; 11: 214.

Veltman JD, Lambers ME, van Ninwegen M, et al. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. BMC Cancer 2010; 10: 464.

Kalender A, Selvaraj A, Kim SY, et al. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell Metab 2010; 11: 390–401.

Alimova IN, Liu B, Fan Z, et al. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. Cell Cycle 2009; 8: 909–915.

Barrière G, Tartary M, Rigaud M. Metformin: a rising star to fight the epithelial mesenchymal transition in oncology. Anticancer Agents Med Chem 2013; 13: 333–340.

Kordes S, Pollak MN, Zwindinger AH, et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol 2015; 16: 839–847.

NCT01101438. A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer. https://clinicaltrials.gov/ct2/show/NCT01101438 Date last updated: March 24, 2017.

NCT02065687. Paclitaxel and Carboplatin With or Without Metformin Hydrochloride in Treating Patients with NCT02560337. Cabazitaxel vs. Tocotrienol in Patients with Recurrent Ovarian Cancer After Failure of Standard
corticosteroids. Cancer Biol Ther 2014; 14: 81–101.

Siveen KS, Ahn KS, Ong TH, et al. γ-Tocotrienol inhibits angiogenesis-dependent growth of human hepatocellular carcinoma through abrogation of AKT/mTOR pathway in an orthotopic mouse model. Oncotarget 2014; 1897–1911.

Shah SJ, Sylvester PW. γ-Tocotrienol inhibits neoplastic mammary epithelial cell proliferation by decreasing Akt and nuclear factor κB activity. Exp Biol Med 2005; 230: 235–241.

Nakashima K, Virgona N, Miyazawa M, et al. The tocotrienol-rich fraction from rice bran enhances cisplatin-induced cytotoxicity in human mesothelioma H28 cells. Phytother Res 2010; 24: 1317–1321.

Nesaratnam K, Selvaduray KR, Abdul Razak G, et al. Effectiveness of tocotrienol-rich fraction combined with tamoxifen in the management of women with early breast cancer: a pilot clinical trial. Breast Cancer Res Treat 2010; 12: R81.

NCT02560337. Cabazitaxel vs. Tocotrienol in Patients with Recurrent Ovarian Cancer After Failure of Standard Therapy (CaTo-ROC), https://clinicaltrials.gov/ct2/show/NCT02560337 Date last updated: November 17, 2017.

Kashivagi K, Virgona N, Harada K, et al. A redox-silent analogue of tocotrienol acts as a potential cytotoxic agent against human mesothelioma cells. Life Sci 2009; 84: 650–656.

Slipicic A, Oy GF, Rosnes AK, et al. Low-dose anisomycin sensitizes melanoma cells to TRAIL induced apoptosis. Cancer Biol Ther 2013; 14: 146–154.

Abayasiwardana KS, Barbone D, Kim KU, et al. Malignant mesothelioma cells are rapidly sensitized to TRAIL-induced apoptosis by low-dose anisomycin via Bim. Mol Cancer Ther 2007; 6: 2766–2776.

Leclercm SP, Hughes DR, Coxon FP, et al. Nitrogen-containing bisphosphonates inhibit the neovascular pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. J Bone Miner Res 1998; 13: 581–589.

Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. Curr Pharm Des 2003; 9: 2643–2658.

Green JR. Antitumor effects of bisphosphonates. Cancer 2003; 97: 840–847.

Salaroglou IC, Campia I, Kopecka J, et al. Zoledronic acid overcomes chemo-resistance and immunosuppression of malignant mesothelioma. Oncotarget 2015; 6: 1128–1142.

Early Breast Cancer Trialists’ Collaborative Group, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015; 386: 1353–1361.

Jamil MO, Jerome MS, Miley D, et al. A pilot study of zoledronic acid in the treatment of patients with advanced malignant pleural mesothelioma. Lung Cancer 2017; 12: 39–44.

Mann BS, Johnson JR, Cohen MH, et al. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. Oncologist 2007; 12: 1247–1252.

Göttlicher M, Minucci S, Zhu P, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J 2001; 20: 6969–6978.

Čičnová L, Zdralh Z, Fajkus J. New perspectives of valproic acid in clinical practice. Expert Opin Investig Drugs 2013; 22: 1535–1547.

Camphausen K, Cerna D, Scott T, et al. Enhancement of in vitro and in vivo tumor cell radiosensitivity by valproic acid. Int J Cancer 2005; 114: 380–386.

Traore F, Togo B, Pasquier E, et al. Preliminary evaluation of children treated with metronomic chemotherapy and valproic acid in a low-income country: Metro-Mali-02. Indian J Cancer 2013; 50: 250–253.
Steinbach G, Lynch PM, Phillips RK, Saha S, Mukherjee S, Khan P, Schrör K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in patients with myelodysplastic syndrome and acute myelogenous leukemia. Cancer 2015; 121: 556–561.

Vandermeers F, Hubert P, Delvenne P, et al. Valproate, in combination with penetrexed and cisplatin, provides additional efficiency to the treatment of malignant mesothelioma. Clin Cancer Res 2009; 15: 2818–2828.

Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990; 343: 425–430.

Osmak M. Statins and cancer: current and future prospects. Cancer Lett 2012; 324: 1–12.

Lohinai Z, Dome P, Szilagyi Z, et al. From bench to bedside: attempt to evaluate repositioning of drugs in the treatment of metastatic small cell lung cancer (SCLC). PLoS One 2016; 11: e0144797.

Rubins JB, Greataes T, Kratzke RA, et al. Lovastatin induces apoptosis in malignant mesothelioma cells. Am J Respir Crit Care Med 1998; 157: 1616–1622.

Yamauchi Y, Izumi Y, Asakura K, et al. Lovastatin and valproic acid additively attenuate cell invasion in ACC-MESO-1 cells. Biochem Biophys Res Commun 2011; 410: 328–332.

Nacey BA, Grassi P, Dell A, et al. The antifungal drug itraconazole inhibits vascular endothelial growth factor receptor 2 (VEGFR2) glycosylation, trafficking, and signaling in endothelial cells. J Biol Chem 2011; 286: 44045–44056.

Shi Y, Moura U, Opitz I, et al. Role of hedgehog signaling in malignant pleural mesothelioma. Clin Cancer Res 2012; 18: 4646–4656.

Au WY. A biography of arsenic and medicine in Hong Kong and China. Hong Kong Med J 2011; 17: 507–513.

Ge H, Han Z, Tian P, et al. VEGF expression is inhibited by arsenic trioxide in HUV-ECs through the upregulation of Ets-2 and miRNA-126. PLoS One 2015; 10: e0135795.

Wang H, Liu Y, Wang X, et al. Randomized clinical control study of locoregional therapy combined with arsenic trioxide for the treatment of hepatocellular carcinoma. Cancer 2015; 121: 2917–2925.

Lee YJ, Cho HN, Soh JW, et al. Oxidative stress-induced apoptosis is mediated by ERK1/2 phosphorylation. Exp Cell Res 2003; 291: 251–266.

Slee EA, Lu X. Requirement for phosphorylation of P53 at Ser312 in suppression of chemical carcinogenesis. Sci Rep 2013; 3: 3105.

Sigmund J, Backus HH, Wouters D, et al. Disulfiram is a DNA demethylating agent and inhibits prostate cancer cell growth. Prostate 2011; 71: 333–343.

Valeriote F, Grates HE. Potentiation of nitrogen mustard cytotoxicity by disulfiram, diethyldithiocarbamic acid, and diethylamine in mice. Cancer Res 1989; 49: 6658–6661.

Wang W, McLeod HL, Cassidy J. Disulfiram-mediated inhibition of NF-κB activity enhances cytotoxicity of 5-fluorouracil in human colorectal cancer cell lines. Int J Cancer 2003; 104: 504–511.

Rae C, Tesson M, Babich JW, et al. The role of copper in disulfiram-induced toxicity and radiosensitization of cancer cells. J Nucl Med 2013; 54: 953–960.

Yang H, Pellegrini L, Napolitano A, et al. Aspirin delays mesothelioma growth by inhibiting HMGB1-mediated tumor progression. Cell Death Dis 2015; 6: e1786.

Schrör K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in colorectal cancer. Best Pract Res Clin Gastroenterol 2011; 25: 473–484.

Saha S, Mukherjee S, Khan P, et al. Aspirin suppresses the acquisition of chemoresistance in breast cancer by disrupting an NFκB–IκB signaling axis responsible for the generation of cancer stem cells. Cancer Res 2016; 76: 2000–2012.

Chan AT, Ogino S, Et Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009; 302: 649–658.

Li P, Wu H, Zhang H, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. Gut 2015; 64: 1419–1425.

Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000; 342: 1946–1952.

Schellhorn M, Haustein M, Frank M, et al. Celecoxib increases lung cancer cell lysis by lymphokine-activated killer cells via upregulation of ICAM-1. Oncotarget 2015; 6: 39342–39356.

Hou LC, Huang F, Xu HB. Does celecoxib improve the efficacy of chemotherapy for advanced non-small cell lung cancer? Br J Clin Pharmacol 2016; 81: 23–32.

Sadeghi N, Abbruzzese JL, Yeung SC, et al. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res 2012; 18: 2905–2912.

Lou E, Fujisawa S, Morozov A, et al. Tunneling nanotubes provide a unique conduit for intercellular transfer of cellular contents in human malignant pleural mesothelioma. PLoS One 2012; 7: e33093.

Wu H, Walker J, Damhuis RA, et al. Metformin and survival of people with type 2 diabetes and pleural mesothelioma: a population-based retrospective cohort study. Lung Cancer 2016; 99: 194–199.

Sen CK, Khanna S, Roy S. Tocotrienols in health and disease: the other half of the natural vitamin E family. Mol Aspects Med 2007; 28: 692–728.

Nesaretnam K. Multitargeted therapy of cancer by tocotrienols. Cancer Lett 2008; 269: 388–395.

Lim SW, Loh HS, Ting KN, et al. Cytotoxicity and apoptotic activities of alpha-, gamma- and delta-tocotrienol isomers on human cancer cells. BMC Complement Altern Med 2014; 14: 469.
137 Tsao AS, He D, Saigal B, et al. Inhibition of c-Src expression and activation in malignant pleural mesothelioma tissues leads to apoptosis, cell cycle arrest, and decreased migration and invasion. *Mol Cancer Ther* 2007; 6: 1962–1972.

138 Sato A, Sekine M, Virgona N, et al. Yes is a central mediator of cell growth in malignant mesothelioma cells. *Oncol Rep* 2012; 28: 1889–1893.

139 Grollman AP, et al. Inhibitors of protein biosynthesis. II. Mode of action of anisomycin. *J Biol Chem* 1967; 242: 3226–3233.

140 Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2017; 35: 2062–2081.

141 Zarogoulidis K, Boutsikou E, Zarogoulidi P, et al. The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. *Int J Cancer* 2009; 125: 1705–1709.

142 Gartrel BA, Coleman R, Efstathiou E, et al. Metastatic prostate cancer and the bone: significance and therapeutic options. *Eur Urol* 2015; 68: 850–858.

143 Lee OL, Horvath N, Lee C, et al. Bisphosphonate guidelines for treatment and prevention of myeloma bone disease. *Intern Med J* 2017; 47: 938–951.

144 Okamoto S, Kawamura K, Li Q, et al. Zoledronic acid produces antitumor effects on mesothelioma through apoptosis and S-phase arrest in p53-independent and Ras prenylation-independent manners. *J Thorac Oncology* 2012; 7: 873–882.

145 Wakchoure S, Merrell MA, Aldrich W, et al. Bisphosphonates inhibit the growth of mesothelioma cells in vitro and in vivo. *Clin Cancer Res* 2006; 2006: 2862–2868.

146 Zucali PA, Giaccone G. Biology and management of malignant pleural mesothelioma. *Eur J Cancer* 2006; 42: 2706–2714.