MDACT: A New Principle of Adjunctive Cancer Treatment Using Combinations of Multiple Repurposed Drugs, with an Example Regimen

Richard E. Kast 1,*; Alex Alfieri 2, Hazem I. Assi 3, Terry C. Burns 4, Ashraf M. Elyamany 5, Maria Gonzalez-Cao 6, Georg Karpel-Massler 7, Christine Marosi 8, Michael E. Salacz 9, Iacopo Sardi 10, Pieter Van Vlierberghe 11, Mohamed S. Zaghloul 12 and Marc-Eric Halatsch 2

Abstract: In part one of this two-part paper, we present eight principles that we believe must be considered for more effective treatment of the currently incurable cancers. These are addressed by multidrug adjunctive cancer treatment (MDACT), which uses multiple repurposed non-oncology drugs, not primarily to kill malignant cells, but rather to reduce the malignant cells’ growth drives. Previous multidrug regimens have used MDACT principles, e.g., the CUSP9v3 glioblastoma treatment. MDACT is an amalgam of (1) the principle that to be effective in stopping a chain of events leading to an undesired outcome, one must break more than one link; (2) the principle of Palmer et al. of achieving fractional cancer cell killing via multiple drugs with independent mechanisms of action; (3) the principle of shaping versus decisive operations, both being required for successful cancer treatment; (4) an idea adapted from Chow et al., of using multiple cytotoxic medicines at low doses; (5) the idea behind CUSP9v3, using many non-oncology CNS-penetrant drugs from general medical practice, repurposed to block tumor survival paths and growth drives.

Simple Summary: We present eight core attributes of cancer growth that we must address for a more effective treatment than we currently have. To do this we outline why a regimen simultaneously using many different drugs will be needed. At our current state of knowledge, even adding two or three drugs will not counter all the growth attributes of a currently incurable cancer. We show in this paper, the details of how an example six drug regimen, when added alongside of current traditional treatments, might inhibit enough of the eight core growth driving elements to allow those standard treatments to be more effective. We further show how medicines from general medical practice used to treat pain, fungal infections, psychosis, leprosy and other non-cancer related illnesses can be repurposed to block cancer cells’ survival pathways and growth drives.

1 IIAIGC Study Center, Burlington, VT 05408, USA
2 Department of Neurosurgery, Cantonal Hospital of Winterthur, 8400 Winterthur, Switzerland; alex.alfieri@ksw.ch (A.A.); marc-eric.halatsch@ksw.ch (M.-E.H.)
3 Naef K. Basile Cancer Center, American University of Beirut, Beirut 1100, Lebanon; ha157@aub.edu.lb
4 Department of Neurological Surgery, Mayo Clinic, Rochester, MN 55905, USA; burns.terry@mayo.edu
5 Oncology Unit, Hemato-Oncology Department, SECI Assiut University Egypt/King Saud Medical City, Riyadh 7790, Saudi Arabia; elyamany23@gmail.com
6 Translational Cancer Research Unit, Dexeus University Hospital, 08028 Barcelona, Spain; mgonzalezcao@oncorosell.com
7 Department of Neurosurgery, Ulm University Hospital, 89081 Ulm, Germany; georg.karpel@gmail.com
8 Clinical Division of Medical Oncology, Department of Pediatric Oncology, Meyer Children’s Hospital, Viale Pieraccini 24, 50139 Florence, Italy; iacopo.sardi@meyer.it
9 Department of Biomedical Medicine, Ghent University Hospital, Conneel Heymanslaan 10, 9000 Gent, Belgium; pieter.vanvlierberghe@ugent.be
10 Children’s Cancer Hospital & National Cancer Institute, Cairo University, Cairo 11796, Egypt; mkszagh@yahoo.com
* Correspondence: richarderickast@gmail.com

Citation: Kast, R.E.; Alfieri, A.; Assi, H.I.; Burns, T.C.; Elyamany, A.M.; Gonzalez-Cao, M.; Karpel-Massler, G.; Marosi, C.; Salacz, M.E.; Sardi, I.; et al. MDACT: A New Principle of Adjunctive Cancer Treatment Using Combinations of Multiple Repurposed Drugs, with an Example Regimen. Cancers 2022, 14, 2563. https://doi.org/10.3390/cancers14102563
of achieving the goal increase; and (8) the principle of blocking parallel signaling pathways. Part two gives an example MDACT regimen, gMDACT, which uses six repurposed drugs—celecoxib, dapsone, disulfiram, itraconazole, pyrimethamine, and telmisartan—to interfere with growth-driving elements common to cholangiocarcinoma, colon adenocarcinoma, glioblastoma, and non-small-cell lung cancer. gMDACT is another example of—not a replacement for—previous multidrug regimens already in clinical use, such as CUSP9v3. MDACT regimens are designed as adjuvants to be used with cytotoxic drugs.

**Keywords:** cholangiocarcinoma; colon cancer; CUSP9v3; glioblastoma; lung cancer; multidrug regimen; repurposing

---

**Preface:** gutta cavat lapidem, non vi, sed sæpe cadendo.

**Part One**

1. **Introduction**

Part one of this paper is an overview of eight attributes seen across many common cancers that we interpret as requiring a multidrug approach unless and until a “silver bullet” is found. These attributes are generally well understood in the oncology research community, but bear repeating in a consolidated fashion here. Then, eight principles of a new pharmacological approach—MDACT (multidrug adjuvant cancer treatment), which aims to address many of these attributes—are presented.

Part two of this paper gives specific details of a generalizable six-repurposed-drug regimen that may be considered (gMDACT). Other repurposed multidrug regimens could potentially be constructed with different drugs, or with drugs aiming at a different set of common growth-driving elements. Part two also outlines evidence on how gMDACT may inhibit growth or growth-driving elements active in four representative aggressive human cancers: cholangiocarcinoma, glioblastoma, colon adenocarcinoma, and non-small-cell lung cancer (NSCLC). gMDACT uses the analgesic celecoxib, the antibiotic dapsone, the alcoholism treatment drug disulfiram, the antifungal itraconazole, the antibiotic pyrimethamine, and the antihypertensive telmisartan.

MDACT borrows in principle from several recent repurposing studies in cancer—most prominently from the CUSP9v3 regimen for recurrent glioblastoma, with which MDACT shares three drugs—celecoxib, disulfiram, and itraconazole [1–7]. Initial clinical reports on CUSP9v3 showed that nine repurposed drugs plus a traditional cytotoxic drug (temozolomide) can be safely given daily over 4+ years if close monitoring and individual dose adjustments are in place [1].

MDACT approaches—and specifically the previous CUSP9v3 regimen and the gMDACT regimen given here—are part of the drug repurposing movement where currently approved and marketed drugs are used in cancer treatment based on their mechanisms of action (MOAs) rather than their approved clinical use [1]. The repurposing movement simply takes a deeper look at what a given medicine does to cellular physiology, rather than how the resultant clinical picture changes.

MDACT follows the injunction of Nguyen et al. that an “... effective treatment for radioresistant glioblastomas may require a cocktail containing multiple agents targeting multiple cancer-inducing pathways in order to have a chance to make a substantial impact on improving the overall glioblastoma survival.” [8].

Starting in 1946 with combining penicillin with sulfadiazine [9], through later combining amoxicillin with clavulanate in the 1980s, to today, combining antibacterial drugs is a well-established practice.

Zapletalova et al. published a regimen (COMBAT) in 2012 using three repurposed drugs—celecoxib, vitamin D, and fenofibrate—with the traditional anticancer drugs temozolomide, etoposide, and retinoic acid [10]. Peryl et al., in 2012, reported a clinical trial using
two repurposed drugs—celecoxib and fenofibric acid—to augment five traditional oncology drugs: bevacizumab, thalidomide, etoposide, cyclophosphamide, and cytarabine [11]. In 2016, Rios et al. published a case study using two repurposed drugs—metformin and niacinamide—with the traditional oncology drugs temozolomide,plerixafor, and lapa-
tinib [12]. In 2017, Furuta et al. studied CLOVA—a cocktail that uses four repurposed drugs (cimetidine, lithium, olanzapine, and valproate) with temozolomide [13]. Finally, in 2011, Tatokoro et al. reported on the clinical use of three repurposed drugs—cimetidine, meloxicam, and candesartan—with interferon-alpha [14]. The 3M+Stupp regimen from 2019 of Maraka et al. clinically tested three repurposed non-oncology drugs—memantine, melphoquine, and metformin—as adjuvants to temozolomide, notably without prior testing of the drugs individually [15]. None of the above studies were preceded by individual drug testing or xenograft testing.

A prime example of the multidrug approach that was also not preceded by xenograft study, but is now a well-established treatment for certain lymphomas, is R-CHOP (see discussion of R-CHOP in Section 3.2).

MDACT expands, conceptually consolidates, and follows in the tradition of all of the studies mentioned above.

2. Attributes of Cancer Mandating an MDACT Type of Approach

Although generally well known, it bears repeating here that most deadly cancers share the following eight attributes:

1. Spatial and temporal heterogeneity of growth-driving dependencies;
2. Existence of mutually supporting, bilaterally communicating cell communities;
3. Compensatory tumor responses to treatments;
4. Existence of multiple cross-covering, growth-driving signaling pathways functioning in parallel;
5. Metabolic flexibility reliance shifted to another energy source if one becomes inhibited;
6. Pathological engagement of multiple normally functioning body systems to facilitate growth (e.g., cytokines, trophic factors, innervation, interacting stroma, angiogenesis);
7. A subset of tumor stem cells with the potential to enter dormancy.
8. An inverse relationship often seen between growth and invasion, where inhibiting one enhances the other.

Although some cancers can be eliminated by massive cytotoxic assault, most disseminated cancers will not be cured by this approach. Attempting to address more of the eight attributes above might allow a more effective treatment, absent a “silver bullet”. This implies the necessity of a multidrug regimen. MDACT attempts to address our current “...‘one disease–one target–one drug’ dogma [that] obstruct[s] innovation in the most profound manner.” [16]. Multidrug approaches also address tumor heterogeneity between patients (which can also shift over time), thus resulting in a blind precision medicine by default.

The eight principles behind MDACT are discussed below and summarized in Table 1.

| Table 1 | Overview of the eight pharmacology approaches, woven together to formulate an MDACT-type regimen. |
|---------|---------------------------------------------------------------------------------------------------|
| 1.      | The principle of breaking more than one link in any chain in a series that leads to undesired outcomes. |
| 2.      | The principle of Palmer et al., of achieving fractional cell killing with multiple drugs with independent MOAs. |
| 3.      | The principle of shaping versus decisive operations—both required for a successful cancer treatment, with MDACT regimens being largely shaping operations. |
| 4.      | A principle adapted from Chow et al. of using multiple simultaneous cytotoxic medicines at low doses. |
5. As in CUSP9v3, the principle of using non-oncology drugs from general medical practice, repurposed to block multiple survival paths.

6. The concept borrowed from chess that every move (i.e., medical or other intervention) creates weaknesses and strengths.

7. The principle of mass, where inadequate response is redressed by simply adding more force.

8. The Nile Distributary Problem, where the existence of parallel growth-driving pathways allows signaling flow to proceed when a given pathway is blocked.

3. Eight Overarching Principles Driving the Construction of MDACT-Type Regimens

3.1. The Principle of Breaking More than One Link in a Chain

If one wishes to stop or impede any chain of events that leads to an unwanted result, that chain should be broken at more than one link. Modern critical machines are designed with this principle in mind, in that failure is averted by requiring several redundant systems to simultaneously fail before the overall function of the machine fails. Modern jet aircraft, for example, have multiple redundant systems—in the event that any one should fail, a second system will fulfill the functions of the failed system. Vulnerable critical systems or machines have many such backup systems, and often a backup to the backups. Competently designed robust machines have compensatory pathways at hand so as to tolerate multiple subsystem failures without major critical end-function dropout. Metastatic cancers tend to be robustly competent, so interrupting a metabolic or growth signaling chain at a single point is too easily repaired, compensated for, or circumvented.

3.2. The Principle of Palmer et al.

A second related principle behind the MDACT approach is that of Palmer et al. [17]. CHOP, developed in the late 1970s (and now R-CHOP—rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), is a treatment of certain lymphomas [18]. None of these drugs are specific to certain malignant lymphoma clones. However, 87% of lymphomas typically achieve a complete response, with multiyear remissions being common [19]. Not all of the drugs of CHOP or R-CHOP have been tested individually, and no xenograft study preceded clinical trial of the ensemble. Nor would it make sense to decline the combination of amoxicillin and clavulanate because clavulanate did not show any antibacterial effect. This would miss the point of the combination in the same manner as would objections to individually testing the drugs of gMDACT. Individually testing components of the ensemble undercuts the rationale of using the combination.

By analyzing R-CHOP, Palmer et al. concluded that “the 50 years old hypothesis that a curative cancer therapy can be constructed on the basis of independently effective drugs having non-overlapping mechanisms of resistance, without synergistic interaction … has immediate significance for the design of new drug combinations” [17]. Additionally, making parallels with multidrug regimens required to treat tuberculosis, Palmer et al. showed that both original clonal heterogeneity and cytotoxic-drug-driven clonal evolution require a multidrug approach.

Both MDACT and the specific examples of CUSP9v3 and gMDACT engage Palmer et al.’s principle of independent action as well as coordinated actions of drugs (e.g., in shaping operations, vide infra, synthetic cytotoxicity, circumvention prevention actions, CUSP9v3’s Nile Distributary Problem, etc.).

3.3. The Chess Principle of Shaping Versus Decisive Operations

Whenever two opposing forces meet—for example, in chess, soccer (football), boxing, or tennis—opponents make a clear distinction between shaping versus decisive operations [20]. Decisive operations are direct efforts to achieve the mission. In chess, this would be to checkmate the opponent’s king. In our case, this would correspond to the use of cytotoxins, surgery, or irradiation to directly kill or remove all cancer cells.
Shaping operations are interventions that set conditions for the decisive operation to be more effective, but do not themselves directly aim to achieve the primary objective. Shaping operations set the stage and prepare the environment to increase the chance that a decisive operation will succeed. In chess, a shaping operation would be to capture one of an opponent’s pieces. With the defenses thus weakened, a checkmating plan—the decisive operation—is more likely to succeed.

Examples of shaping operations in oncology would include rigorous anti-nausea measures to allow the use of highly emetic cytotoxins, the use of mesna to avoid ifosfamide-induced cystitis, forced diuresis for renal protection, etc. Even anesthesia is an oncological shaping operation that allows a decisive operation—surgical removal of a cancer. MDACT-type regimens tend to be largely shaping operations.

3.4. The Principle of Chow et al.

In 2021, Chow et al. published an interesting study on the treatment of hypertension [21]. Chow et al. treated arterial hypertension with four different traditional antihypertensive drugs at \( \frac{1}{4} \) the usual dose of each. They used a Ca++ channel blocker (amlodipine), a beta blocker (bisoprolol), a diuretic (indapamide), and an angiotensin receptor blocker (irbesartan) at doses that, when used individually, would not be expected to lower blood pressure much, but did so effectively when all used together, without the side effects characteristic of any of the drugs [21]. MDACT applies this principle to cancer treatment. Granted, we cannot assume that this same method would work in treating cancer as it did in treating hypertension, but it might.

Potential benefits in terms of increased effectiveness with lower side effect burdens make experimental studies of this method worthwhile, remembering that few of us would have predicted the positive results of Chow et al. Others are also considering this translation of Chow et al. to cytotoxic cancer treatments, citing the need to “disrupt paracrine substitutional [growth] signaling” [22].

3.5. The Principle of CUSP9v3

CUSP9v3 uses the deeper attributes of ordinary general medicine drugs already in use, seeking to find the intersections between these attributes and identified cancer-growth-driving elements (see previous works for details [1–7]).

As things stand in 2022, drug repurposing must be a core feature of any regimen that aims to achieve a comprehensive addressing of the many aspects of malignancy as itemized in Section 2 above. Specifically, for intracranial tumors, the drugs chosen must have evidence that they cross the blood–brain barrier. Selection and tailoring of multiple similar cancer-specific drugs is required.

3.6. The Chess Aphorism—All Moves Create Strengths and Weaknesses

The concept borrowed from chess is that every move creates weaknesses and strengths. The redundant systems that make aircraft safer also make them heavier and more expensive. An attack in chess, boxing, or fencing creates an opening for the opponent’s counterattack. As applied to the practice of medicine, this means that all of our interventions to cure or ameliorate disease will have aspects of harm inherent to them. These can be trivial or serious. Much of medical research is devoted to determining the relative proportion of harm to benefit. MDACT aims to be conservative, i.e., far towards the low-risk end of that spectrum.

However, as Frederick the Great said, “He who tries to hold onto everything, holds onto nothing”. Accepting some risk is unavoidable if one is to constructively intervene in a disease process. Reluctance to accept harms wrought by a treatment may intrinsically lead to accepting greater harm wrought by the disease. The risk of harm must be commensurate with the threats of the given disease. Commensurate with that dictum, target doses are at the higher end of a standard dosing range, but reduced on an individual basis to eliminate side effects.
As a consequence of this principle, drug selection must put ensuring a low side effect profile first. This will allow greater numbers of drugs to hit a wider array of targets and over longer time periods than we could otherwise with drugs with more burdensome side effects.

3.7. The Principle of Mass

This principle is unstated but obvious and accepted throughout medicine. As in the orthopedics aphorism “if a little force didn’t work, maybe more force will”, the principle of mass simply states that by adding mass and force, to a given effort, the chances of achieving the goal increase. Before combat—in chess, military engagements, fencing, football, boxing, and similar clashes of forces—the calculation of mass ratio tends to predict outcomes. Adding mass to one’s effort in such meetings of opposing forces is a well-known maneuver to enhance one’s chances of victory. Mass in this context should be understood as force, or as that which increases inertia.

Applied here, piling on many medicines increases our mass in combating a cancer’s growth. A corollary to this would be, again, that the medicines being piled on must be designed to have fairly low side effect burdens, as in CUSP9v3 and gMDACT.

3.8. The Principle of Blocking Parallel Pathways—The Nile Distributary Problem

A cellular consequence of blocking one growth-signaling pathway is often a rerouting of signaling to a parallel pathway, as we see in city traffic or the River Nile Delta. When they exist, an in-parallel flow circuit will take up flow increases, compensating for a blocked route (see discussions of this in the preceding CUSP9v3 papers [1,3,4,6,7]). CUSP9v3 and gMDACT aim to block both in-series growth drives (as in Section 3.1 above) and in-parallel growth-driving circuits.

Part Two

4. The Drugs of gMDACT

gMDACT is an example of the MDACT pharmacological principle, created with the intent of being applicable across several cancers. gMDACT does not replace CUSP9v3 for glioblastoma, but is perhaps a potential alternative.

A winnowing process answered two questions: What are some commonly upregulated growth-facilitating systems across common cancers? What FDA- or EMA-approved drugs already exist that have evidence of being able to inhibit or block them? The result is gMDACT, which is designed to be used with a low-dose cytotoxic drug, e.g., temozolomide.

The six repurposed drugs of gMDACT are (1) the analgesic drug celecoxib, (2) the antibiotic dapsone, (3) the alcoholism treatment drug disulfiram, (4) the antifungal drug itraconazole, (5) the anti-protozoan drug pyrimethamine, and (6) the antihypertensive telmisartan, together with a continuous low dose of a disease-appropriate classical cytotoxic drug. See Table 2 for an overview of the gMDACT drugs and their putative MOAs. Some of these are depicted in the schematic overview shown in Figure 1.

Table 2. Overview of the gMDACT regimen.

| Drug          | Dose   | Usual Use—Target Use in gMDACT                |
|---------------|--------|-----------------------------------------------|
| Celecoxib     | 600 mg | Analgesic—COX-2, CA-IX, P-gp                  |
| Dapsone       | 100 mg | Antibiotic—neutrophils, IL-8, VEGF             |
| Disulfiram    | 250 mg | Anti-alcoholism—ALDH, P-gp                    |
| Itraconazole  | 200 mg | Antifungal—Hh, 5-LO, P-gp                     |
Table 2. Cont.

| Drug             | Dose  | Usual Use—Target Use in gMDACT                             |
|------------------|-------|------------------------------------------------------------|
| Pyrimethamine    | 50 mg | Antibiotic—STAT3, DHFR, IL-8, thymidine phosphorylase      |
| Telmisartan      | 80 mg | Anti-hypertensive—PPAR-gamma, ARB, IL-8                    |

Target doses are down-titrated to mitigate any unpleasant side effects or lab abnormalities should these occur. References in text. ALDH = aldehyde dehydrogenase; ARB = angiotensin receptor blocker; CA = carbonic anhydrase; COX-2 = cyclooxygenase-2; DHFR = dihydrofolate reductase; Hh = hedgehog; 5-LO = 5-lipoxygenase; P-gp = p-glycoprotein efflux pump, synonymous with ABCB1. With respect to dose suggestions, these are ideal target doses. Many people will require dose reductions from this ideal due to side effects or adverse reactions.

In general, with multidrug regimens such as gMDACT or CUSP9v3, we aim to give the standard doses as used in the drugs’ non-oncology indication. As with the nine-repurposed-drug regimen CUSP9v3, it should be expected that all people receiving an MDACT-type
4.1. Celecoxib

Celecoxib is an older analgesic drug that inhibits two enzymes important in facilitating cancer growth—cyclooxygenase-2 (COX-2), and carbonic anhydrase (CA-IX) [23]. It also inhibits the function of a major drug efflux transporter—P-glycoprotein (P-gp). The P-gp 170-kDa efflux pump (synonymous with ABCB1) is active in cell export of xenobiotics, including chemotherapy drugs such as temozolomide and doxorubicin [24–26]. This drug, exporting via upregulated P-gp, becomes a contributor to cancer cells’ resistance to cytotoxic drugs [27–29]. Celecoxib reduces cells’ expression of P-gp [30–32].

Dozens of recent papers review the hundreds of research studies on the growth-promoting role of prostaglandins in cancer growth generally, and specifically the therapeutic benefits of its synthesis inhibition by COX-2 inhibitors such as celecoxib [33–36]. The limited clinical benefits of adding celecoxib to standard cancer treatments in previous studies should not discourage its use [36]. Doses used in previous studies were generally far too low (see Reckamp et al. [37]) and, as discussed in part one of this paper, we would not expect any single intervention to be markedly effective, due to the multiple circumvention paths a cancer cell might take.

Reckamp et al. showed data pivotal to the use of celecoxib in treating any cancer. Prostaglandin E2 urinary metabolites in humans only became effectively suppressed at 600 mg of celecoxib twice daily. The nonlinearity of prostaglandin synthesis inhibition by celecoxib should be noted. In humans, after 8 weeks of use, one sees a urinary metabolite decline of only <10% at doses of celecoxib of 200 or 300 mg twice daily, of only 65% after 400 mg twice daily, and 87% at 600 mg twice daily [37]. Therefore, 600 mg of celecoxib twice daily would be the minimum dose in adjunctive treatment of any cancer.

The safety profile of celecoxib differs little from placebo, although large safety studies have investigated lower doses than those of CUSP9v3 or gMDACT [38].

The increased metabolism frequently found in cancer cells requires cell export of the resulting excess H+. Many mechanisms are used in cancers to achieve this export, of which upregulated CA-IX is a major one [39]. CA-IX is an element in maintaining the lower extracellular pH and higher intracellular pH compatible with cancer cells’ survival. This is depicted schematically and simplified in Figure 2. Elevated CA-IX is characteristically found in many cancers where a greater degree of elevation is associated with shorter survival [39,40].

Figure 2. Celecoxib’s CA-IX action in cancer: by inhibiting the interconversion of bicarbonate and CO₂, depicted by the red arrows, celecoxib reduces cancer cells’ ability to maintain extracellular milieu acidification and maintenance of their intracellular alkaline milieu.
A. Celecoxib in cholangiocarcinoma: High COX-2 expression is associated with shorter cholangiocarcinoma survival [41]. Preclinical studies have shown inhibition of cholangiocarcinoma growth by celecoxib [42–44]. Around 92% of cholangiocarcinoma tumors have strong CA-IX immunohistochemistry staining [45].

B. Colon adenocarcinoma: COX-2-driven overproduction of prostaglandin E is an element of dysregulated excess growth across cancers, including colon adenocarcinoma [46–49]. CA-IX: CA-IX inhibitors increase colon adenocarcinoma cells’ sensitivity to temozolomide and other genotoxic chemotherapies [50]. CA-IX generally tends to be upregulated in hypoxic areas of cancers, and is found specifically in colon adenocarcinoma [51–53]. H+ export function by CA-IX has been shown to be crucial for keeping intracellular pH high enough to be compatible with growth in colon adenocarcinoma [54].

C. Celecoxib in glioblastoma: COX-2 and CA-IX are elevated in glioblastoma, and are growth-facilitating elements. The potential usefulness of celecoxib in glioblastoma by inhibiting the function of both of these enzymes was recently reviewed in detail [36]. CA-IX upregulation characteristic of glioblastoma is crucial for this cancer’s adaptation to the hypoxic conditions in which it grows [55].

D. Celecoxib in NSCLC: The roles of elevated COX-2 and CA-IX in NSCLC growth promotion, along with the potential benefit of celecoxib in NSCLC treatment, were recently reviewed [56–58]. Several studies show celecoxib’s potential for increasing immune response to NSCLC [59,60]. A recent human clinical immunization study in NSCLC showed that celecoxib enhanced immune responses to a lung cancer lysate vaccine [61]. COX-2 mediates aspects of NSCLC resistance to common traditional cytotoxic drugs, and celecoxib reduces that resistance in experimental models [62–66].

4.2. Dapsone

Neutrophils’ tumor trophic function is seen across the common cancers [67–74]. Dapsone is an old sulfone antibiotic that has seen a recent revival of use in treating cancer and nonmalignant neutrophilic dermatoses [75–79]. In treating both the non-malignant dermatoses (e.g., bullous pemphigoid, dermatitis herpetiformis, etc.) and in its anticancer role, dapsone blinds and reduces neutrophils’ homing along an IL-8 gradient. IL-8, synonymous with CXCL8, signals through the receptors CXCR1 or CXCR2, is a neutrophil chemokine, is elevated in the common cancers, and contributes to their associated angiogenesis, and epithelial-to-mesenchymal transition [80–82]. In dermatological use, it is established that dapsone inhibits IL-8 function and reduces neutrophil chemotaxis [83–86]. Dapsone also lowers IL-8 levels in a variety of settings [75,78,87–90].

Neutrophil-to-lymphocyte ratio (NLR) is elevated across the common cancers, and higher NLR predicts shorter overall survival. Dapsone potentially diminishes some of tumors’ trophic consequences of high NLR by inhibiting neutrophil IL-8 chemotaxis.

Multiple signaling systems converge to upregulate IL-8 [89]. Increased IL-8 goes on to initiate and maintain a growth-promoting role in many cancers, including the four under discussion here.

A. Dapsone in cholangiocarcinoma: IL-8-driven chemotaxis of neutrophils infiltrating cholangiocarcinoma constitutes a trophic function in the growing tumor [91–101]. IL-8 drives angiogenesis, and is elevated in cholangiocarcinoma, where higher levels are associated with shorter survival [102–110]. As with other cancers, a higher NLR is strongly associated with shorter survival in cholangiocarcinoma [111].

B. Dapsone in colon adenocarcinoma: Specifically in colon adenocarcinoma, a higher NLR is associated with shorter survival, while a low NLR is associated with longer survival [112–114]. Bevacizumab, a pharmaceutical monoclonal antibody to vascular endothelial growth factor (VEGF), is often used in the treatment of colon adenocarcinoma and NSCLC. The benefit of bevacizumab diminishes as the circulating absolute neutrophil count or NLR increases [75,115–118]. This inverse relationship is due to neutrophils’ delivery of intracellular VEGF, protected from circulating be-
vacizumab [119–121]. IL-8 is actively synthesized by both the malignant cells and their supporting nonmalignant stromata to support growth and angiogenesis in colon adenocarcinoma [122–127].

C. Dapsone in glioblastoma: Dapsone’s suppression of IL-8-directed neutrophil chemotaxis and its consequent contributions to glioblastoma growth and angiogenesis were recently reviewed in detail [75]. IL-8 signaling at CXCR2 is a prominent member of the flood of cytokines driving glioblastoma growth [128]. Circulating neutrophils chemotactic to glioblastoma due to IL-8 are an element driving glioblastoma growth and related angiogenesis [129].

D. Dapsone in NSCLC: IL-8 levels are elevated in NSCLC, and a degree of pretreatment elevation is associated with shorter OS [130]. IL-8 elevation in NSCLC is also associated with—and partially drives—increased myeloid-derived suppressor cells [131]. NSCLC tissue, sera, and pleural effusions have increased levels of IL-8 and its receptors, where the degree of elevation is correlated with shorter survival [132–137]. As seen commonly in other cancers, an NLR > 4 strongly predicts shorter OS in NSCLC [138–142]. Neutrophil extracellular traps, the presence of which shortens survival in NSCLC, are driven in part by excess IL-8 in NSCLC [68,71].

4.3. Disulfiram

Disulfiram is an old alcoholism treatment drug currently used in a wide range of oncology research programs and clinical trials, repurposed for treating cancers. It inhibits aldehyde dehydrogenase (ALDH), resulting in unpleasant accumulation of acetaldehyde if ethanol is consumed. ALDH is a central marker for stemness in both cancer cells and normal cells [143–150]. ALDH might be more properly termed a mediator of stem attributes. Disulfiram deletes or limits ALDH’s mediation of stemness [5–7,150–156]. Empirical in vitro inhibition of multiple cancers’ growth by disulfiram has been demonstrated [157,158]. Disulfiram is currently being investigated in over a dozen human clinical studies as an adjunct in treating cancer stem cell function (clinicaltrials.gov, accessed on 28 February 2022).

A. Disulfiram in cholangioma: The relationship of ALDH with stemness also holds in cholangiocarcinoma, and contributes to its cytotoxic drug resistance [159–163].

B. Disulfiram and colon adenocarcinoma: ALDH is also a core marker/mediator of stemness in colon adenocarcinoma [164–168]. The preclinical activity of disulfiram in inhibition of colon adenocarcinoma cells has been known for over a decade [169,170].

C. Disulfiram in glioblastoma: With potential utility in treating glioblastoma with temozolomide, disulfiram irreversibly inactivates P-gp [171–173]. As with other cancers, the ALDH-positive glioblastoma subpopulation has other stem attributes, and is more chemotherapy resistant than the ALDH-negative subpopulation [158,174–176].

D. Disulfiram in NSCLC: As it does in other cancers, ALDH contributes to driving stemness and, hence, cytotoxicity resistance, in NSCLC [177–181]. ALDH-driven stemness and chemotherapy resistance in NSCLC are reduced after disulfiram or other inhibitors of ALDH [179,181–183].

4.4. Itraconazole

Itraconazole is a generic broad-spectrum antifungal drug that is also seeing a renaissance in anticancer applications [184–189]. It has three attributes that recommend its use during cancer treatment: (1) it inhibits Hedgehog (Hh) signaling [189–193], (2) it inhibits 5-lipoxygenase (5-LO) [193–196], and (3) it inhibits the P-gp efflux pump [188,197–199].

Hh signaling is essential for embryological development, but is often inappropriately engaged to drive malignant growth [200–203]. Hh is a common marker/mediator of stemness across cancers [148,204,205]. Hh signaling has a potentially felicitous relationship with pyrimethamine (vide infra) in that low folate states activate compensatory Hh signaling in colon adenocarcinoma [206].
A branch point in arachidonic acid metabolism leads either to the prostaglandin pathway via COX-1/COX-2 or the leukotriene pathway via 5-LO. Itraconazole’s inhibition of 5-LO makes it a particularly good partner drug for COX-2 inhibitors such as celecoxib.

A. Itraconazole in cholangiocarcinoma: 5-LO and its leukotriene products contribute to the growth of cholangiocarcinoma [207–209]. Hh signaling is a core growth-driving element in cholangiocarcinoma, and prominently so in the stem subset [210–215]. 5-LO is one of the drivers of both myeloid-derived suppressor cell immunosuppression and stemness in cholangiocarcinoma [216].

B. Itraconazole in colon adenocarcinoma: Colon adenocarcinomas overexpress 5-LO, as well as COX-2 [217–219]. As found in other cancers, breast cancer’s overexpression of both COX-2 and 5-LO is associated with enhanced aggressiveness [220]. Dual inhibition of COX-2/5-LO inhibits colon cancer proliferation, migration, and invasion to a greater degree than either alone. Specifically, inhibition of 5-LO increases celecoxib’s cytotoxicity to colon cells [221–223]. Coordinated participation of COX-2 and 5-LO in carcinogenesis and cancer growth is recognized in several common cancers [220,221,224–227]. Hh signaling is a major growth-driving element in a variety of cancers, including colon adenocarcinoma [228]. Itraconazole interferes with colon cancer’s cytotoxicity resistance and growth by inhibiting Hh [229–231]. Hh signaling is a major driver of colon adenocarcinoma growth [232]. Itraconazole’s inhibition of Hh inhibits colon adenocarcinoma growth [229].

C. Itraconazole in glioblastoma: The rationale for the use of itraconazole during glioblastoma treatment is based on its attributes of Hh inhibition, leukotriene signaling reduction, and reduction in P-gp-mediated cell export of temozolomide, as outlined in the three preceding CUSP9 papers [1–3,6]. 5-LO-generated leukotrienes promote glioblastoma migration, growth, and stem attributes [233].

D. Itraconazole in NSCLC: A 2013 study showed that itraconazole plus pemetrexed in NSCLC doubled progression-free survival (PFS) and gave a fourfold increase in overall survival (OS) [234]. In 2017, three reviews of itraconazole’s attributes were published, suggesting its usefulness in interfering with cancer cells’ growth—two in general, and one specifically in NSCLC [235–237]. In 2018, Lee et al. outlined the potential of inhaled itraconazole to inhibit NSCLC growth [238]. In 2019, itraconazole was reformulated for superior pharmacokinetics in NSCLC treatment [239]. NSCLC patients given 300 mg of itraconazole orally, twice daily, for two weeks prior to surgery, had decreased tumor volume and reduced vascularity [240]. 5-LO-generated leukotrienes promote NSCLC migration and growth [233,241].

4.5. Pyrimethamine

Pyrimethamine is a 248 Da lipophilic drug used to treat malaria for over 50 years, and continues in this role to this day. Three pharmacodynamic attributes of pyrimethamine recommend its use in disseminated human cancer: (1) inhibition of human dihydrofolate reductase (DHFR), (2) inhibition of thymidine phosphorylase, and (3) inhibition of STAT3. Pyrimethamine is seeing increasing adjunctive use in treating cancer [242–244].

Pyrimethamine’s Ki = 38 nM at DHFR is comparable to that of the archetypal DHFR inhibitor methotrexate (MTX) (Ki = 2.3 nM) or folic acid (Ki = 320 nM) and folinic acid (Ki = 830 nM) [245,246]. DHFR catalyzes NADPH-dependent reduction of dihydrofolate to tetrahydrofolate. MTX is a high-affinity inhibitor of DHFR commonly used in treating several cancers, which blocks DNA synthesis by disrupting metabolism of methionine, S-adenosyl-methionine, purines, and thymidylate.

The thymidine synthetic pathway depends on the methylation of deoxyuridine, the methyl donor being methylenetetrahydrofolate [247–250]. The standard DHFR inhibitor used for over 50 years in cancer treatment has been MTX [251,252].

Pyrimethamine is readily exported by P-gp [245]. Thus, the three P-gp-inhibiting drugs of gMDACT—celecoxib, disulfiram, and itraconazole—have the potential to augment pyrimethamine’s effects.
In an acute myelogenous leukemia model, pyrimethamine was more effective in inhibiting growth than MTX. In vitro proliferation was reduced 2.5-fold by pyrimethamine at 0.1 µM, and 12.7-fold at 0.5 µM [253]. Clinically, several patients with polycythemia rubra vera and essential thrombocytopenia were successfully controlled with pyrimethamine, as reported in 1987 [254]. It is unclear why early reports in the 1970s of successful pyrimethamine treatment (2 mg/kg/day for 7 days) of meningeal recurrence of acute lymphoblastic leukemia in children have not been followed up, or why such use is currently rare to nonexistent [255].

Pyrimethamine also inhibits mammalian thymidine phosphorylase [256,257]. Thymidine phosphorylase catalyzes the following reaction:

\[
\text{Thymidine + phosphate} \rightleftharpoons \text{thymine + 2-deoxy-alpha-D-ribose 1-phosphate}. 
\]

Thymidine phosphorylase activity enhances NF-κB-mediated IL-8 expression in a variety of settings [258–261].

Pyrimethamine is an inhibitor of STAT3 phosphorylation [262–267]. STAT3 is a cytosolic signaling hub, at the middle point of a signaling chain from cell surface receptors to the nucleus. STAT3’s activation by surface growth-stimulating receptors results in STAT3’s phosphorylation, dimerization, and subsequent transport to the nucleus, where it acts as a transcription factor for growth systems identified across cancers [268–270]. Many upstream signaling pathways converge on STAT3 to activate it. Pyrimethamine’s STAT3-inhibitory effects are traceable to reduced intracellular folate from DHFR inhibition [266].

The STAT3 signaling hub is overactive in many cancers, including the four under discussion here [271–275]. Of additional potential benefit of STAT3 inhibition, STAT3 activation is an element in myeloid-derived suppressor cells’ function, where inhibiting STAT3 activation was found to reduce myeloid-derived suppressor cell function [275,276].

A. Pyrimethamine in cholangiocarcinoma: In cholangiocarcinoma, upregulated thymidine phosphorylase also contributes to chemotherapy resistance, and furthers survival [109,277–279]. Thymidine phosphorylase overexpression enhances growth and suppresses apoptosis in human umbilical vein endothelial cells, as well as increasing VEGF, IL-8, and the growth of cholangiocarcinoma cells [109]. STAT3 activation is an identified growth driver in cholangiocarcinoma [280–282].

B. Pyrimethamine in colon adenocarcinoma: As commonly found in other cancers, STAT3 overactivation also constitutes a driving force in colon adenocarcinoma, and particularly so in the stem subpopulation [282–288]. Multiple experimental, non-marketed inhibitors of STAT3 reduced colon cancer growth in preclinical models [289–291]. Growth of colon cancer cells is suppressed when DNA binding of activated STAT3 is prevented [292].

C. Pyrimethamine in glioblastoma: Of great interest for potential use in treating glioblastoma or brain metastases from breast or lung cancer is the unusual property of pyrimethamine in being concentrated in the brain at several times greater levels than in plasma [293,294]. Pyrimethamine is synergistically cytotoxic with temozolomide—the mainstay in current glioblastoma treatment—in melanoma and pituitary adenoma cell lines [295,296]. Glioblastomas have a greatly upregulated thymidine phosphorylase content and activity [297]. Experimental (non-marketed) thymidine phosphorylase inhibitors have no cytotoxicity alone, but are synergistic with temozolomide against glioblastoma cell lines [297].

D. Pyrimethamine in NSCLC: STAT3 is also an active signaling hub identified in NSCLC growth [298]. A preclinical study showed in vitro and xenograft growth inhibition of NSCLC by pyrimethamine [257,258,299].

4.6. Telmisartan

Telmisartan is a generic angiotensin-receptor-blocking drug (ARB) used to treat hypertension. Angiotensin-converting enzyme (ACE) converts angiotensin I to the eight-amino-acid peptide angiotensin II. Angiotensin II signals widely throughout the body, mostly to increase blood pressure. Investigation of the potential of ARBs to inhibit cancer’s growth
in general has a long history [300]. ACE and ACE-related signaling are recognized drivers across the common cancers [301, 302]. A second attribute of telmisartan is its stimulation of PPAR-γ [302–305].

Patients being treated for hypertension with telmisartan show decreased IL-8 [306].

A. Telmisartan in cholangiocarcinoma: Telmisartan triggers cholangiocarcinoma G0/G1 cell-cycle arrest in vitro [307]. Telmisartan also triggers cell-cycle arrest in a wide variety of gastrointestinal and other common cancers [308–318]. ACE and ACE-related signaling are active specifically as elements driving cholangiocarcinoma growth [319–321].

B. Telmisartan in colon adenocarcinoma: Telmisartan blocks angiotensin II receptor type 1. Marketed to treat hypertension, it has several other attributes and uses. Colon adenocarcinoma cells express angiotensin II receptor 1. Telmisartan’s IC\textsubscript{50} to several colon cancer cell lines in vitro is between 1 and 5 µM [322]. Irbesartan, a marketed pharmaceutical ARB similar to telmisartan, inhibits colitis-associated colon cancer development [323]. Candesartan, another pharmaceutical ARB similar to telmisartan, inhibits colon adenocarcinoma xenograft growth and tumor-related fibrosis [324]. Other studies have found that colon cancer cell growth inhibition is greater with telmisartan compared to candesartan [325]. Candesartan decreased the immune suppression function of tumor-associated CD11b\textsuperscript{+} T cells and decreased their production of VEGF and arginase, and increased interferon-γ synthesis in the lymph nodes of colon-cancer-bearing mice, without having effect on in vivo tumor growth [326].

C. Telmisartan in glioblastoma: Telmisartan was cytotoxic via peroxisome proliferator-activated receptor gamma (PPAR-γ) agonism in glioblastoma cells in vitro, at low concentrations [327]. Telmisartan-induced inhibition of glioblastoma growth via angiotensin receptor inhibition has been extensively reviewed previously [328]. PPAR-γ is upregulated in mesenchymal glioblastoma stem cells, with agonism suppressing growth [329].

D. Telmisartan in NSCLC: Several studies show longer survival in NSCLC in patients receiving an ARB [330–333]. This effect, although slight, has been consistently found across studies. Empirically, telmisartan inhibits experimental NSCLC growth [334]. Various putative MOAs for telmisartan’s inhibition of NSCLC have been identified [334–339].

5. Conclusions

As in point number 3 in Table 1, MDACT-type regimens are designed to be shaping operations more than decisive operations. MDACT regimens are designed primarily to delay the development of resistance and impede tumor regrowth, and to limit normal growth-driving signals that are abnormally engaged by a malignant tumor to further its growth. MDACT regimens aim to set the conditions for cytotoxic medications to be more active, to prepare malignant cells for a cytotoxin by defeating some of the signaling systems responsible for their hardiness.

Part one of this paper outlined what we are up against in trying to treat human cancer—stromata’s trophic functions, engagement of remote physiological systems (e.g., bone marrow, adrenal, thyroid, neural inputs to tumors, etc.), immunological/inflammatory contributions to tumor growth, immunological/inflammatory contributions to tumor elimination, interacting malignant cell communities within the main tumor, the evolution of those communities, entry to a treatment-resistant quiescent state, and other currently unknown elements driving discrepancies between lab results and clinical disease. Thus, there is a lot to consider.

The MDACT approach aims to address as many of these tumor growth and survival elements as possible with already-marketed, non-oncology drugs to augment the effects of traditional cytotoxic, kinase-inhibitory, or other traditional current oncology drugs. Clinical experience with CUSP\textsubscript{9v3} and other similar preceding regimens shows that this can be done safely over years of treatment [1, 340]. The risks of unanticipated drug–drug
interaction are mitigated by gradual one-by-one drug addition at low doses over several weeks, followed by several weeks of gradual dose up-titration. As shown by Chow et al. in CUSP9v3 treatment of glioblastoma, multidrug regimens can be given safely if three conditions are met: (1) careful pharmacological evaluation during drug selection to obviate known interaction potential, (2) adding drugs one at a time with weekly appropriate lab and clinical evaluations, and (3) gradual dose up-titration [1,3,6,7,21]. Related to this, we expect in any MDACT-type regimen that individual patients will require dose reduction from target doses of one or more of the drugs, as was the case in the CUSP9v3 trial [1]. Target doses for MDACT-type regimens are the upper end of the standard doses for the individual drugs when used in their non-oncology setting, with certain physiologically based exceptions, e.g., for celecoxib.

Part two of this paper gave an example of a six-repurposed-drug regimen, gMDACT, which might be applicable across a range of cancers. The six gMDACT drugs—celecoxib, dapsone, disulfiram, itraconazole, pyrimethamine, and telmisartan—interfere with multiple growth-driving elements commonly elevated in common cancers. gMDACT does not replace CUSP9v3.

Multiple synergies between the gMDACT drugs have been mentioned and referenced in the text above. (1) Three of the gMDACT medicines (celecoxib, disulfiram, and itraconazole) inhibit P-gp. (2) Augmentation of temozolomide’s cytotoxicity to various cancer cell types has been either empirically demonstrated or predicted by theory for four of the gMDACT drugs (celecoxib, itraconazole, pyrimethamine, and telmisartan), making low-dose metronomic temozolomide a potentially good choice of cytotoxic drug with gMDACT. (3) Four of the gMDACT drugs (celecoxib, dapsone, pyrimethamine, and telmisartan) have shown the potential to downregulate IL-8 synthesis.

We have wide clinical non-oncology experience with the gMDACT drugs. They are low-risk for adverse events. The gMDACT mix of drugs might be applicable adjuvants to a broad range of common cancers.

Author Contributions: This paper was an international group effort. Primary conceptualization was by R.E.K. and M.-E.H. but all authors contributed to this. All authors contributed to writing, editing, and reviewing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The Cantonal Hospital of Winterthur, Winterthur, Switzerland paid the article processing charge.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors are happy to provide further references to matters discussed in this work. Contact corresponding author R.E.K.

Acknowledgments: Thanks to the IIAIGC Study Center for coordinating this international effort.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ACE Angiotensin-converting enzyme
ALDH Aldehyde dehydrogenase
ARB Angiotensin receptor-blocking drug
CA Carbonic anhydrase
COX-2 Cyclooxygenase-2
DHFR Dihydrofolate reductase
Hh Hedgehog
5-LO 5-Lipoxygenase
Cancers 2022, 14, 2563

References

1. Halatsch, M.-E.; Kast, R.E.; Karpel-Massler, G.; Mayer, B.; Zolk, O.; Schmitz, B.; Scheuerle, A.; Maier, L.; Bullinger, L.; Mayer-Steinacker, R.; et al. A phase Ib/Ia trial of 9 repurposed drugs combined with temozolomide for the treatment of recurrent glioblastoma: CUSP9v3. *Neurooncol. Adv.* 2021, 3, vda073. [CrossRef] [PubMed]

2. Skaga, E.; Skaga, I.O.; Grieg, Z.; Sandberg, C.J.; Langmoen, I.A.; Vik-Mo, E.O. The efficacy of a coordinated pharmacological blockade in glioblastoma stem cells with nine repurposed drugs using the CUSP9 strategy. *J. Cancer Res. Clin. Oncol.* 2019, 145, 1495–1507. [CrossRef] [PubMed]

3. Halatsch, M.-E.; Dwucet, A.; Schmidt, C.J.; Mühlnickel, J.; Heiland, T.; Zeiler, K.; Siegelin, M.D.; Kast, R.E.; Karpel-Massler, G. In Vitro and Clinical Compassionate Use experiences with the Drug Repurposing Approach CUSP9v3 in Glioblastoma. *Pharmaceuticals* 2021, 14, 1241. [CrossRef] [PubMed]

4. Mettang, M.; Meyer-Pannwitt, V.; Karpel-Massler, G.; Zhou, S.; Carragher, N.O.; Föhr, K.J.; Baumann, B.; Nonnenmacher, L.; Enzenmüller, S.; Dahlhaus, M.; et al. Blocking distinct interactions between Glioblastoma cells and their tissue microenvironment: A novel multi-targeted therapeutic approach. *Sci. Rep.* 2018, 8, 5527. [CrossRef]

5. Kast, R.E.; Dwucet, A.; Schmidt, C.J.; Kiel, C.; Casas, A.I.; Schmidt, H.H. Network pharmacology: Curing causal mechanisms instead of treating symptoms. *Trends Pharmacol. Sci.* 2021, 43, 249–247. [CrossRef]

6. Kast, R.E.; Karpel-Massler, G.; Halatsch, M.-E. CUSP9 treatment protocol for recurrent glioblastoma: Aprepitant, artesunate, auranofin, captopril, celecoxib, disulfiram, irtraconazole, ritonavir, sertraline augmenting continuous low dose temozolomide. *Oncotarget* 2014, 5, 8052–8082. [CrossRef]

7. Kast, R.E.; Boockvar, J.A.; Brüning, A.; Cappello, F.; Chang, W.-W.; Cvek, B.; Dou, Q.P.; Duenas-Gonzalez, A.; Efferth, T.; Focosi, D.; et al. Conceptually new treatment approach for relapsed glioblastoma: Coordinated undermining of survival paths with nine repurposed drugs (CUSP9) by the International Initiative for Accelerated Improvement of Glioblastoma Care. *Oncotarget* 2013, 4, 502–530. [CrossRef]

8. Nguyen, H.S.; Shabani, S.; Awad, A.J.; Kaushal, M.; Doan, N. Molecular Markers of Therapy Resistant Glioblastoma and Potential Strategy to Combat Resistance. *Int. J. Mol. Sci.* 2018, 19, 1765. [CrossRef]

9. Collen, M.F.; Sellers, A.L.; Kast, E.C. Combined penicillin and sulfadiazine therapy in pneumococcic pneumonia. *Am. J. Med. Sci.* 1946, 211, 299–306. [CrossRef]

10. Zapletalova, D.; André, N.; Deak, L.; Kyr, M.; Bajciova, V.; Mudry, P.; Dubskla, L.; Demlova, R.; Pavelka, Z.; Zitterbart, K.; et al. Metronomic chemotherapy with the COMBAT regimen in advanced pediatric malignancies: A multicenter experience. *Oncology* 2012, 82, 249–260. [CrossRef]

11. Peyrl, A.; Chocholous, M.; Kieran, M.W.; Azizi, A.A.; Prucker, C.; Czech, T.; Dieckmann, K.; Schmook, M.-T.; Haberler, C.; Leiss, U.; et al. Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors. *Pediatr. Blood Cancer* 2012, 59, 511–517. [CrossRef] [PubMed]

12. Rios, A.; Hsu, S.H.; Blanco, A.; Buryanek, J.; Day, A.L.; McGuire, M.F.; Brown, R.E. Durable response of glioblastoma to adjuvant therapy consisting of temozolomide and a weekly dose of AMD3100 (plerixafor), a CXCR4 inhibitor, together with laptatinib, metformin and niacinamide. *Oncoscience* 2016, 3, 156–163. [CrossRef] [PubMed]

13. Furuta, T.; Sabit, H.; Dong, Y.; Miyashita, K.; Kinoshita, M.; Uchiyama, N.; Hayashi, Y.; Hayashi, Y.; Minamoto, T.; Nakada, M. Biological basis and clinical study of glycogen synthase kinase-3β-targeted therapy by drug repositioning for glioblastoma. *Oncotarget* 2017, 8, 22811–22824. [CrossRef] [PubMed]

14. Tatokoro, M.; Fujii, Y.; Kawakami, S.; Saito, K.; Koga, F.; Matsuoka, Y.; Iimura, Y.; Masuda, H.; Kihara, K. Phase-II trial of combination treatment of interferon-α, cimetidine, cyclooxygenase-2 inhibitor and renin-angiotensin-system inhibitor (I-CCA therapy) for advanced renal cell carcinoma. *Cancer Sci.* 2011, 102, 137–143. [CrossRef]

15. Maraka, S.; Groves, M.D.; Mammoser, A.G.; Melguizo-Gavilanes, I.; Conrad, C.A.; Tremont-Lukats, I.W.; Loghin, M.E.; O’Brien, B.J.; Puduvalki, V.K.; Sulman, E.P.; et al. Phase 1 lead-in to a phase 2 factorial study of temozolomide plus memantine, mefloquine, auranofin, captopril, celecoxib, disulfiram, itraconazole, ritonavir, sertraline augmenting continuous low dose temozolomide. *Oncotarget* 2017, 8, 16291–16307. [CrossRef] [PubMed]

16. Nogales, C.; Mamdouh, Z.M.; List, M.; Kiel, C.; Casas, A.L.; Schmidt, H.H. Network pharmacology: Curing causal mechanisms instead of treating symptoms. *Trends Pharmacol. Sci.* 2021, 43, 136–150. [CrossRef]

17. Palmer, A.C.; Chidley, C.; Sorg, P.K. A curative combination cancer therapy achieves high fractional cell killing through low cross-resistance and drug additivity. *Elife* 2019, 8, e50036. [CrossRef]

18. Candelaria, M.; Dueñas-Gonzalez, A.R. Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in diffuse large B-cell lymphoma. *Ther. Adv. Hematol.* 2021, 12, 2040620721989579. [CrossRef]
19. Cruzman, M.S.; Weaver, R.; Alkuwzney, B.; Berlfein, J.; Grillo-López, A.J. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin’s lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J. Clin. Oncol. 2004, 22, 4711–4716. [CrossRef]

20. Moore, D.R. Decisive, Shaping, Sustaining Operations: An Operational Organization for the Contemporary Mission Environment. School of Advanced Military Studies United States Army Command and General Staff College Fort Leavenworth, Kansas, USA. Available online: https://apps.dtic.mil (accessed on 28 February 2022).

21. Chow, C.K.; Atkins, E.R.; Hillis, G.S.; Nelson, M.R.; Reid, C.M.; Schlaich, M.P.; Hay, P.; Rogers, K.; Billot, L.; Burke, M.; et al. QUARTET Investigators. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): A phase 3, randomised, double-blind, active-controlled trial. Lancet 2021, 398, 1043–1052. [CrossRef]

22. Gürgen, D.; Conrad, T.; Becker, M.; Sebens, R.; Röcken, C.; Hoffmann, J.; Langhammer, S. Breaking the crosstalk of the Cellular Tumorigenic Network by low-dose combination therapy in lung cancer patient-derived xenografts. Commun. Biol. 2022, 5, 59. [CrossRef] [PubMed]

23. De Monte, C.; Carradori, S.; Gentili, A.; Mollica, A.; Trisciuglio, D.; Supuran, C.T. Dual Cyclooxygenase and Carbonic Anhydrase Inhibition by Nonsteroidal Anti-Inflammatory Drugs for the Treatment of Cancer. Curr. Med. Chem. 2015, 22, 2812–2818. [CrossRef] [PubMed]

24. De Gooijer, M.C.; de Vries, N.A.; Buckle, T.; Buil, L.C.; Beijnen, J.H.; Boogerd, W.; van Tellingen, O. Improved Brain Penetration of Temozolomide by Low-Dose Combination Therapy. Clin. Cancer Res. 2009, 15, 696–701. [CrossRef] [PubMed]

25. Robinson, K.; Tiriveedhi, V. Perplexing Role of P-Glycoprotein in Tumor Microenvironment. Front. Oncol. 2020, 3381–3388. [CrossRef]

26. Munoz, J.L.; Walker, N.D.; Scotto, K.W.; Rameshwar, P. Temozolomide competes for P-glycoprotein and contributes to chemoresistance in glioblastoma cells. Cancer Lett. 2015, 367, 69–75. [CrossRef]

27. De Gooijer, M.C.; de Vries, N.A.; Buckle, T.; Buil, L.C.; Beijnen, J.H.; Boogerd, W.; van Tellingen, O. Improved Brain Penetration of Temozolomide by Low-Dose Combination Therapy. Clin. Cancer Res. 2009, 15, 696–701. [CrossRef] [PubMed]

28. Zhang, H.; Xu, H.; Ashby, C.R., Jr.; Assaraf, Y.G.; Chen, Z.S.; Liu, H.M. Chemical molecular-based approach to overcome multidrug resistance in cancer by targeting P-glycoprotein (P-gp). Med. Res. Rev. 2021, 41, 525–555. [CrossRef]

29. Robinson, K.; Tiriveedhi, V. Perplexing Role of P-Glycoprotein in Tumor Microenvironment. Front. Oncol. 2020, 3381–3388. [CrossRef]

30. Lim, J.S.; Park, Y.; Lee, B.M.; Kim, H.S.; Yoon, S. Co-treatment with Celecoxib or NS398 Strongly Sensitizes Resistant Cancer Cells to Antimitotic Drugs Independent of P-gp Inhibition. Anticancer Res. 2016, 36, 5063–5070. [CrossRef]

31. Dharmapuri, G.; Doneti, R.; Philip, G.H.; Kalle, A.M. Celecoxib sensitizes imatinib-resistant K562 cells to imatinib by inhibiting carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH. Mol. Cancer Ther. 2018, 17, 2812–2818. [CrossRef]

32. Pagliarulo, V.; Ancona, P.; Niso, M.; Colabufo, N.A.; Contino, M.; Cormio, L.; Azzariti, A.; Pagliarulo, A. The interaction of celecoxib with MDR transporters enhances the activity of mitomycin C in a bladder cancer cell line. Mol. Cancer 2013, 12, 47. [CrossRef] [PubMed]

33. Ceci, D.L.; Gad, E.A.; Corulli, L.R.; Drovetto, N.; Lubet, R.A.; Disis, M.L. COX-2 Inhibitors Decrease Expression of PD-L1 in Colon Tumors and Increase the Influx of Type I Tumor-infiltrating Lymphocytes. Cancer Prev. Res. 2011, 4, 338–348. [CrossRef] [PubMed]

34. Tudor, D.V.; Băldea, I.; Lupu, E.A.M.; Kacso, T.; Kutasi, E.; Hopártean, A.; Stretea, R.; Filip, A.G. COX-2 as a potential biomarker and therapeutic target in melanoma. Cancer Biol. Med. 2020, 17, 20–31. [CrossRef] [PubMed]

35. Kast, R.E. Adding high-dose celecoxib to increase effectiveness of standard glioblastoma chemoradiation. Ann. Pharm. Fr. 2021, 79, 481–488. [CrossRef]

36. Mostafa, T.M.; Alm El-Din, M.A.; Rashdan, A.R. Celecoxib as an adjuvant to chemotherapy for patients with metastatic colorectal cancer: A randomized controlled clinical study. Saudi Med. J. 2022, 43, 37–44. [CrossRef]

37. Reckamp, K.L.; Krysan, K.; Morrow, J.D.; Milne, G.L.; Newman, R.A.; Tucker, C.; Elashoff, R.M.; Dabinett, S.M.; Figlin, R.A. A phase I trial to determine the optimal biological dose of celecoxib when combined with erlotinib in advanced non-small cell lung cancer. Cancer Res. 2006, 66, 3821–3829. [CrossRef] [PubMed]

38. Cheng, B.R.; Chen, J.Q.; Zhang, X.W.; Gao, Q.Y.; Li, W.H.; Yan, L.J.; Zhang, Y.Q.; Wu, C.J.; Xing, J.L.; Liu, J.P. Cardiovascular safety of celecoxib in rheumatoid arthritis and osteoarthritis patients: A systematic review and meta-analysis. PLoS ONE 2012, 16, e0261239. [CrossRef]

39. Chiche, J.; Ilc, K.; Laferrière, J.; Trottier, E.; Dayan, F.; Mazure, N.M.; Brahim-Horn, M.C.; Pouysségur, J. Hypoxia-inducible carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH. Cancer Res. 2009, 69, 358–368. [CrossRef]

40. Aldera, A.P.; Govender, D. Carbonic anhydrase IX: A regulator of pH and participant in carcinogenesis. J. Clin. Pathol. 2021, 74, 350–354. [CrossRef]

41. Yeh, C.N.; Chiang, K.C.; Jiang, H.H.; Pang, J.H.S.; Yu, C.S.; Lin, K.J.; Yeh, T.S.; Jan, Y.Y. Reappraisal of the therapeutic role of celecoxib in cholangiocarcinoma. PLoS ONE 2013, 8, e69928. [CrossRef]
42. Kim, C.H.; Chung, C.W.; Lee, H.M.; Kim, D.H.; Kwak, T.W.; Jeong, Y.I.; Kang, D.H. Synergistic effects of 5-aminolevulinic acid based photodynamic therapy and celecoxib via oxidative stress in human cholangiocarcinoma cells. *Int. J. Nanomed.* 2013, 8, 2173–2186. [CrossRef]

43. Wu, T.; Leng, J.; Han, C.; Demetris, A.J. The cyclooxygenase-2 inhibitor celecoxib blocks phosphorylation of Akt and induces apoptosis in human cholangiocarcinoma cells. *Mol. Cancer Ther.* 2004, 3, 299–307. [PubMed]

44. Zhang, Z.; Lai, G.H.; Sirica, A.E. Celecoxib-induced apoptosis in rat cholangiocarcinoma cells mediated by Akt inactivation and Bax translocation. *Hepatology* 2004, 38, 1028–1037. [CrossRef] [PubMed]

45. Sadot, E.; Simpson, A.L.; De, R.K.; Gonen, M.; Shia, J.; Allen, P.J.; D’Angelica, M.I.; DeMatteo, R.P.; Kingham, T.P.; Jarnagin, W.R. Cholangiocarcinoma: Correlation with Molecular Profiling and Imaging Phenotypes. *PLoS ONE* 2015, 10, e0132953. [CrossRef]

46. Sheng, J.; Sun, H.; Yu, F.-B.; Li, B.; Zhang, Y.; Zhu, Y.-T. The Role of Cyclooxygenase-2 in Colorectal Cancer. *Int. J. Med. Sci.* 2020, 17, 1095–1101. [CrossRef]

47. Karpisheh, V.; Nikkhoo, A.; Hojjat-Farsangi, M.; Namdar, A.; Azizi, G.; Ghalamfarsa, G.; Sabz, G.; Yousefi, M.; Yousefi, B.; Jadidi-Niaragh, F. Prostaglandin E2 as a potent therapeutic target for treatment of colon cancer. *Prostaglandins Other Lipid Mediat.* 2019, 144, 106338. [CrossRef] [PubMed]

48. Tolloloczko-Iwanuk, N.; Dziemiantsczyk-Pakielka, D.; Nowaszeewska, B.K.; Celinińska-Janowicz, K.; Miltyk, W. Celecoxib in Cancer Therapy and Prevention—Review. *Curr. Drug Targets* 2019, 20, 302–315. [CrossRef]

49. Aoki, T.; Narumiya, S. Prostaglandin E2-EPE2 signaling as a node of chronic inflammation in the colon tumor microenvironment. *Inflamm. Regen.* 2017, 37, 4. [CrossRef]

50. Andreucci, E.; Ruzzolini, J.; Peppicelli, S.; Bianchini, F.; Laurenzana, A.; Carta, F.; Supuran, C.T.; Calorini, L. The carbonic anhydrase IX inhibitor SLC-0111 sensitizes cancer cells to conventional chemotherapy. *Eur. J. Inhib. Mol. Chem.* 2019, 34, 117–123. [CrossRef]

51. Kopecka, J.; Campia, I.; Jacobs, A.; Frei, A.P.; Ghigo, D.; Wollscheid, B.; Riganti, C. Carbonic anhydrase XII is a new therapeutic target to overcome chemoresistance in cancer cells. *Oncotarget* 2015, 6, 6776–6793. [CrossRef]

52. Suzuki, J.; Kojima, M.; Aokage, K.; Sakai, T.; Nakamura, H.; Ohara, Y.; Tane, K.; Miyoshi, T.; Sugano, M.; Fujii, S.; et al. Clinicopathological characteristics associated with necrosis in pulmonary metastases from colorectal cancer. *Virchows Arch.* 2019, 474, 569–575. [CrossRef] [PubMed]

53. Nakada, N.; Mikami, T.; Horie, K.; Nagashio, R.; Sakurai, Y.; Sanoyma, I.; Yoshida, T.; Sada, M.; Kobayashi, K.; Sato, Y.; et al. Expression of CA2 and CA9 carbonic anhydrases in ulcerative colitis and ulcerative colitis-associated colorectal cancer. *Pathol. Int.* 2020, 70, 523–532. [CrossRef]

54. Parks, S.K.; Cornerais, Y.; Durivault, J.; Pouysegu, J. Genetic disruption of the pH-regulating proteins Na+/H+ exchanger 1 (SLC9A1) and carbonic anhydrase 9 severely reduces growth of colon cancer cells. *Oncotarget* 2017, 8, 10225–10237. [CrossRef] [PubMed]

55. Huang, B.-R.; Liu, Y.-S.; Lai, S.-W.; Lin, H.-J.; Shen, C.-K.; Yang, L.-Y.; Lu, D.-Y. CAIX Regulates GBM Motility and TAM Adhesion through the EGFR/PI3K/AKT axis. *J. Cancer.* 2021, 11, 697227. [CrossRef]

56. Liu, Y.; Long, X.; Han, M.; Huang, M.-Q.; Lu, J.-F.; Sun, X.-D.; Han, W. Clinical benefit of COX-2 inhibitors in the adjuvant chemotherapy of advanced non-small cell lung cancer: A systematic review and meta-analysis. *World J. Clin. Cases* 2021, 9, 581–601. [CrossRef]

57. Kim, J.; Koh, M.H.; Hur, D.Y.; Kim, B.; Kim, Y.S.; Lee, H.-K. Celecoxib upregulates ULBP-1 expression in lung cancer cells via the JNK/PI3K signaling pathway and increases susceptibility to natural killer cell cytotoxicity. *Oncol. Lett.* 2020, 20, 279. [CrossRef]

58. Bu, D.; Yin, L.; Huang, L.; Qin, C.; Zhou, Y.; Wu, Q.; Li, Y.; Zhou, Q.; Li, L. Cyclooxygenase-2 Inhibitor: A Potential Combination Strategy With Immunotherapy in Cancer. *Front. Oncol.* 2021, 11, 637504. [CrossRef]

59. Zhang, M.; Hong, J.A.; Kunst, T.F.; Bond, C.D.; Kenney, C.M.; Warga, C.L.; Yeray, J.; Lee, M.-J.; Yun, A.; Lee, S.; et al. Randomized phase II trial of a first-in-human cancer cell lysate vaccine in patients with thoracic malignancies. *Clin. Cancer Res.* 2021, 10, 3079–3092. [CrossRef]

60. Pan, C.; Zhang, Y.; Meng, Q.; Dai, G.; Jiang, Z.; Bao, H. Down Regulation of the Expression of ELMO3 by COX2 Inhibitor Suppresses Tumor Growth and Metastasis in Non-Small-Cell Lung Cancer. *Front. Oncol.* 2019, 9, 363. [CrossRef] [PubMed]

61. Kim, B.; Kim, J.; Kim, Y.S. Celecoxib induces cell death on non-small cell lung cancer cells through endoplasmic reticulum stress. *Anat. Cell Biol.* 2017, 50, 293–300. [CrossRef]

62. Deng, Q.-F.; Fang, Q.-Y.; Ji, X.-X.; Zhou, S.-W. Cyclooxygenase-2 mediates gefitinib resistance in non-small cell lung cancer through the EGFR/PI3K/AKT axis. *J. Cancer.* 2020, 11, 3667–3674. [CrossRef] [PubMed]

63. Jiang, G.-B.; Fang, H.-Y.; Tao, D.-Y.; Chen, X.-P.; Cao, F.-L. COX-2 potentiates cisplatin resistance of non-small cell lung cancer cells by promoting EMT in an AKT signaling pathway-dependent manner. *Eur. Rev. Med. Pharmacol. Sci.* 2019, 23, 3838–3846. [CrossRef] [PubMed]
66. Zhang, P.; He, D.; Song, E.; Jiang, M.; Song, Y. Celecoxib enhances the sensitivity of non-small-cell lung cancer cells to radiation-induced apoptosis through downregulation of the Akt/mTOR signaling pathway and COX-2 expression. *PloS ONE* 2019, 14, e0223760. [PubMed]
67. Chandra, R.; Karalis, J.D.; Liu, C.; Murimwa, G.Z.; Park, J.V.; Heid, C.A.; Reznik, S.I.; Huang, E.; Minna, J.D.; Brekken, R.A. The Colorectal Cancer Tumor Microenvironment and Its Impact on Liver and Lung Metastasis. *Cancers* 2021, 13, 6206. [CrossRef]
68. Zhou, Y.; Tao, W.; Shen, F.; Du, W.; Xu, Z.; Liu, Z. The Emerging Role of Neutrophil Extracellular Traps in Arterial, Venous and Cancer Associated Thrombosis. *Front. Cardiovasc. Med.* 2021, 8, 786387. [CrossRef]
69. Valadez-Cosmes, P.; Raftopoulou, S.; Mihalic, Z.N.; Marsche, G.; Kargl, J. Myeloperoxidase: Growing importance in cancer pathogenesis and potential drug target. *Pharmacol. Ther.* 2021, 236, 108052. [CrossRef]
70. Duits, D.E.; de Visser, K.E. Impact of cancer cell-intrinsic features on neutrophil behavior. *Semin. Immunol.* 2021, 101546, in press. [CrossRef]
71. Kaltenmeier, C.; Simmons, R.L.; Tohme, S.; Yazdani, H.O. Neutrophil Extracellular Traps (NETs) in Cancer Metastasis. *Cancers* 2021, 13, 6131. [CrossRef]
72. Taucher, E.; Taucher, V.; Fink-Neuboeck, N.; Lindenmann, J.; Smolle-Juettner, F.-M. Role of Tumor-Associated Neutrophils in the Pathogenesis of Mucosal Inflammation. *Front. Immunol.* 2021, 12, 189. [Pubmed]
73. Mangrolia, U.; Osborne, J.W. Probiotics in Counteracting the Role of Neutrophils in Cancer Metastasis. *Int. J. Mol. Sci.* 2021, 22, 10952. [CrossRef] [PubMed]
74. Xiong, S.; Dong, L.; Cheng, L. Neutrophils in cancer carcinogenesis and metastasis. *J. Hematol. Oncol.* 2021, 14, 173. [CrossRef] [PubMed]
75. Kast, R.E. Research Supporting a Pilot Study of Metronomic Dapsone during Glioblastoma Chemoradiation. *Med. Sci.* 2021, 9, 12. [CrossRef]
76. Kast, R.E. Dapsone as treatment adjunct in ARDS. *Exp. Lung Res.* 2020, 46, 157–161. [CrossRef]
77. Kast, R.E.; Hill, Q.; Wion, D.; Mellstedt, H.; Focosi, D.; Karpel-Massler, G.; Heiland, T.; Halatsch, M.-E. Dapsone as Treatment Adjunct in ARDS. *Cancers* 2021, 13, 5972. [CrossRef] [PubMed]
78. Kast, R.E. Erlotinib augmentation with dapsone for rash mitigation and increased anti-cancer effectiveness. *Springerplus* 2015, 4, 638. [CrossRef] [PubMed]
79. Boccellino, M.; Quagliuolo, L.; Aliaia, C.; Grimaldi, A.; Addeo, R.; Nicoletti, G.F.; Kast, R.E.; Caraglia, M. The strange connection between epidermal growth factor receptor tyrosine kinase inhibitors and dapsone: From rash mitigation to the increase in anti-tumor activity. *Curr. Med. Res. Opin.* 2016, 32, 1839–1848. [CrossRef]
80. Asokan, S.; Bandapalli, O.R. CXCL8 Signaling in the Tumor Microenvironment. *Adv. Exp. Med. Biol.* 2021, 1302, 25–39. [CrossRef]
81. Chattopadhyay, I.; Ambati, R.; Gundamaraju, R. Exploring the Crosstalk between Inflammation and Epithelial-Mesenchymal Transition in Cancer. *Mediat. Inflamm.* 2021, 2021, 9918379. [CrossRef]
82. Korbecki, J.; Siimińska, D.; Gassowska-Dobrowolska, M.; Listos, J.; Gutowska, I.; Chlubek, D.; Baranowska-Bosiacka, I. Chronic and Cycling Hypoxia: Drivers of Cancer Chronic Inflammation through HIF-1 and NF-κB Activation: A Review of the Molecular Mechanisms. *Int. J. Mol. Sci.* 2021, 22, 10701. [CrossRef] [PubMed]
83. Wozel, G.; Blasum, C. Dapsone in dermatology and beyond. *Arch. Dermatol. Res.* 2014, 306, 103–124. [CrossRef] [PubMed]
84. Geyfman, M.; Debabov, D.; Poloso, N.; Alvandi, N. Mechanistic insight into the activity of a sulfone compound dapsone on Propionibacterium (Newly Reclassified as Cutibacterium) Acnes-mediated cytokine production. *Exp. Dermatol.* 2019, 28, 190–197. [CrossRef]
85. Lan, C.-C.E.; Wu, C.-S.; Huang, S.-M.; Wu, I.-H.; Chen, G.-S. High-glucose environment enhanced oxidative stress and increased interleukin-8 secretion from keratinocytes: New insights into impaired diabetic wound healing. *Diabetes* 2013, 62, 2530–2538. [CrossRef]
86. Ghaoui, N.; Hanna, E.; Abbass, O.; Kibbi, A.-G.; Kurban, M. Update on the use of dapsone in dermatology. *Int. J. Dermatol.* 2020, 59, 787–795. [CrossRef] [PubMed]
87. Karpel-Massler, G.; Kast, R.E.; Siegel, M.D.; Dwucut, A.; Schneider, E.; Westhoff, M.-A.; Wirtz, C.R.; Chen, X.Y.; Halatsch, M.-E.; Bolm, C. Anti-glioma Activity of Dapsone and Its Enhancement by Synthetic Chemical Modification. *Neurochem. Res.* 2017, 42, 3382–3389. [CrossRef]
88. Zhao, C.Y.; Liu, R.C.; Consuegra, G.; Hui, R.; Fernandez-Penas, P. Epidermal growth factor receptor inhibitor-induced papulopustular eruption successfully treated with low-dose oral dapsone. *Australas. J. Dermatol.* 2018, 59, e219–e220. [CrossRef]
89. Yan, P.; Zhu, H.; Yin, L.; Wang, L.; Xie, P.; Ye, J.; Jiang, X.; He, X. Integrin αvβ6 Promotes Lung Cancer Proliferation and Metastasis through Upregulation of IL-8-Mediated MAPK/ERK Signaling. *Transl. Oncol.* 2018, 11, 619–627. [CrossRef]
90. Kanwar, B.A.; Khattak, A.; Balementie, J.; Lee, J.H.; Kast, R.E. Benefits of Using Dapsone in Patients Hospitalized with COVID-19. *Vaccines* 2022, 10, 195. [CrossRef]
91. Kaltenmeier, C.T.; Yazdani, H.; van der Windt, D.; Molinari, M.; Geller, D.; Tsung, A.; Tohme, S. Neutrophil extracellular traps as a novel biomarker to predict recurrence-free and overall survival in patients with primary hepatic malignancies. *HPB* 2021, 23, 309–320. [CrossRef]
92. Huh, G.; Ryu, J.K.; Chun, J.W.; Kim, J.S.; Park, N.; Cho, I.R.; Paik, W.H.; Lee, S.H.; Kim, Y.-T. High platelet-to-lymphocyte ratio is associated with poor prognosis in patients with unresectable intrahepatic cholangiocarcinoma receiving gemcitabine plus cisplatin. *BMC Cancer* **2020**, *20*, 907. [CrossRef] [PubMed]

93. Lee, S.C.; Kim, S.J.; Yu, M.H.; Lee, K.J.; Cha, Y.S. Uses of Inflammatory Markers for Differentiation of Intrahepatic Mass-Forming Cholangiocarcinoma from Liver Abscess: Case-Control Study. *J. Clin. Med.* **2019**, *8*, 3194. [CrossRef] [PubMed]

94. Ji, F.; Kang, Q.; Wang, L.; Liu, L.; Ke, Y.; Zhu, Y.; Zhang, N.; Xiong, S.; Li, Y.; Zou, H. Prognostic significance of the neutrophil-to-lymphocyte ratio with distal cholangiocarcinoma patients. *Medicine* **2020**, *99*, e22827. [CrossRef] [PubMed]

95. Lemaire, C.C.; Portilho, A.L.C.; Pinheiro, L.V.; Vivas, R.A.; Britto, M.; Montenegro, M.; Rodrigues, L.F.D.F.; Arruda, S.; Lyra, A.C.; Cavalcante, L.N. Sweet syndrome as a paraneoplastic manifestation of cholangiocarcinoma: A case report. *World J. Clin. Cases* **2020**, *8*, 4122–4127. [CrossRef] [PubMed]

96. Zhang, Z.; Zhou, Y.; Hu, K.; Huang, Y. Investigating effects of preoperative inflammatory biomarkers on predicting survival outcomes of intrahepatic cholangiocarcinoma after curative resection. *World J. Surg. Oncol.* **2020**, *18*, 272. [CrossRef]

97. Chiu, T.-J.; Chen, Y.-J.; Kuo, F.-Y.; Chen, Y.-Y. Elevated neutrophil-to-lymphocyte ratio and predominance of intrahepatic cholangiocarcinoma prediction of poor hepatocyte outcomes in patients with combined hepatocellular-cholangiocarcinoma. *PLoS ONE* **2020**, *15*, e0240791. [CrossRef]

98. Ren, A.; Li, Z.; Cheng, P.; Zhang, X.; Deng, R.; Ma, Y. Systemic Immune Inflammation Index Is a Prognostic Predictor in Patients with Intrahepatic Cholangiocarcinoma Undergoing Liver Transplantation. *Mediat. Inflamm.* **2021**, *2021*, 6656996. [CrossRef] [PubMed]

99. Zhou, Z.; Wang, P.; Sun, R.; Li, J.; Hu, Z.; Xin, H.; Luo, C.; Zhou, J.; Fan, J.; Zhou, S. Tumor-associated neutrophils and macrophages interaction contributes to intrahepatic cholangiocarcinoma progression by activating STAT3. *J. Immunother. Cancer* **2021**, *9*, e001946. [CrossRef]

100. Branchi, V.; Jürgensen, B.; Esser, L.; Gonzalez-Carmona, M.; Weismüller, T.; Strassburg, C.; Henn, J.; Semaan, A.; Lingohr, P.; Manekeller, S.; et al. Tumor Infiltrating Neutrophils Are Frequently Found in Adenocarcinomas of the Biliary Tract and Their Precursor Lesions with Possible Impact on Prognosis. *J. Pers Med.* **2021**, *11*, 233. [CrossRef]

101. Ma, B.; Meng, H.; Shen, A.; Ma, Y.; Zhao, D.; Liu, G.; Zheng, S.; Tian, Y.; Zhang, W.; Li, Q.; et al. Prognostic Value of Inflammatory and Tumour Markers in Small-Duct Subtype Intrahepatic Cholangiocarcinoma after Curative-Intent Resection. *Gastroenterol. Res. Pract.* **2021**, *2021*, 6616062. [CrossRef] [PubMed]

102. Roy, S.; Kumaravel, S.; Banerjee, P.; White, T.K.; O’Brien, A.; Seelig, C.; Chauhan, R.; Ekser, B.; Bayless, K.J.; Alpini, G.; et al. Tumor Lymphatic Interactions Induce CXCR2-CXCL5 Axis and Alter Cellular Metabolism and Lymphangiogenic Pathways to Promote Cholangiocarcinoma. *Cells* **2021**, *10*, 3093. [CrossRef] [PubMed]

103. Sasaki, M.; Tsuneyama, K.; Ishikawa, A.; Nakanuma, Y. Intrahepatic cholangiocarcinoma in cirrhosis presents granulocyte and granulocyte-macrophage colony-stimulating factor. *Hum. Pathol.* **2003**, *34*, 1337–1344. [CrossRef] [PubMed]

104. Boonyanugomol, W.; Chomvarin, C.; Hahnvajanawong, C.; Sripa, B.; Kaparakis-Liaskos, M.; Ferrero, R.L. Helicobacter pylori cag pathogenicity island (cagPAI) involved in bacterial internalization and IL-8 induced responses via NOD1- and MyD88-dependent mechanisms in human biliary epithelial cells. *PLoS ONE* **2013**, *8*, e77358. [CrossRef] [PubMed]

105. Sueoka, H.; Hirano, T.; Uda, Y.; Imuro, Y.; Yamanaka, J.; Fujimoto, J. Blockage of CXCR2 suppresses tumor growth of intrahepatic cholangiocellular carcinoma. *Surgery* **2014**, *155*, 640–649. [CrossRef]

106. Sun, Q.; Li, F.; Sun, F.; Niu, J. Interleukin-8 is a prognostic indicator in human hilar cholangiocarcinoma. *Int. J. Exp. Pathol.* **2015**, *8*, 8376–8384. [CrossRef]

107. Thongchot, S.; Ferraresi, A.; Vidoni, C.; Loliome, W.; Yongyanit, P.; Namwat, N.; Isidoro, C. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. *Cancer Lett.* **2018**, *430*, 160–171. [CrossRef]

108. Yamanaka, T.; Harimoto, N.; Yokobori, T.; Muranushi, R.; Hoshino, K.; Hagiwara, K.; Gantumur, D.; Handa, T.; Ishii, N.; Tsukagoshi, M.; et al. Nintedanib inhibits intrahepatic cholangiocarcinoma aggressiveness via suppression of cytokines extracted from activated cancer associated fibroblasts. *Br. J. Cancer* **2020**, *122*, 986–994. [CrossRef]

109. Li, S.; Yang, H.; Li, K.; Fan, G.; Deng, L.; Xu, C. Thymidine phosphorylase promotes angiogenesis and tumour growth in intrahepatic cholangiocarcinoma. *Cell Biochem. Funct.* **2020**, *38*, 743–752. [CrossRef]

110. Dana, P.; Kariya, R.; Lert-Itthiporn, W.; Seubwai, W.; Saisomboon, S.; Wongkham, C.; Okada, S.; Wongkham, S.; Vaeetewoottacharn, K. Homophilic Interaction of CD147 Promotes IL-6-Mediated Cholangiocarcinoma Invasion via the NF-kB-Dependent Pathway. *Int. J. Mol. Sci.* **2021**, *22*, 13496. [CrossRef]

111. Filippi, R.; Montagnani, F.; Lombardi, P.; Fornaro, L.; Aprile, G.; Casadei-Gardini, A.; Faloppo, L.; Palloni, A.; Satolli, M.A.; Scartozzi, M.; et al. A prognostic model in patients with advanced biliary tract cancer receiving first-line chemotherapy. *Acta Oncol.* **2021**, *60*, 1317–1324. [CrossRef]

112. Biró, Á.; Kolozsi, P.; Nagy, A.; Varga, Z.; Káposztás, Z.; Tóth, D. Significance of preoperative blood tests in the prognosis of colorectal cancer: A prospective study from Hungary. *J. Clin. Lab. Anal.* **2022**, *36*, e24128. [CrossRef] [PubMed]

113. Turhan, V.B.; Ünsal, A.; Gök, H.F.; Öztürk, B.; Öztürk, D.; Simsek, G.G.; Buluş, H. Predictive Value of Preoperative Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratio in Determining the Stage of Colon Tumors. *Cureus* **2021**, *13*, e18381. [CrossRef] [PubMed]

114. Mazaki, J.; Katsumata, K.; Sujino, H.; Udo, R.; Tago, T.; Kasahara, K.; Kuwabara, H.; Enomoto, M.; Ishizaki, T.; Nagakawa, Y.; et al. Neutrophil-to-lymphocyte Ratio as a Prognostic Factor for Colon Cancer in Elderly Patients: A Propensity Score Analysis. *Anticancer Res.* **2021**, *41*, 4471–4478. [CrossRef] [PubMed]
115. Bertaut, A.; Truntzer, C.; Madkouri, R.; Kaderbhai, C.G.; Derangère, V.; Vincent, J.; Chauffert, B.; Aubriot-Lorton, M.H.; Farah, W.; Mourier, K.L.; et al. Blood baseline neutrophil count predicts bevacizumab efficacy in glioblastoma. *Oncotarget* **2016**, *7*, 70948–70958. [CrossRef]

116. Clarke, S.J.; Burge, M.; Feeney, K.; Gibbs, P.; Jones, K.; Marx, G.; Molloy, M.P.; Price, T.; Reece, W.H.H.; Segelov, E.; et al. The prognostic role of inflammatory markers in patients with metastatic colorectal cancer treated with bevacizumab: A translational study. *PLoS ONE* **2020**, *15*, e0229900. [CrossRef]

117. Schiffermann, L.M.; Fritsch, M.; Gebauer, F.; Günther, S.D.; Stair, N.R.; Seeger, J.M.; Thangarajah, F.; Diepinger, G.; Bludau, M.; Alakus, H.; et al. Tumour-infiltrating neutrophils counteract anti-VEGF therapy in metastatic colorectal cancer. *Br. J. Cancer* **2019**, *120*, 69–78. [CrossRef]

118. Yu, J.; Cheng, T.; Liu, L.; Heng, J.; Liu, X.; Sun, Z.; Wang, W.; Li, K.; Yang, N. Mast cells induce epithelial-to-mesenchymal transition and migration in non-small cell lung cancer through IL-8/Wnt/β-catenin pathway. *J. Cancer* **2019**, *10*, 5567. [CrossRef] [PubMed]

119. Tan, K.W.; Chong, S.Z.; Wong, F.H.S.; Evrard, M.; Tan, S.M.-L.; Keeble, J.; Kemeny, D.M.; Ng, L.G.; Abastado, J.-P.; Angeli, V. Neutrophils contribute to inflammatory lymphangiogenesis by increasing VEGF-A bioavailability and secreting VEGF-D. *Blood* **2013**, *122*, 3666–3677. [CrossRef]

120. Mizuno, R.; Kawada, K.; Itatani, Y.; Ogawa, R.; Kiyasu, Y.; Sakai, Y. The Role of Tumor-Associated Neutrophils in Colorectal Cancer. *Int. J. Mol. Sci.* **2019**, *20*, 529. [CrossRef]

121. Itatani, Y.; Yamamoto, T.; Zhong, C.; Molinolo, A.A.; Ruppel, J.; Hegde, P.; Taketo, M.M.; Ferrara, N. Suppressing neutrophil-dependent angiogenesis abrogates resistance to anti-VEGF antibody in a genetic model of colorectal cancer. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 21598–21608. [CrossRef]

122. Fisher, R.C.; Bellamkonda, K.; Molina, L.A.; Price, T.; Reece, W.H.H.; Petrides, L.; Sultan, M.; Mason, W.; et al. Plasmatic MMP9 released from tumour-infiltrating neutrophils is predictive for bevacizumab efficacy in glioblastoma patients: An AVAglio ancillary study. *Acta Neuropathol. Commun.* **2022**, *1*, 1–14. [CrossRef]

123. Yang, F.; Zhang, S.; Meng, Q.; Zhou, F.; Pan, B.; Liu, F.; Yu, Y. CXCR1 correlates to poor outcomes of EGFR-TKI against advanced non-small cell lung cancer patients. *Thorac. Cancer* **2021**, *12*, 219–227. [CrossRef] [PubMed]

124. Ying, L.; Lenz, H.-J. Targeting IL-8 in colorectal cancer. *Expert Opin. Ther. Targets.* **2012**, *16*, 491–497. [CrossRef]

125. Urbantat, R.; Vajkoczy, P.; Brandenburg, S. Advances in Chemokine Signaling Pathways as Therapeutic Targets in Glioblastoma. *Expert Opin. Ther. Targets.* **2012**, *16*, 236, 3114–3128. [CrossRef] [PubMed]

126. Watanabe, K.; Shiga, K.; Maeda, A.; Harata, S.; Yanagita, T.; Suzuki, T.; Ushigome, H.; Maeda, Y.; Hirokawa, T.; Ogawa, R.; et al. Chitinase 3-like 1 secreted from cancer-associated fibroblasts promotes tumor angiogenesis via interleukin-8 secretion in colorectal cancer. *Int. J. Oncol.* **2022**, *60*, 3. [CrossRef]

127. Ning, Y.; Lenz, H.-J. Targeting IL-8 in colorectal cancer. *Expert Opin. Ther. Targets.* **2012**, *16*, 491–497. [CrossRef]

128. Urbantat, R.; Vajkoczy, P.; Brandenburg, S. Advances in Chemokine Signaling Pathways as Therapeutic Targets in Glioblastoma. *Cancers* **2021**, *13*, 2983. [CrossRef]

129. Basheer, A.S.; Abas, F.; Othman, I.; Naidu, R. Role of Inflammatory Mediators, Macrophages, and Neutrophils in Glioma *Oncotarget* **2016**, *7*, 70948–70958. [CrossRef]

130. Shi, Y.; Liu, X.; Du, J.; Zhang, D.; Liu, J.; Chen, M.; Zhao, J.; Zhong, W.; Xu, Y.; Wang, M. Circulating cytokines associated with clinical outcomes in advanced non-small cell lung cancer patients who received chemoimmunotherapy. *Thorac. Cancer* **2022**, *13*, 219–227. [CrossRef]

131. Zadian, S.S.; Adcock, I.M.; Salimi, B.; Mortaz, E. Circulating Levels of Monocytic Myeloid-Derived Suppressor Cells (M-MDSC) and CXCL8 in Non-Small Cell Lung Cancer (NSCLC). *Tannafos* **2021**, *20*, 15–21.

132. Yang, F.; Zhang, S.; Meng, Q.; Zhou, F.; Pan, B.; Liu, F.; Yu, Y. CXCR1 correlates to poor outcomes of EGFR-TKI against advanced non-small cell lung cancer by activating chemokine and JAK/STAT pathway. *Pulm. Pharmacol. Ther.* **2021**, *67*, 102001. [CrossRef] [PubMed]

133. Hayama, N.; Hattori, S.; Takahashi, G.; Takahashi, F.; Takeuchi, T.; Tanaka, J.; Horio, Y.; Takiguchi, H.; Tomomatsu, K.; Kitahara, A.; et al. Cytokine/Chemokine/Growth Factor Levels in Malignant Pleural Effusion of Non-Small Cell Lung Cancer. *Tokai J. Exp. Clin. Med.* **2020**, *45*, 224–229. [PubMed]

134. Qu, J.; Cheng, T.; Liu, L.; Heng, J.; Liu, X.; Sun, Z.; Wang, W.; Li, K.; Yang, N. Mast cells induce epithelial-to-mesenchymal transition and migration in non-small cell lung cancer through IL-8/Wnt/β-catenin pathway. *J. Cancer* **2019**, *10*, 5567. [CrossRef] [PubMed]

135. Cai, D.; Xu, Y.; Ding, R.; Qu, K.; Zhang, R.; Wang, H.; Huang, L.; Xie, X.; Yan, H.; Deng, Y.; et al. Extensive serum biomarker analysis in patients with non-small-cell lung carcinoma. *Cytokine* **2020**, *126*, 154868. [CrossRef] [PubMed]
161. Shuang, Z.-Y.; Wu, W.-C.; Xu, J.; Lin, G.; Liu, Y.-C.; Lao, X.-M.; Zheng, L.; Li, S. Transforming growth factor-β1-induced epithelial-mesenchymal transition generates ALDH-positive cells with stem cell properties in cholangiocarcinoma. Cancer Lett. 2014, 354, 320–328. [CrossRef]

162. Wang, M.; Xiao, J.; Jiang, J.; Qin, R. CD133 and ALDH may be the molecular markers of cholangiocarcinoma stem cells. Int. J. Cancer 2011, 128, 1996–1997. [CrossRef] [PubMed]

163. Modarai, S.R.; Gupta, A.; Opdenaker, L.M.; Kowash, R.; Masters, G.; Viswanathan, V.; Zhang, T.; Fields, J.Z.; Boman, B.M. The anti-cancer effect of retinoic acid signaling in CRC occurs via decreased growth of ALDH+ colon cancer stem cells and increased differentiation of stem cells. Oncotarget 2018, 9, 34658–34669. [CrossRef]

164. McGrath, N.; Fu, J.; Gu, S.Z.; Xie, C. Targeting cancer stem cells in cholangiocarcinoma. Int. J. Oncol. 2020, 57, 397–408. [CrossRef] [PubMed]

165. Holah, N.S.; Aida, H.A.; Asaad, N.Y.; Elkhouly, E.A.; Lasheen, A.G. Evaluation of the Role of ALDH1 as Cancer Stem Cell Marker in Colorectal Carcinoma: An Immunohistochemical Study. J. Clin. Diagn Res. 2017, 11, EC17–EC23. [CrossRef]

166. Shenoy, A.; Butterworth, E.; Huang, E.H. ALDH as a marker for enriching tumorigenic human colonic stem cells. Methods Mol. Biol. 2012, 916, 373–385. [CrossRef]

167. Wang, Y.; Li, K.; Zhao, W.; Liu, Z.; Liu, J.; Shi, A.; Chen, T.; Mu, W.; Xu, Y.; Pan, C.; et al. Aldehyde dehydrogenase 3B2 promotes the proliferation and invasion of cholangiocarcinoma by increasing Integrin Beta 1 expression. Cell Death Dis. 2021, 12, 1158. [CrossRef] [PubMed]

168. Liu, C.-C.; Wu, C.-L.; Lin, M.-X.; Sze, C.-I.; Gean, P.-W. Disulfiram Sensitizes a Therapeutic-Resistant Glioblastoma to the TGF-β/Smad3 Pathway and Enhances Its Response to Necroptosis Induction by Necrostatin-1. Front. Immunol. 2022, 13, 756606. [CrossRef] [PubMed]

169. Liu, C.-C.; Wu, C.-L.; Lin, M.-X.; Sze, C.-I.; Gean, P.-W. Disulfiram Sensitizes a Therapeutic-Resistant Glioblastoma to the TGF-β Receptor Inhibitor. Int. J. Mol. Sci. 2020, 21, 10496. [CrossRef] [PubMed]

170. Wang, Z.; Mo, Y.; Tan, Y.; Wen, Z.; Dai, Z.; Zhang, H.; Zhang, X.; Feng, S.; Liang, X.; Song, T.; et al. The ALDH Family Contributes to Immune Infiltration, Proliferation and Epithelial Mesenchymal Transformation in Glioma. Front. Immunol. 2022, 12, 756606. [CrossRef] [PubMed]

171. Sauna, Z.E.; Peng, X.-H.; Nandigama, K.; Tekle, S.; Ambudkar, S.V. The molecular basis of the action of disulfiram as a modulator of the multidrug resistance-linked ATP binding cassette transporters MDR1 (ABCB1) and MRP1 (ABCC1). Mol. Pharmacol. 2004, 65, 675–684. [CrossRef] [PubMed]

172. Holah, N.S.; Aida, H.A.; Asaad, N.Y.; Elkhouly, E.A.; Lasheen, A.G. Evaluation of the Role of ALDH1 as Cancer Stem Cell Marker in Colorectal Carcinoma: An Immunohistochemical Study. J. Clin. Diagn Res. 2017, 11, EC17–EC23. [CrossRef]

173. Loo, T.W.; Bartlett, M.C.; Clarke, D.M. Disulfiram metabolites permanently inactivate the human multidrug resistance P-glycoprotein. Mol. Pharm. 2004, 1, 426–433. [CrossRef] [PubMed]

174. Loo, T.W.; Clarke, D.M. Disulfiram metabolites permanently inactivate the human multidrug resistance P-glycoprotein. Mol. Pharm. 2004, 1, 426–433. [CrossRef] [PubMed]

175. Wang, Z.; Mo, Y.; Tan, Y.; Wen, Z.; Dai, Z.; Zhang, H.; Zhang, X.; Feng, S.; Liang, X.; Song, T.; et al. The ALDH Family Contributes to Immune Infiltration, Proliferation and Epithelial Mesenchymal Transformation in Glioma. Front. Immunol. 2022, 12, 756606. [CrossRef] [PubMed]

176. Liu, C.-C.; Wu, C.-L.; Lin, M.-X.; Sze, C.-I.; Gean, P.-W. Disulfiram Sensitizes a Therapeutic-Resistant Glioblastoma to the TGF-β Receptor Inhibitor. Int. J. Mol. Sci. 2020, 21, 10496. [CrossRef] [PubMed]

177. Gelardi, E.; Colombo, G.; Picarazzi, F.; Ferraris, D.; Mangione, A.; Petrarolo, G.; Aronica, E.; Rizzi, M.; La Motta, C.; et al. The ALDH Family Contributes to Immune Infiltration, Proliferation and Epithelial Mesenchymal Transformation in Glioma. Front. Immunol. 2022, 12, 756606. [CrossRef] [PubMed]

178. Sullivan, J.P.; Spinoila, M.; Dodge, M.; Raso, M.G.; Behrens, C.; Gao, B.; Schuster, K.; Shao, C.; Larsen, J.; Sullivan, L.A.; et al. Aldehyde dehydrogenase activity selects for lung adenocarcinoma stem cells dependent on notch signaling. Cancer Res. 2010, 70, 104–113. [CrossRef] [PubMed]

179. Sauna, Z.E.; Peng, X.-H.; Nandigama, K.; Tekle, S.; Ambudkar, S.V. The molecular basis of the action of disulfiram as a modulator of the multidrug resistance-linked ATP binding cassette transporters MDR1 (ABCB1) and MRP1 (ABCC1). Mol. Pharmacol. 2004, 65, 675–684. [CrossRef] [PubMed]

180. Modarai, S.R.; Gupta, A.; Opdenaker, L.M.; Kowash, R.; Masters, G.; Viswanathan, V.; Zhang, T.; Fields, J.Z.; Boman, B.M. The anti-cancer effect of retinoic acid signaling in CRC occurs via decreased growth of ALDH+ colon cancer stem cells and increased differentiation of stem cells. Oncotarget 2018, 9, 34658–34669. [CrossRef] [PubMed]

181. Holah, N.S.; Aida, H.A.; Asaad, N.Y.; Elkhouly, E.A.; Lasheen, A.G. Evaluation of the Role of ALDH1 as Cancer Stem Cell Marker in Colorectal Carcinoma: An Immunohistochemical Study. J. Clin. Diagn Res. 2017, 11, EC17–EC23. [CrossRef]

182. Shao, C.; Sullivan, J.P.; Girard, L.; Augustyn, A.; Yenerall, P.; Rodriguez-Canales, J.; Liu, H.; Behrens, C.; Shay, J.W.; Wistuba, I.I.; et al. Essential role of aldehyde dehydrogenase 1A3 for the maintenance of non-small cell lung cancer stem cells is associated with the STAT3 pathway. Clin. Cancer Res. 2014, 20, 4154–4166. [CrossRef] [PubMed]

183. Terzuoli, E.; Bellan, C.; Aversa, S.; Ciccone, V.; Morbidelli, L.; Giachetti, A.; Donnini, S.; Ziche, M. ALDH3A1 Overexpression in Melanoma and Lung Tumors Drives Cancer Stem Cell Expansion, Impairing Immune Surveillance through Enhanced PD-L1 Output. Cancers 2019, 11, 163. [CrossRef] [PubMed]

184. Masciale, V.; Grisendi, G.; Banchelli, F.; D’Amico, R.; Maiorana, A.; Sighinolfi, P.; Stefani, A.; Morandi, U.; Dominici, M.; Aramini, B. CD44+/EPCAM+ cells detect a subpopulation of ALDHhigh cells in human non-small cell lung cancer: A chance for targeting cancer stem cells? Oncotarget 2020, 11, 1545–1555. [CrossRef] [PubMed]
183. Liu, X.; Wang, L.; Cui, W.; Yuan, X.; Lin, L.; Cao, Q.; Wang, N.; Li, Y.; Guo, W.; Zhang, X.; et al. Targeting ALDH1A1 by disulfiram/copper complex inhibits non-small cell lung cancer recurrence driven by ALDH-positive cancer stem cells. Oncotarget 2016, 7, 58516–58530. [CrossRef] [PubMed]

184. Wu, X.; Xue, X.; Wang, L.; Wang, W.; Han, J.; Sun, X.; Zhang, H.; Liu, Y.; Che, X.; Yang, J.; et al. Suppressing autophagy enhances disulfiram/copper-induced apoptosis in non-small cell lung cancer. Eur. J. Pharmacol. 2018, 827, 1–12. [CrossRef] [PubMed]

185. Lee, S.-H.; Jeon, Y.; Kang, J.H.; Jang, H.; Lee, H.; Kim, S.-Y. The Combination of Loss of ALDH1L1 Function and Phenformin Treatment Decreases Tumor Growth in KRAS-Driven Lung Cancer. Cancers 2020, 12, 1382. [CrossRef] [PubMed]

186. Mohamed, A.W.; Elbassiouny, M.; Elkhodary, D.A.; Shawki, M.A.; Saad, A.S. The effect of itraconazole on the clinical outcomes of patients with advanced non-small cell lung cancer receiving platinum based chemotherapy: A randomized controlled study. Med. Oncol. 2021, 38, 23. [CrossRef]

187. Shen, P.-W.; Chou, Y.-M.; Li, C.-L.; Liao, E.-C.; Huang, H.-S.; Yin, C.-H.; Chen, C.-L.; Yu, S.-J. Itraconazole improves survival outcomes in patients with colon cancer by inducing autophagic cell death and inhibiting transketolase expression. Oncol. Lett. 2021, 22, 768. [CrossRef]

188. Zhang, W.; Bhagwath, A.S.; Ramzan, Z.; Williams, T.A.; Subramaniyan, I.; Edpuganti, V.; Kallem, R.R.; Dunbar, K.B.; Ding, P.; Gong, K.; et al. Itraconazole Exerts Its Antitumor Effect in Esophageal Cancer By Suppressing the HER2/AKT Signaling Pathway. Mol. Cancer Ther. 2021, 20, 1904–1915. [CrossRef]

189. El-Sheridy, N.A.; El-Moslemany, R.M.; Ramadan, A.A.; Helmy, M.W.; El-Khordagui, L.K. Enhancing the in vitro and in vivo activity of itraconazole against breast cancer using miltefosine modified lipid nanocapsules. Drug Deliv. 2021, 28, 906–919. [CrossRef]

190. Ghadi, M.; Hosseinimehr, S.J.; Amirii, F.T.; Mardanshahi, A.; Noaparast, Z. Data on the in vitro and in vivo anti-tumor effects of itraconazole, paclitaxel, and the two in combination in HT-29 and YM-1 cancer cell line and HT-29 colon cancer xenograft models. Data Brief. 2021, 35, 108662. [CrossRef]

191. Li, K.; Fang, D.; Xiong, Z.; Luo, R. Inhibition of the hedgehog pathway for the treatment of cancer using Itraconazole. Oncol Targets Ther. 2019, 12, 6875–6886. [CrossRef]

192. Ban, L.; Mei, T.; Su, Q.; Li, W.; Huang, Z.; Liu, L.; Wu, Y.; Lv, S.; Wang, A.; Li, S. Anti-fungal drug itraconazole exerts anti-cancer effects in oral squamous cell carcinoma via suppressing Hedgehog pathway. Life Sci. 2020, 254, 117695. [CrossRef] [PubMed]

193. Wei, X.; Liu, W.; Wang, J.Q.; Tang, Z. “Hedgehog pathway”: A potential target of itraconazole in the treatment of cancer. J. Cancer Res. Clin. Oncol. 2020, 146, 297–304. [CrossRef] [PubMed]

194. Chen, C.; Zhang, W. Itraconazole Alters the Stem Cell Characteristics of A549 and NCI-H460 Human Lung Cancer Cells by Suppressing Wnt Signaling. Med. Sci. Monit. 2019, 25, 9509–9516. [CrossRef] [PubMed]

195. Freitas, R.D.; Dias, R.B.; Valverde, L.D.F.; Costa, R.G.A.; Damasceno, A.K.A.; Sales, C.B.S.; Rocha, L.D.O.S.D.; dos Reis, M.G.; Soares, M.B.P.; et al. Inhibition of CAL27 Oral Squamous Carcinoma Cell by Targeting Hedgehog Pathway With Vismodegib or Itraconazole. Front. Oncol. 2020, 10, 563838. [CrossRef]

196. Lin, Y.; Cai, Q.; Chen, Y.; Shi, T.; Liu, W.; Mao, L.; Deng, B.; Ying, Z.; Gao, Y.; Luo, H.; et al. CAFs shape myeloid-derived suppressor cells to promote stemness of intrahepatic cholangiocarcinoma through 5-lipoxygenase. Hepatology 2022, 75, 28–42. [CrossRef]

197. Jaschonek, K.; Steinbilsber, D.; Einsele, H.; Ehningger, G.; Roth, H.J. 5-Lipoxygenase inhibition by antifungal azole derivatives: New tools for immunosuppression? Eicosanoids 1989, 2, 189–190.

198. Steel, H.C.; Tintinger, G.R.; Theron, A.J.; Anderson, R. Itraconazole mediated inhibition of calcium entry into platelet-activating factor-stimulated human neutrophils is due to interference with production of leukotriene B4. Clin. Exp. Immunol. 2007, 150, 144–150. [CrossRef]

199. Steinbilsber, D.; Jaschonek, K.; Knospe, J.; Morof, O.; Roth, H.J. Effects of novel antifungal azole derivatives on the 5-lipoxygenase and cyclooxygenase pathway. Arzneimittelforschung 1990, 40, 1260–1263.

200. Lempers, V.J.C.; Heuvel, J.J.M.W.V.D.; Russel, F.G.M.; Aarnoutse, R.E.; Burger, D.M.; Brüggemann, R.J.; Koenderink, J.B. Inhibitory Potential of Antifungal Drugs on ATP-Binding Cassette Transporters P-Glycoprotein, MRPI and MRPs, and BSEP. Antimicrob. Agents Chemother. 2006, 50, 3357–3359. [CrossRef]

201. Kobayashi, K.; Abe, Y.; Kawai, A.; Furihata, T.; Endo, T.; Takeda, H. Pharmacokinetic Drug Interactions of an Orally Available Disulfiram/Copper Complex Inhibiting Non-Small Cell Lung Cancer. Curr. Top. Med. Chem. 2010, 10, 1381–1393. [PubMed]

202. Ghadi, M.; Hosseinimehr, S.J.; Amiri, F.T.; Mardanshahi, A.; Noaparast, Z. Itraconazole synergistically increases therapeutic effect of paclitaxel and 99mTc-MIBI accumulation, as a probe of P-gp activity, in HT-29 tumor-bearing nude mice. Eur. J. Pharmacol. 2021, 895, 2563. [CrossRef]

203. Quatannens, D.; Verhoeven, Y.; Van Dam, P.; Lardon, F.; Prenen, H.; Roeyen, G.; Peeters, M.; Smits, E.L.J.; Van Audenaerde, J. Targeting hedgehog signaling in pancreatic ductal adenocarcinoma. Pharmacol. Ther. 2007, 117, 108107. [CrossRef]

204. Jain, R.; Dubey, S.K.; Singhvi, G. The Hedgehog pathway and its inhibitors: Emerging therapeutic approaches for basal cell carcinoma. Drug Discov. Today 2021, 27, 1176–1183. [CrossRef] [PubMed]

205. Gampala, S.; Yang, J.-Y. Hedgehog Pathway Inhibitors against Tumor Microenvironment. Cells 2021, 10, 3135. [CrossRef]

206. Jeng, K.-S.; Chang, C.-F.; Lin, S.-S. Sonic Hedgehog Signaling in Organogenesis, Tumors, and Tumor Microenvironments. Int. J. Mol. Sci. 2020, 21, 758. [CrossRef] [PubMed]
207. Skoda, A.M.; Simovic, D.; Karin, V.; Cardum, V.; Vranic, S.; Serman, L. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. *Bosn. J. Basic Med. Sci.* 2018, 18, 8–20. [CrossRef] [PubMed]

208. Jia, Y.; Wang, Y.; Xie, J. The Hedgehog pathway: Role in cell differentiation, polarity and proliferation. *Arch. Toxicol.* 2015, 89, 179–191. [CrossRef]

209. Feng, H.-C.; Lin, J.-Y.; Hsu, S.-H.; Lan, W.-Y.; Kuo, C.-S.; Tian, Y.-F.; Sun, D.-P.; Huang, R.-S. Low folate metabolic stress reprograms DNA methylation-activated sonic hedgehog signaling to mediate cancer stem cell-like signatures and invasive tumour stage-specific malignancy of human colorectal cancers. *Int. J. Cancer.* 2017, 141, 2537–2550. [CrossRef]

210. Cho, K.; Moon, H.; Seo, S.H.; Ro, S.W.; Kim, B.K. Pharmacological Inhibition of Sonic Hedgehog Signaling Suppresses Tumor Development in a Murine Model of Intrahepatic Cholangiocarcinoma. *Int. J. Mol. Sci.* 2021, 22, 13214. [CrossRef]

211. Möbius, C.; Aust, G.; Wiedmann, M.; Wittekind, C.; Mössner, J.; Hauss, J.; Witzigmann, H. Prognostic value of eicosanoid signaling in cholangiocarcinoma. *Anticancer Res.* 2008, 28, 873–878.

212. Khophai, S.; Thanee, M.; Techasen, A.; Namwat, N.; Klanrit, P.; Titapun, A.; Jarearnrat, A.; Sa-Ngiamwibool, P.; Loilome, W. Zileuton suppresses cholangiocarcinoma cell proliferation and migration through inhibition of the Akt signaling pathway. *Onco Targets Ther.* 2018, 11, 7019–7029. [CrossRef] [PubMed]

213. Anichini, G.; Carrassa, L.; Stecca, B.; Marra, F.; Raggi, C. The Role of the Hedgehog Pathway in Cholangiocarcinoma. *Cancers* 2021, 13, 4774. [CrossRef] [PubMed]

214. Ding, J.; Li, H.-Y.; Zhang, L.; Zhou, Y.; Wu, J. Hedgehog Signaling, a Critical Pathway Governing the Development and Progression of Hepatocellular Carcinoma. *Cells* 2021, 10, 123. [CrossRef] [PubMed]

215. Sirica, A.E. The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 2011, 9, 44–54. [CrossRef]

216. Omenetti, A.; Diehl, A.M. Hedgehog signaling in cholangiocytes. *Curr. Opin. Gastroenterol.* 2011, 27, 268–275. [CrossRef]

217. Khamko, R.; Daduang, J.; Settasatian, C.; Limpaiboon, T. OPCML Exerts Antitumor Effects in Cholangiocarcinoma via AXL/STAT3 Inactivation and Rho GTPase Down-regulation. *Cancer Genom. Proteomics* 2021, 18, 771–780. [CrossRef]

218. Wasielewicz, M.P.; Kołodziej, B.; Bojułko, T.; Kaczmarczyk, M.; Sulzyc-Bielicka, V.; Bielicki, D.; Ciepiela, K. Overexpression of 5-lipoxygenase in sporadic colonic adenomas and a possible new aspect of colon carcinogenesis. *Int. J. Colorectal Dis.* 2010, 25, 1079–1085. [CrossRef]

219. Che, X.H.; Chen, C.L.; Ye, X.L.; Weng, G.B.; Guo, X.Z.; Yu, W.Y.; Tao, J.; Chen, Y.C.; Chen, X. Dual inhibition of COX-2/5-LOX blocks colon cancer proliferation, migration and invasion in vitro. *Oncol. Rep.* 2016, 35, 1680–1688. [CrossRef]

220. Barresi, V.; Grosso, M.; Vitarelli, E.; Tuccari, G.; Barresi, G. 5-Lipoxygenase is coexpressed with Cox-2 in sporadic colorectal cancer: A correlation with advanced stage. *Dis. Colon Rectum* 2007, 50, 1576–1584. [CrossRef]

221. Shen, J.; Li, W.; Xiao, Z.; Zhang, L.; Li, M.; Li, L.; Hu, W.; Lu, L.; Boudreau, F.; Cho, C. The Co-regulatory Role of 5-Lipoxygenase and Cyclooxygenase-2 in the Carcinogenesis and their Promotion by Cigarette Smoking in Colon. *Curr. Med. Chem.* 2016, 23, 1131–1138. [CrossRef]

222. Rao, C.V.; Janakiram, N.B.; Mohammed, A. Lipoxygenase and Cyclooxygenase Pathways and Colorectal Cancer Prevention. *Curr. Colorectal Cancer Rep.* 2012, 8, 316–324. [CrossRef] [PubMed]

223. Orlando, U.D.; Garona, J.; Ripoll, G.V.; Maloberti, P.M.; Solano, A.R.; Avagnina, A.; Gomez, D.E.; Alonso, D.F.; Podesta, E.J. The Role of the Hedgehog Pathway in Cholangiocarcinoma. *Am. J. Transl Res.* 2018, 10, 7019–7029. [CrossRef] [PubMed]

224. Cummings, M.; Massey, K.A.; Mappa, G.; Wilkinson, N.; Hutson, R.; Munot, S.; Saidi, S.; Nugent, D.; Broadhead, T.; Wright, A.I.; et al. Integrated eicosanoid lipidomics and gene expression reveal decreased prostaglandin catabolism and increased 5-lipoxygenase expression in aggressive subtypes of endometrial cancer. *J. Pathol.* 2019, 245, 2083–2095. [CrossRef]

225. Cianchi, F.; Cortesini, C.; Magnelli, L.; Fanti, E.; Papucci, L.; Schiavone, N.; Messerini, L.; Vannacci, A.; Capaccioli, S.; Perna, F.; et al. Inhibition of 5-lipoxygenase by MK886 augments the antitumor activity of celecoxib in human colon cancer cells. *Biochem. Biophys. Res. Commun.* 2010, 393, 253–258. [CrossRef] [PubMed]

226. Ghatak, S.; Vyas, A.; Misra, S.; O’Brien, P.; Zambre, A.; Fresco, V.M.; Markwald, R.R.; Swamy, K.V.; Afrasiabi, Z.; Choudhury, A.; et al. Novel di-tertiary-butyl phenylhydrazones as dual cyclooxygenase-2/5-lipoxygenase inhibitors: Synthesis, COX/LOX inhibition, molecular modeling, and insights into their cytotoxicities. *Bioorg. Med. Chem. Lett.* 2014, 24, 316–324. [CrossRef] [PubMed]

227. Knab, L.M.; Grippo, P.J.; Bentrem, D.J. Involvement of eicosanoids in the pathogenesis of pancreatic cancer: The roles of cyclooxygenase-2 and 5-lipoxygenase. *World J. Gastroenterol.* 2014, 20, 10729–10739. [CrossRef]

228. Costa, H.; Touma, J.; Davoudi, B.; Benard, M.; Sauer, T.; Geisler, J.; Vetvik, K.; Rahbar, A.; Süderberg-Naucle, C. Human cytomegalovirus infection is correlated with enhanced cyclooxygenase-2 and 5-lipoxygenase protein expression in breast cancer. *J. Cancer Res. Clin. Oncol.* 2019, 145, 2083–2095. [CrossRef]

229. Lu, X.; Huang, L.; Zhang, W.; Ning, X. Tepoxalin a dual 5-LOX-COX inhibitor and erlotinib an EGFR inhibitor halts progression of gastric cancer in tumor xenograft mice. *Am. J. Transl Res.* 2018, 10, 3847–3856.

230. Cummings, M.; Massey, K.A.; Mappa, G.; Wilkinson, N.; Hutson, R.; Munot, S.; Saidi, S.; Nugent, D.; Broadhead, T.; Wright, A.I.; et al. Integrated eicosanoid lipidomics and gene expression reveal decreased prostaglandin carcinogenesis and increased 5-lipoxygenase expression in aggressive subtypes of endometrial cancer. *J. Pathol.* 2019, 247, 21–34. [CrossRef]

231. Douard, R.; Moutereau, S.; Pernet, P.; Chimingqi, M.; Allory, Y.; Manivet, P.; Conti, M.; Vaubourdolle, M.; Cugnenc, P.-H.; Loric, S. Sonic Hedgehog-dependent proliferation in a series of patients with colorectal cancer. *Surgery* 2006, 139, 665–670. [CrossRef]
Cancers 2022, 14, 2563

232. Deng, H.; Huang, L.; Liao, Z.; Liu, M.; Li, Q.; Xu, R. Itraconazole inhibits the Hedgehog signaling pathway thereby inducing autophagy-mediated apoptosis of colon cancer cells. *Cell Death Dis.* 2020, 11, 539. [CrossRef] [PubMed]

233. Popova, S.A.; Buczacki, S.J.A. Itraconazole perturbs colorectal cancer dormancy through SUFU-mediated WNT inhibition. *Mol. Cell. Oncol.* 2018, 5, e1494950. [CrossRef] [PubMed]

234. Buczacki, S.J.A.; Popova, S.; Biggs, E.; Koukorava, C.; Buzzelli, J.; Vermeulen, L.; Hazelwood, L.; Francies, H.; Garnett, M.J.; Winton, D.J. Itraconazole targets cell cycle heterogeneity in colorectal cancer. *J. Exp. Med.* 2018, 215, 1891–1912. [CrossRef] [PubMed]

235. Geyer, N.; Gerling, M. Hedgehog Signaling in Colorectal Cancer: All in the Stroma? *Int. J. Mol. Sci.* 2013, 14, 619–623. [CrossRef]

236. Rudin, C.M.; Brahmer, J.R.; Juergens, R.A.; Hann, C.L.; Ettinger, D.S.; Sebree, R.; Smith, R.; Aftab, B.T.; Huang, P.; Liu, J.O. 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. [CrossRef]

237. Liu, M.; Liang, G.; Liu, M.; Wang, Q.; Shen, Y.; Mei, H.; Li, D.; Liu, W. Itraconazole exerts its anti-melanoma effect by suppressing Tsubamoto, H.; Ueda, T.; Inoue, K.; Sakata, K.; Shibahara, H.; Sonoda, T. Repurposing itraconazole as an anticancer agent. *Lancet Neurol.* 2006, 5, 949–960. [CrossRef]

238. Luik, A.; Wahlund, C.J.; Gómez, C.; Brodin, D.; Samuelsson, B.; Wheelock, C.E.; Gabrielson, S.; Rådmark, O. Exosomes and cells from lung cancer pleural exudates transform LTC4 to LTD4, promoting cell migration and survival via CysLT1. *Cancer Lett.* 2019, 444, 1–8. [CrossRef]

239. Zhang, L.; Liu, Z.; Yang, K.; Kong, C.; Liu, C.; Chen, H.; Huang, J.; Qian, F. Tumor Progression of Non-Small Cell Lung Cancer Controlled by Albumin and Micellar Nanoparticles of Itraconazole, a Multitarget Angiogenesis Inhibitor. *Mol. Pharm.* 2017, 14, 4705–4713. [CrossRef]

240. Li, W.-H.; Loo, J.C.Y.; Ghadiri, M.; Leong, C.-R.; Young, P.; Traini, D. The potential to treat lung cancer via inhalation of repurposed drugs. *Adv. Drug Deliv. Rev.* 2018, 133, 107–130. [CrossRef]

241. Alhakamy, N.A.; Md, S. Repurposing Itraconazole Loaded PLGA Nanoparticles for Improved Antitumor Efficacy in Non-Small Cell Lung Cancers. *Pharmaceutics* 2019, 11, 685. [CrossRef] [PubMed]

242. Gerber, D.E.; Putnam, W.C.; Fahat, F.J.; Kernstine, K.H.; Brekken, R.A.; Pedrosa, I.; Skelton, R.; Saltarsi, J.M.; Lenkinski, R.E.; Leff, R.D.; et al. Concentration-dependent Early Antivascular and Antitumor Effects of Itraconazole in Non-Small Cell Lung Cancer. *Clin. Cancer Res.* 2020, 26, 6017–6027. [CrossRef] [PubMed]

243. Ramchandani, S.; Mohan, C.D.; Mistry, J.R.; Su, Q.; Naz, I.; Rangappa, K.S.; Ahn, K.S. The multifaceted antineoplastic role of pyrimethamine against different human malignancies. *IUBMB Life* 2021, 73, 198–212. [CrossRef]

244. Lee, W.-H.; Loo, J.C.Y.; Ghadiri, M.; Leong, C.-R.; Young, P.; Traini, D. The potential to treat lung cancer via inhalation of repurposed drugs. *Adv. Drug Deliv. Rev.* 2018, 133, 107–130. [CrossRef]

245. Hage, A.; Schoemaker, H.E.; Wever, R.; Zennaro, E.; Heipieper, H.J. Pyrimethamine in prevention of relapses of meningeval leukemia: Report of two cases. *Cancer* 1978, 42, 1216–1218. [CrossRef]

246. Brown, J.R.; Walker, S.R.; Heppler, L.N.; Tyekucheva, S.; Nelson, E.A.; Klitgaard, J.; Nicolais, M.; Kroll, Y.; Xiang, M.; Yeh, J.E.; et al. Targeting constitutively active STAT3 in chronic lymphocytic leukemia: A clinical trial of the STAT3 inhibitor pyrimethamine. *Pharmacol. Ther.* 2021, 208, 107587. [CrossRef] [PubMed]

247. Kozi´ nski, P.; Halik, P.K.; Chesori, R.; Gniazdowska, E. Overview of Dual-Acting Drug Methotrexate in Different Neurological Screening. *Curr. Cancer Drug Targets* 2016, 16, 818–828. [CrossRef] [PubMed]

248. Reynolds, E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol.* 2006, 5, 949–960. [CrossRef]

249. Newman, A.C.; Maddocks, O.D.K. One-carbon metabolism in cancer. *Clin. Pharmacol. Ther.* 2017, 116, 1499–1504. [CrossRef]

250. Seitz, M. Molecular and cellular effects of methotrexate. *Curr. Opin. Rheumatol.* 1999, 11, 226–232. [CrossRef] [PubMed]

251. Bedoui, Y.; Guillot, X.; Sé lambarom, J.; Guiraud, P.; Giry, C.; Jaffar-Bandjee, M.C.; Ralandison, S.; Gasque, P. Methotrexate as an Old Drug with New Tricks. *Int. J. Mol. Sci.* 2019, 20, 5023. [CrossRef] [PubMed]

252. Bowcock, S.; Linch, D.; Machin, S.; Stewart, J. Pyrimethamine in the myeloproliferative disorders: A forgotten treatment? *Clin. Lab. Haematol.* 1987, 9, 129–136. [CrossRef]

253. Smyth, A.C.; Wiernik, P.H. Combination chemotherapy of acute lymphocytic leukemia. *Clin. Pharmacol. Ther.* 1976, 19, 240–245. [CrossRef]
Cancers 2022, 14, 2563

259. Liu, H.; Qin, Y.; Zhai, D.; Zhang, Q.; Gu, J.; Tang, Y.; Yang, J.; Li, K.; Yang, L.; Chen, S.; et al. Antimalarial Drug Pyrimethamine Plays a Dual Role in Antitumor Proliferation and Metastasis through Targeting DHFR and TP. Mol. Cancer Ther. 2019, 18, 541–555. [CrossRef]

260. Tertil, M.; Skrzypek, K.; Florczyk, U.; Węglarczyk, K.; Was, H.; Collet, G.; Guichard, A.; Gil, T.; Kuzdzal, J.; Jozkowicz, A.; et al. Regulation and novel action of thymidine phosphorylase in non-small cell lung cancer: Crossstalk with Nrf2 and HO-1. PLoS ONE 2014, 9, e97070. [CrossRef]

261. Furukawa, T.; Tabata, S.; Yamamoto, M.; Kawahara, K.; Shinsato, Y.; Minami, K.; Shimokawa, M.; Akiyama, S.-I. Thymidine phosphorylase in cancer aggressiveness and chemoresistance. Pharmacol. Res. 2018, 132, 15–20. [CrossRef]

262. Tabata, S.; Yamamoto, M.; Goto, H.; Hirayama, A.; Ohishi, M.; Kuramoto, T.; Mitsuhashi, A.; Ikeda, R.; Haraguchi, M.; Kawahara, K.; et al. Thymidine Catabolism as a Metabolic Strategy for Cancer Survival. Cell Rep. 2017, 19, 1313–1321. [CrossRef]

263. Tabata, S.; Ikeda, R.; Yamamoto, M.; Shimaoka, S.; Mukaida, N.; Takeda, Y.; Yamada, K.; Soga, T.; Furukawa, T.; Akiyama, S.-I. Thymidine phosphorylase activates NFκB and stimulates the expression of angiogenic and metastatic factors in human cancer cells. Oncotarget 2014, 5, 10473–10485. [CrossRef]

264. Akiyama, S.-I.; Tabata, S.; Ikeda, R.; Yamamoto, M.; Furukawa, T.; Kuramoto, T.; Takeda, Y.; Yamada, K.; Haraguchi, M.; Nishioka, Y.; et al. Thymidine phosphorylase enhances reactive oxygen species generation and interleukin-8 expression in human cancer cells. Oncol. Rep. 2012, 28, 895–902. [CrossRef] [PubMed]

265. Khan, M.W.; Saadalla, A.; Ewida, A.H.; Al-Katranji, K.; Al-Saoudi, G.; Giaccone, Z.T.; Gounari, F.; Zhang, M.; Frank, D.A.; Khazaie, K. The STAT3 inhibitor pyrimethamine displays anti-cancer and immune stimulatory effects in murine models of breast cancer. Cancer Immunol. Immunother. 2018, 67, 13–23. [CrossRef]

266. Wu, B.; Fathi, S.; Mortley, S.; Mohiuddin, M.; Jang, Y.C.; Oyelere, A.K. Pyrimethamine conjugated histone deacetylase inhibitors: Design, synthesis and evidence for triple negative breast cancer selective cytotoxicity. Biorg. Med. Chem. 2020, 28, 115345. [CrossRef] [PubMed]

267. Egusquiguirre, S.P.; Yeh, J.E.; Walker, S.R.; Liu, S.; Frank, D.A. The STAT3 Target Gene TNFRSF1A Modulates the NF-κB Pathway in Breast Cancer Cells. Neoplasia 2018, 20, 489–498. [CrossRef] [PubMed]

268. Lapidot, M.; Case, A.E.; Larios, D.; Gandler, H.I.; Meng, C.; Tošić, I.; Weisberg, E.L.; Poitras, M.J.; Gokhale, P.C.; Paweletz, C.P.; et al. Inhibitors of the Transcription Factor STAT3 Decrease Growth and Induce Immune Response Genes in Models of Malignant Pleural Mesothelioma (MPM). Cancers 2020, 13, 7. [CrossRef]

269. Peppler, L.N.; Attarha, S.; Persaud, R.; Brown, J.; Wang, P.; Petrova, B.; Tošić, I.; Burton, F.B.; Flammard, Y.; Walker, S.R.; et al. The antimicrobial drug pyrimethamine inhibits STAT3 transcriptional activity by targeting the enzyme dihydrofolate reductase. J. Biol. Chem. 2022, 298, 101531. [CrossRef] [PubMed]

270. Wu, B.; Payero, B.; Taylor, S.; Oyelere, A.K. Discovery of novel STAT3 DNA binding domain inhibitors. Future Med. Chem. 2021, 13, 1253–1269. [CrossRef]

271. Li, Y.; Chen, Z.; Han, J.; Ma, X.; Zheng, X.; Chen, J. Functional and Therapeutic Significance of Tumor-Associated Macrophages in Colorectal Cancer. Front. Oncol. 2020, 11, 281. [CrossRef]

272. El-Tanani, M.; Al Khatib, A.O.; Aladwan, S.M.; Abuelhana, A.; McCarron, P.A.; Tambuwala, M.M. Importance of STAT3 signalling in cancer, metastasis and therapeutic interventions. Cell Signal. 2022, 92, 110275. [CrossRef] [PubMed]

273. Ayele, T.M.; Muche, Z.T.; Teklemariam, A.B.; Bogale, A.; Abebe, E.C. Role of JAK2/STAT3 Signaling Pathway in the Tumorigenesis, Metastasis and Therapeutic Interventions in Breast Cancer. J. Inflamm. Res. 2022, 15, 1349–1364. [CrossRef] [PubMed]

274. Gu, Y.; Mohammad, I.S.; Liu, Z. Overview of the STAT-3 signaling pathway in cancer and the development of specific inhibitors. Oncol. Lett. 2020, 19, 2585–2594. [CrossRef] [PubMed]

275. Allam, A.; Yakou, M.; Pang, L.; Ernst, M.; Huynh, J. Exploiting the STAT3 Nexus in Cancer-Associated Fibroblasts to Improve Cancer Therapy. Front. Immunol. 2021, 12, 767939. [CrossRef]

276. Parakh, S.; Ernst, M.; Poh, A.R. Multicellular Effects of STAT3 in Non-small Cell Lung Cancer: Mechanistic Insights and Therapeutic Opportunities. Cancers 2021, 13, 6228. [CrossRef]

277. Tošić, I.; Frank, D.A. STAT3 as a mediator of oncogenic cellular metabolism: Pathogenic and therapeutic implications. Neoplasia 2021, 23, 1167–1178. [CrossRef]

278. Su, Y.-L.; Banerjee, S.; White, S.V.; Kortylewski, M. STAT3 in Tumor-Associated Myeloid Cells: Multitasking to Disrupt Immunity. Int. J. Mol. Sci. 2018, 19, 1803. [CrossRef]

279. Hildebrand, D.; Uhle, F.; Sahin, D.; Krauser, U.; Weigand, M.A.; Heeg, K.; Hildebrand, D.; Uhle, F.; Sahin, D.; Krauser, U.; et al. The Interplay of Notch Signaling and STAT3 in TLR-Activated Human Primary Monocytes. Front. Cell. Infect. Microbiol. 2018, 8, 241. [CrossRef]

280. Kang, M.H.; Lee, W.S.; Go, S.-I.; Kim, M.J.; Lee, U.S.; Choi, H.J.; Kim, D.C.; Lee, J.-H.; Kim, H.-G.; Bae, K.S.; et al. Can thymidine phosphorylase be a predictive marker for gemcitabine and oxifluoridine combination chemotherapy in cholangiocarcinoma?: Case series. Medicine 2014, 93, e305. [CrossRef]

281. Ge, X.; Wang, Y.; Li, Q.; Yu, H.; Ji, G.; Miao, L. NK4 regulates 5-fluorouracil sensitivity in cholangiocarcinoma cells by modulating the intrinsic apoptosis pathway. Oncol. Rep. 2013, 30, 448–454. [CrossRef]
282. Thanasaie, J.; Limpaiboon, T.; Jearanaikoon, P.; Sripa, B.; Pairojkul, C.; Tantimavanich, S.; Miwa, M. Effects of thymidine phosphorylase on tumor aggressiveness and 5-fluourouracil sensitivity in cholangiocarcinoma. *World J. Gastroenterol.* 2010, 16, 1631–1638. [CrossRef] [PubMed]

283. Yang, J.; Farren, M.; Ahn, D.; Bekaii-Saab, T.; Lesinski, G.B. Signaling pathways as therapeutic targets in biliary tract cancer. *Expert Opin. Ther. Targets* 2017, 21, 485–498. [CrossRef] [PubMed]

284. Isomoto, H. Epigenetic alterations in cholangiocarcinoma sustained IL-6/STAT3 signaling in cholangio-carcinoma due to SOCS3 epigenetic silencing. *Digestion* 2009, 79 (Suppl. 1), 2–8. [CrossRef] [PubMed]

285. Sia, D.; Tovar, V.; Moeini, A.; Llovet, J.M. Intrahepatic cholangiocarcinoma: Pathogenesis and rationale for molecular therapies. *Oncogene.* 2013, 32, 4861–4870. [CrossRef] [PubMed]

286. Mohassab, A.M.; Hassan, H.A.; Abdelhamid, D.; Abdel-Aziz, M. STAT3 transcription factor as target for anti-cancer therapy. *Oncogene.* 2015, 34, 3493–3503. [CrossRef]

287. Heichler, C.; Scheibe, K.; Schmied, A.; Geppert, C.I.; Schmid, B.; Wirtz, S.; Thoma, O.-M.; Kramer, V.; Waldner, M.J.; Büttner, C.; et al. STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis. *Gut* 2020, 69, 1269–1282. [CrossRef]

288. Shi, X.; Kaller, M.; Rokavec, M.; Kirchner, T.; Horst, D.; Heremeking, H. Characterization of a p53/miR-34a/CSF1R/STAT3 Feedback Loop in Colorectal Cancer. *Cell Mol. Gastroenterol. Hepatol.* 2020, 10, 391–418. [CrossRef]

289. Wei, N.; Li, J.; Fang, C.; Chang, J.; Xirou, V.; Syrigos, N.; Marks, B.J.; Chu, E.; Schmitz, J.C. Targeting colon cancer with the novel STAT3 inhibitor bruceantinol. *Oncogene* 2013, 38, 1676–1687. [CrossRef]

290. De Simone, V.; Franzè, E.; Ronchetti, G.; Colantoni, A.; Fantini, M.C.; Di Fusco, D.; Sica, G.S.; Sileri, P.; Macdonald, T.T.; Pallone, F.; et al. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. *Oncogene* 2015, 34, 3493–3503. [CrossRef]

291. Lin, L.; Liu, A.; Peng, Z.; Lin, H.-J.; Li, P.-K.; Li, C.; Lin, J. STAT3 is necessary for proliferation and survival in colon cancer-initiating cells. *Cancer Res.* 2011, 71, 7226–7237. [CrossRef]

292. Mi, C.; Cao, X.; Ma, K.; Wei, M.; Xu, W.; Lin, Y.; Zhang, J.; Wang, T.-Y. Digitoxin promotes apoptosis and inhibits proliferation and migration by reducing HIF-1α and STAT3 in KRAS mutant human colon cancer cells. *Chem. Biol. Interact.* 2022, 351, 107929. [CrossRef] [PubMed]

293. Su, C.; Liu, S.; Ma, X.; Liu, J.; Liu, J.; Lei, M.; Cao, Y. The effect and mechanism of erianin on the reversal of oxaliplatin resistance in colon cancer cells. *Cell Biol. Int.* 2021, 45, 2420–2428. [CrossRef] [PubMed]

294. Mi, C.; Cao, X.; Ma, K.; Wei, M.; Xu, W.; Lin, Y.; Zhang, J.; Wang, T.-Y. Digitoxin promotes apoptosis and inhibits proliferation and migration by reducing HIF-1α and STAT3 in KRAS mutant human colon cancer cells. *Chem. Biol. Interact.* 2022, 351, 107929. [CrossRef] [PubMed]

295. Xiong, Y.-J.; Liu, D.-Y.; Shen, R.-R.; Xiong, Y. A short deletion in the DNA-binding domain of STAT3 suppresses growth and progression of colon cancer cells. *Aging* 2021, 13, 5185–5196. [CrossRef]

296. Leport, C.; Meulemans, A.; Robine, D.; Dameron, G.; Vallé, J.L. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS* 1992, 6, 1040–1041. [CrossRef]

297. Schoondermark-van, d.V.; Galama, J.; Vree, T.; Camps, W.; Baars, I.; Eskes, T.; Miwa, M. Effects of thymidine infection in rhesus monkeys with pyrimethamine and sulfadiazine. *Antimicrob. Agents Chemother.* 1995, 39, 137–144. [CrossRef]

298. Chen, M.; Osman, I.; Orlow, S.J. Antifolate activity of pyrimethamine enhances temozolomide induced cytotoxicity in melanoma cells. *Mol. Cancer Res.* 2009, 7, 703–712. [CrossRef]

299. Dai, C.; Zhang, B.; Liu, X.; Guo, K.; Ma, S.; Cai, F.; Yang, Y.; Yao, Y.; Feng, M.; Bao, X.; et al. Pyrimethamine sensitizes pituitary adenomas to temozolomide through cathepsin B-dependent and caspase-dependent apoptotic pathways. *Int. J. Cancer* 2013, 133, 1982–1993. [CrossRef]

300. Warfield, B.M.; Matheson, C.J.; McArthur, D.G.; Backos, D.S.; Reigan, P. Evaluation of Thymidine Phosphorylase Inhibitors in Glialblastaoma and Their Capacity for Temozolomide Potentiation. *ACS Chem. Neurosci.* 2021, 12, 3477–3486. [CrossRef]

301. Servat, C.C.; Codony-Servat, J.; Karachaliou, N.; Molina, M.A.; Chaib, I.; Ramirez, J.L.; Gil, M.D.L.L.; Solca, F.; Bivona, T.G.; Rosell, R. Activation of signal transducer and activator of transcription 3 (STAT3) signaling in EGFR mutant non-small-cell lung cancer (NSCLC). *Oncotarget* 2017, 8, 47305–47316. [CrossRef]

302. Lin, M.-X.; Lin, S.-H.; Lin, C.-C.; Yang, C.-C.; Yuan, S.-Y. In Vitro and In Vivo Antitumor Effects of Pyrimethamine on Non-small Cell Lung Cancers. *Anticancer Res.* 2013, 33, 3435–3442. [CrossRef] [PubMed]

303. Menamin, M.C.; Murray, L.J.; Cantwell, M.M.; Hughes, C.M. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: A systematic review. *Cancer Causes Control.* 2012, 23, 221–230. [CrossRef] [PubMed]

304. Meiners, J.; Jansen, K.; Gorbokon, N.; Büscheck, F.; Luebke, A.M.; Kluth, M.; Höflmayer, D.; Weidemann, S.; Fraune, C.; et al. Angiotensin Converting Enzyme 2 Protein Is Overexpressed in a Wide Range of Human Tumour Types: A Systematic Tissue Microarray Study on >15,000 Tumours. *Histol. Histopathol.* 2009, 24, 109729. [CrossRef]

305. Kilmister, E.J.; Tan, S.T. The Role of the Renin-Angiotensin System in the Cancer Stem Cell Niche. *Int. J. Histol. Histopathol.* 2021, 69, 835–847. [CrossRef]

306. Bernardino, A.; Malaria, M.; Bertucucci, L.; De Nuccio, C.; Visentin, S.; Minghetti, L. The Antihypertensive Drug Telmisartan Protects Oligodendrocytes from Cholesterol Accumulation and Promotes Differentiation by a PPAR-γ-Mediated Mechanism. *Int. J. Mol. Sci.* 2021, 22, 9434. [CrossRef] [PubMed]
Abdelhamid, A.M.; Elsheakh, A.R.; Suddde, G.M.; Abdelaziz, R.R. Telmisartan alleviates alcohol induced liver injury by activation of PPAR-γ/ Nrf-2 crosstalk in mice. *Int. Immunopharmacol.* 2021, 99, 107963. [CrossRef] [PubMed]

Devan, A.R.; Nair, B.; Kumar, A.R.; Nath, L.R. An insight into the role of telmisartan as PPAR-γ/a dual activator in the management of nonalcoholic fatty liver disease. *Biotechnol. Appl. Biochem.* 2021, 69, 461–468. [CrossRef] [PubMed]

Kubik, M.; Chudek, J.; Adamczak, M.; Wieczek, A. Telmisartan improves cardiometabolic profile in obese patients with arterial hypertension. *Kidney Blood Press. Res.* 2012, 35, 281–289. [CrossRef]

Samukawa, E.; Fujihara, S.; Oura, K.; Iwama, H.; Yamana, Y.; Tadokoro, T.; Chiyo, T.; Kobayashi, K.; Morishita, A.; Nakahara, M.; et al. Angiotensin receptor blocker telmisartan inhibits cell proliferation and tumor growth of cholangiocarcinoma through cell cycle arrest. *Int. J. Oncol.* 2017, 51, 1674–1684. [CrossRef]

Tsujita, Y.; Yamamori, M.; Hasegawa, A.; Yamamoto, Y.; Yashiro, M.; Okamura, N. Telmisartan Exerts Cytotoxicity in Scirrhous Gastric Cancer Cells by Inducing GI/G1 Cell Cycle Arrest. *Anticancer Res.* 2021, 41, 5461–5468. [CrossRef]

Fujita, N.; Fujita, K.; Iwama, H.; Kobara, H.; Fujihara, S.; Chiyo, T.; Namima, D.; Yamana, H.; Kono, T.; Takuma, K.; et al. Antihypertensive drug telmisartan suppresses the proliferation of gastric cancer cells in vitro and in vivo. * Oncol. Rep.* 2020, 44, 339–348. [CrossRef] [PubMed]

Kobara, H.; Fujihara, S.; Iwama, H.; Matsui, T.; Fujimori, A.; Chiyo, T.; Tingting, S.; Kobayashi, N.; Nishiyama, Y.; Yachida, T.; et al. Antihypertensive drug telmisartan inhibits cell proliferation of gastrointestinal stromal tumor cells in vitro. *Mol. Med. Rep.* 2020, 22, 1063–1071. [CrossRef] [PubMed]

Saber, S.; Khodir, A.E.; Soliman, W.E.; Salama, M.M.; Abdo, W.S.; Elsaeed, B.; Nader, K.; Abdelnasser, A.; Megahed, N.; Basuony, M.; et al. Telmisartan attenuates N-nitrosodiethylyamine induced hepatocellular carcinoma in mice by modulating the NF-κB-TAK1-ERK1/2 axis in the context of PPARγ agonistic activity. *Naunyn-Schmiedeberg’s Arch. Pharmacol.* 2019, 392, 1591–1604. [CrossRef] [PubMed]

Fujita, T.; Chiyo, T.; Kobara, H.; Fujihara, S.; Fujita, K.; Namima, D.; Nakahara, M.; Kobayashi, N.; Nishiyama, Y.; Yachida, T.; et al. Telmisartan Inhibits Cell Proliferation and Tumor Growth of Esophageal Squamous Cell Carcinoma by Inducing S-Phase Arrest In Vitro and In Vivo. *Int. J. Mol. Sci.* 2019, 20, 3197. [CrossRef]

Oura, K.; Tadokoro, T.; Fujihara, S.; Morishita, A.; Chiyo, T.; Samukawa, E.; Yamana, Y.; Fujita, K.; Sakamoto, T.; Nomura, M.; et al. Telmisartan inhibits hepatocellular carcinoma cell proliferation in vitro by inducing cell cycle arrest. * Oncol. Rep.* 2017, 38, 2825–2835. [CrossRef]

Fujihara, S.; Morishita, A.; Ogawa, K.; Tadokoro, T.; Chiyo, T.; Kato, K.; Kobara, H.; Mori, H.; Iwama, H.; Masaki, T. The angiotensin II type 1 receptor antagonist telmisartan inhibits cell proliferation and tumor growth of esophageal adenocarcinoma via the AMPKα/mTOR pathway in vitro and in vivo. *Oncotarget* 2017, 8, 8536–8549. [CrossRef]

De Araújo, R.F., Jr.; Oliveira, A.L.C.L.; Silveira, R.F.D.M.; Rocha, H.A.D.O.; Cavalcanti, P.D.F.; Araújo, A. Telmisartan induces apoptosis and regulates Bcl-2 in human renal cancer cells. *Exp. Biol. Med.* 2015, 240, 34–44. [CrossRef]

Koyama, N.; Nishida, Y.; Ishii, T.; Yoshihida, T.; Furutaka, Y.; Narahara, H. Telmisartan induces growth inhibition, DNA double-strand breaks and apoptosis in human endometrial cancer cells. *PLoS ONE* 2014, 9, e93050. [CrossRef]

Nenciu, A.; Korbel, C.; Gu, Y.; Menger, M.D.; Laschke, M.W. Combined blockade of angiotensin II type 1 receptor and activation of peroxisome proliferator-activated receptor-γ by telmisartan effectively inhibits vascularization and growth of murine endometriosis-like lesions. *Hum. Reprod.* 2014, 29, 1011–1024. [CrossRef]

Yoshimura, R.; Funao, K.; Matsuyama, M.; Kawahito, Y.; Sano, H.; Chargui, J.; Touraine, J.-L.; Nakatani, T. Telmisartan is a potent target for prevention and treatment in human prostate cancer. *Oncol. Rep.* 2008, 20, 295–300. [CrossRef]

Okamoto, K.; Tajima, H.; Ohta, T.; Nakamura, S.; Hayashi, H.; Nakagawa, H.; Onishi, I.; Takamura, H.; Ninomiya, I.; Kitagawa, H.; et al. Angiotensin II induces tumor progression and fibrosis in intrahepatic cholangiocarcinoma through an interaction with hepatic stellate cells. *Int. J. Oncol.* 2010, 37, 1251–1259. [CrossRef] [PubMed]

Beyazit, Y.; Purnak, T.; Suvak, B.; Kurt, M.; Sayilir, A.; Turhan, T.; Tas, A.; Torun, S.; Celik, T.; Ibis, M.; et al. Increased ACE in extrahepatic cholangiocarcinoma as a clue for activated RAS in biliary neoplasms. *Clin. Res. Hepatol. Gastroenterol.* 2011, 35, 644–649. [CrossRef] [PubMed]

Saikawa, S.; Kaji, K.; Nishimura, N.; Seki, K.; Sato, S.; Nakashima, K.; Kitagawa, K.; Kawaratan, H.; Kitade, M.; Moriya, K.; et al. Angiotensin receptor blocker attenuates cholangiocarcinoma cell growth by inhibiting the oncogenic activity of Yes-associated protein. *Cancer Lett.* 2018, 434, 120–129. [CrossRef] [PubMed]

Lee, L.D.; Mafura, B.; Lauscher, J.C.; Seeliger, H.; Kreis, M.E.; Gröne, J. Antiproliferative and apoptotic effects of telmisartan in human colon cancer cells. *Oncol. Lett.* 2014, 8, 2681–2686. [CrossRef] [PubMed]

Hachiya, K.; Masuya, M.; Kuroda, N.; Yoneda, M.; Tsuboi, J.; Nagaharu, K.; Nishimura, K.; Shiotani, T.; Ohishi, K.; Tawara, I.; et al. Irbesartan, an angiotensin II type 1 receptor blocker, inhibits colitis-associated tumourigenesis by blocking the MCP-1/CCR2 pathway. *Sci. Rep.* 2021, 11, 9943. [CrossRef]

Tabatabai, E.; Khazaei, M.; Asgharzadeh, F.; Nazari, S.E.; Shakour, N.; Fiui, H.; Ziaeemehr, A.; Mostafapour, A.; Parizadeh, M.R.; Nouri, M.; et al. Inhibition of angiotensin II type 1 receptor by candesartan reduces tumor growth and ameliorates fibrosis in colorectal cancer. *EXCLI J.* 2021, 20, 863–878. [CrossRef]

Ozeki, K.; Tanida, S.; Morimoto, C.; Inoue, Y.; Mizohsita, T.; Tsukamoto, H.; Shimura, T.; Kataoka, H.; Kamiya, T.; Nishiwaki, E.; et al. Telmisartan inhibits cell proliferation by blocking nuclear translocation of ProHB-EGF C-terminal fragment in colon cancer cells. *PLoS ONE* 2013, 8, e56770. [CrossRef]
329. Nakamura, K.; Yaguchi, T.; Ohmura, G.; Kobayashi, A.; Kawamura, N.; Iwata, T.; Kiniwa, Y.; Okuyama, R.; Kawakami, Y. Involvement of local renin-angiotensin system in immunosuppression of tumor microenvironment. *Cancer Sci.* 2018, 109, 54–64. [CrossRef]

330. Wang, Y.; Zhang, T.; Li, C.; Guo, J.; Xu, B.; Xue, L. Telmisartan attenuates human glioblastoma cells proliferation and oncogenicity by inducing the lipid oxidation. *Asia-Pac. J. Clin. Oncol.* 2021, *ahead of print*. [CrossRef]

331. Kast, R.E. Paths for Improving Bevacizumab Available in 2018: The ADZT Regimen for Better Glioblastoma Treatment. *Med. Sci.* 2018, 6, 84. [CrossRef]

332. Hua, T.N.M.; Oh, J.; Kim, S.; Antonio, J.M.; Vo, V.T.A.; Om, J.; Choi, J.-W.; Kim, J.-Y.; Jung, C.-W.; Park, M.-J.; et al. Peroxisome proliferator-activated receptor gamma as a theragnostic target for mesenchymal type glioblastoma patients. *Exp. Mol. Med.* 2020, 52, 629–642. [CrossRef] [PubMed]

333. Wilop, S.; Von Hobe, S.; Crysandt, M.; Esser, A.; Osieka, R.; Jost, E. Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. *J. Cancer Res. Clin. Oncol.* 2009, 135, 1429–1435. [CrossRef] [PubMed]

334. Arthur, P.; Patel, N.; Surapaneni, S.K.; Mondal, A.; Gebeeyehu, A.; Bagde, A.; Kutlehria, S.; Nottingham, E.; Singh, M. Targeting lung cancer stem cells using combination of Tel and Docetaxel liposomes in 3D cultures and tumor xenografts. *Toxicol. Appl. Pharmacol.* 2020, 401, 115112. [CrossRef] [PubMed]

335. Aydiner, A.; Ciftci, R.; Sen, F. Renin-Angiotensin system blockers may prolong survival of metastatic non-small cell lung cancer patients receiving erlotinib. *Medicine* 2015, 94, e887. [CrossRef] [PubMed]

336. Menter, A.R.; Carroll, N.M.; Sakoda, L.C.; Delate, T.; Hornbrook, M.C.; Jain, R.K.; Kushi, L.H.; Quinn, V.P.; Ritzwoller, D.P. Effect of Angiotensin System Inhibitors on Survival in Patients Receiving Chemotherapy for Advanced Non-Small-Cell Lung Cancer. *Clin. Lung Cancer* 2017, 18, 189–197.e3. [CrossRef] [PubMed]

337. Miao, L.; Chen, W.; Zhou, L.; Wan, H.; Gao, B.; Feng, Y. Impact of Angiotensin I-converting Enzyme Inhibitors and Angiotensin II Type-1 Receptor Blockers on Survival of Patients with NSCLC. *Sci Rep.* 2016, 6, 21359. [CrossRef] [PubMed]

338. Zhang, S.; Wang, Y. Telmisartan inhibits NSCLC A549 cell proliferation and migration by regulating the PI3K/AKT signaling pathway. *Oncol. Lett.* 2018, 15, 5859–5864. [CrossRef]

339. Surapaneni, S.K.; Nottingham, E.; Mondal, A.; Patel, N.; Arthur, P.; Gebeeyehu, A.; Kalvala, A.K.; Rishi, A.K.; Singh, M. Telmisartan Facilitates the Anticancer Effects of CARP-1 Functional Mimetic and Sorafenib in Rociletinib Resistant Non-small Cell Lung Cancer. *Anticancer Res.* 2021, 41, 4215–4228. [CrossRef]

340. Halatsch, M.-E.; Kast, R.; Karpel-Massler, G.; Mayer, B.; Zolk, O.; Schmitz, B.; Scheuerle, A.; Maier, L.; Bullinger, L.; Mayer-Steinacker, R.; et al. CTNI-04. RECURRENT GLIOBLASTOMA LONG-TERM SURVIVORS TREATED WITH CUSP9v3. *Neuro-Oncology* 2021, 23 (Suppl. 6), vi59. [CrossRef]