Antigenic Targets for the Immunotherapy of Acute Myeloid Leukaemia

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Abstract: One of the most promising approaches to preventing relapse is the stimulation of the body’s own immune system to kill residual cancer cells after conventional therapy has destroyed the bulk of the tumour. In acute myeloid leukaemia (AML), the high frequency with which patients achieve first remission, and the diffuse nature of the disease throughout the periphery, makes immunotherapy particularly appealing following induction and consolidation therapy, using chemotherapy, and where possible stem cell transplantation. Immunotherapy could be used to remove residual disease, including leukaemic stem cells from the farthest recesses of the body, reducing, if not eliminating, the prospect of relapse. The identification of novel antigens that exist at disease presentation and can act as targets for immunotherapy have also proved useful in helping us to gain a better understand of the biology that belies AML. It appears that there is an additional function of leukaemia associated antigens as biomarkers of disease state and survival. Here, we discuss these findings.

Keywords: Acute myeloid leukaemia; cancer-testis antigen; human; clinical trial; immunotherapy

1. Introduction

Acute Myeloid Leukaemia (AML) is rare in children, but is more commonly observed in adults over the age of 65. For context, in the United Kingdom (UK) there were 3126 new cases of AML in 2015 and 2601 deaths from AML in 2016, in a population of 65 million. AML incidence has increased more than 30% since the 1990s and the mortality rate has increased more than 79% since the early 1970s (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence) [1]. This likely reflects the ageing population and prior exposure to treatments for cancer, radiation, benzene, and pre-conditions, such as Down Syndrome (www.nhs.uk/conditions.acute-myeloid-leukaemia) [2]. Typically, at diagnoses, the bone marrow sample comprises of about $1 \times 10^{12}$ blast cells and prognosis depends on the severity of the illness at the point of diagnosis. Patients with AML usually present with complications of disordered haematopoesis: bleeding, fatigue, refractory infections, or the clinical consequences of an extremely high white blood cell count: difficulty breathing, confusion, or other symptoms of organ failure [3]. We have been interested in identifying the antigens that are expressed by AML cells for three reasons. They can (i) act as targets for immunotherapy, (ii) provide new information about the biology of the disease, and (iii) act as biomarkers for the best treatment options or survival.

Immunotherapy stimulates the body’s own immune system to recognise and kill cancer cells and potentially protect against cancer development in the future. It is known that one of the functions of the immune system is to prevent tumour growth, and this is exemplified by the increased tumour frequencies seen in immunocompromised patients following organ transplantation, those with acquired immune deficiency syndrome (AIDS), and in patients with severe combined immunodeficiency (SCID)
syndrome [4]. A range of immunotherapy strategies that engage the innate and more often the adaptive immune system have been developed to treat AML (recently reviewed in [5]).

Survival for patients with AML has the potential to be greatly impacted by immunotherapy. Similar to all leukaemias, AML rapidly spreads throughout the body making localised treatments used for solid tumours, such as radiotherapy, of no real benefit. In addition, almost all AML patients will achieve first remission where minimal residual disease (MRD) can be monitored in anticipation of an all too frequent relapse. Around 70–80% of AML patients that were aged less than 65 achieve remission through chemotherapy treatment [6], but around half relapse in the absence of stem cell transplantation (SCT). During this period the immune system can recover and residual disease in difficult to reach places could be eliminated by immunotherapy. Indeed, we already use immunotherapy to treat AML patients through allo-SCT [7]. To boost this anti-tumour response, patients are given donor leukocyte infusions (DLIs) as follow-up treatments post-transplant to maximise the chances of the transplant being successful. Even with SCT, over one-third of patients will relapse [8], and we know that the mortality rates that are associated with SCT, though decreased with the advent of peripheral blood (PB) based haematopoietic-SCT (HSCT), still remain high. Indeed, patients are often exempted from SCT due to a lack of a suitable donor or because they are too fragile to cope with the rigours of SCT, although reduced intensity regimens have made SCT available to a broader base of older patients [9].

We already know a lot about how the immune system works from transplantation studies for AML patients, especially around the importance of graft-versus-host disease (GvHD) to achieve graft-versus-leukaemia (GvL) through twin studies and T cell depletions [10], the boosting of GvHD through repeated DLI transfusions [11] and the role of reduced intensity conditioning allo-transplants to improve the outcomes for older patients [12]. However many patients, especially those who are ineligible to have a HSCT transplant, will relapse after first remission and require further chemotherapeutic treatments [13]. Ideally, patients could be treated with immunotherapy in first remission, to delay or hopefully prevent relapse.

Currently, the median survival for AML is around one year; however, there has been a steady increase in the overall survival in younger patients [14]. The shift from bone marrow SCTs to PB SCTs has increased donor availability and MRD allows for the prediction of relapse and prophylactic care. However, to date, the largest improvements in survival remain due to improvements in palliative and supportive care [3].

2. Immunotherapy

Although conventional treatments can be successful for patients with leukaemia, with five-year survival rates for those patients treated with conventional chemotherapeutics (e.g., cytarabine and daunorubicin), being at 27.4% (National Cancer Institute, https://seer.cancer.gov/statfacts/html/amy1.html) [15] in comparison to those who were treated with SCTs being at 44.1%, at five-years post-diagnosis [16]. The success of SCTs needs to be considered in a background of 15–25% mortality [17], due to the treatment itself. On the whole aggressive types and stages are still particularly challenging to diagnose and treat. The future of cancer treatment is increasingly focussed on immunotherapy [18] used in combination with conventional treatments, which is seen as the best opportunity for personalised and more effective treatments that could significantly increase survival rates [19], and in the case of liquid tumours, could remove residual disease at diffuse sites in the body.

The ideal immunotherapy targets should play a role in tumour progression [20], so that tumour destruction targets those cells that are responsible for the tumours aggression as well as starting a cascade of activation induced cell death (AICD), immune stimulation in the context of ‘danger’ and inflammation, and epitope spreading. To ensure monies from National Institute of Health (NIH) grants prioritised immunotherapeutic treatments that focussed on a limited number of antigenic targets, maximising the speed with which treatments reached clinical trials, Cheever and colleagues [21] identified 75 cancer antigens and evaluated them based on nine characteristics that were identified as being essential for effective treatment. p53 [22] was identified as one of the most desirable targets for
immunotherapy as targeting p53 can kill both the evolving tumour cell population and any cancer “stem” cell that harbours this as an early stage aberration. By targeting p53, you prevent its support of further tumour growth and genomic instability [23]. However p53, like many other antigens is found to be expressed in solid tumours, but is absent or expressed at low frequencies in haematological malignancies [24]. Indeed, of the antigens considered, those that have been found with any frequency in AML were limited to Wilms’ Tumour protein (WT1) (3rd out of 75) and survivin (12th out of 75), reflecting the authors’ need to provide a shortlist of antigens relevant to as many solid and haematological malignancies as possible. However, the re-expression of some of the antigens listed has been demonstrated through demethylation agents, such as 5′aza-2′-deoxy-cytidine, in recent studies, including, but not limited to, melanoma antigen (MAGE)-A3 (29th of 75), NY-ESO-1 (34th of 75) [25], and synovial sarcoma X breakpoint 2 (SSX2) (53rd of 75) [26].

3. The Role of Immunotherapy to Prevent or Delay Relapse in AML Patients in Remission

Treatment for leukaemia is often successful and a first remission achieved [27] however, recurrence is seen in about 50% of younger patients and 90% of older patients [28]. MRD monitoring can predict relapse 2–3 months prior to the development of clinical symptoms [29], enabling prophylactic treatment to give patients the best chance of remaining in remission. The death of patients with leukaemia are generally due to disease relapse and patients in first complete remission who are positive for MRD prior to SCT were more likely to die (2.61 times) or relapse (4.9 times) a second time than patients who were MRD negative [30].

Immunotherapy provides an opportunity to remove MRD from cancer patients in first remission, when the burden of disease is low and their immune system is recovering from induction and consolidation therapies. In addition, immunotherapy can be specific to the diseased cells, unlike chemotherapy [31], and destroy leukaemic blast cells in the PB and organs throughout the body. There are a number of different types of antigens [32], including differentiation, mutated, overexpressed, and cancer-testis antigens (CTAs), some of which have been found in AML, including antigens from mutated genes such as Nucleophosmin 1 (NPM1), DNA methyltransferase 3A (DNMT3A), Fms Related Tyrosine Kinase 3 (FLT3), and Ten–Eleven Translocation 2 (TET2) (recently reviewed by [33]). The CTAs category includes some of the oldest and best characterized families, and although MAGE family members were not found to be expressed in presentation AML patient samples with any notable frequency [34], helicase antigen (HAGE) and Per ARNT SIM domain containing 1 (PASD1) antigens have been [34,35]. The differentiation antigens category is another large group of molecules that includes, among many others, the well-known Carcinoembryonic antigen (CEA), glycoprotein 100 (gp100), melan A/melanoma antigen recognized by T cells (MART-1), prostate specific antigen (PSA), and tyrosinase antigens, but relatively few AML antigens have come from this category. The myeloid differentiation antigen CD65 is found at low levels in the least differentiated forms of AML (M0, M1), and usually appears as CD34 disappears during normal myeloid development, reflecting the lack of differentiation in the blast cells in these disease states. The largest group are the overexpressed antigens that include human epidermal growth factor receptor 2 (ErbB-2), human telomerase reverse transcriptase (hTERT), Mucin1 (MUC1), mesothelin, PSA, prostate specific membrane antigen (PSMA), survivin, WT1, p53 and cyclin B1, some of whom are discussed below.

4. CTAs

We are particularly interested in CTAs, whose expression is usually restricted to healthy major histocompatibility complex (MHC) class I-deficient germline cells (reviewed by [32]). This feature makes them appealing targets for immunotherapeutic strategies because they provide tumour-specific antigens for MHC class I-restricted CD8+ T cells [36]. Developing immunogenic cancer vaccines that target these antigens has become a priority in how cancer is diagnosed and treated. Boon and colleagues were the first to clone a human tumour antigen, named MAGE-1 [37], through the analyses of responses of cytotoxic T cells to melanoma cells. Subsequently, other CTAs were discovered by the group namely
the B melanoma antigen (BAGE) and G antigen (GAGE) gene families. Common characteristics of CTAs include mostly being encoded by multigene families, often mapping to the X chromosome and having their expression level epigenetically regulated with drugs, such as 5-aza-2′-deoxycytidine [25,26], and although the functions of many are still unidentified, they have been shown to be involved in tumourigenesis [36]. A large number CTAs have been discovered using serological analysis of recombinant cDNA expression libraries (SEREX) [38] showing much promise as biomarkers for disease and providing targets for immunotherapy. Examples include PASD1 in AML [35], LY6K in lung and oesophageal carcinomas [39], sperm protein 17 (Sp17) in head and neck squamous cell carcinoma [40] and transmembrane protein 31 (TMEM31) in metastatic melanoma [41]. The problem is that CTAs are often expressed in less patients (23% for HAGE [34] and 33% for PASD1 [35]) at AML presentation as compared with leukaemia associated antigens (LAAs), such as Survivin [42] and WT1 [43], which are found in most patients and can act as MRD markers in their own right. However CTAs are restricted in their expression to cancer/leukaemia cells and they offer an opportunity to circumvent the initiation of auto-immune responses that could destroy healthy tissues in vulnerable patients.

It has been increasingly apparent that immunotherapy works best when patients have a healthy immune system and low tumour burden. This is exemplified by the increased cancer incidence observed in patients who have been immune suppressed by Human Immunodeficiency virus (HIV) [44], organ transplantation [45], or cancer treatments, such as radiotherapy and/or chemotherapy [46]. It appears likely that immunotherapy will require use in combination with other treatments, such as hypomethylating agents i.e., SGI-110, a derivative of decitabine [47], which has been shown to lead to the re-expression of MAGE-A and NY-ESO-1 in AML blasts, or more recently treatment in a Phase II clinical trial of AML patients with azacitidine and vorinostat, which led to an increased expression of MAGE, renal cell carcinoma antigen (RAGE), LAGE, SSX2, and taxol resistance associated gene-3 (TRAG3) in blasts, which can be recognised when presented to circulating T cells [48]. In addition, anti-CTLA4 or anti-PD-L1 have been shown to enable the memory of the immune system to recognise tumour antigens (reviewed in [49]).

There has been some suggestion of using CTAs vaccines in a preventative manner at the earliest stages before the cancer advances [50], but predicting which patients are at risk of cancer is often limited to inherited cancers, which account for approximately 5% of all of those affected by cancer and predisposing factors such as exposure to carcinogens that may or may not lead to cancer development.

5. CTAs and AML

HAGE is part of the DEAD-box RNA helicases that implies that its function may include RNA metabolism in malignant cells [51]. It has been shown to be expressed in a number of tumour types but not healthy tissues [52]. In 2002, Adams et al. [34] investigated the expression of 10 CTAs in presentation samples from 26 AML and 42 CML. They found little or no expression of MAGE-A1, -A3, -A6, -A12, BAGE, GAGE, LAGE-1, NY-ESO-1 or RAGE. In contrast to previous studies of CTAs in AML, Adams et al. found that HAGE was expressed in 23% of AML patient samples by RT-PCR while it was detected in 14.8% (11/74) AML patients by qPCR analysis by Chen et al. [53]. HAGE has been found to be induced in a dose dependent manner by 5-aza-2′-deoxycytidine [54], a treatment now being used in Phase II clinical trials to overcome T cell exhaustion that is caused by AML blast arginase II activity [48].

The PASD1 gene was identified through the immunoscreening of testes cDNA libraries [35,55] using the SEREX technique [56]. A number of investigations have demonstrated PASD1 expression in haematological malignancies, including 4/12 (33%) AML samples [35]. In a cohort of haematological malignancy derived cell lines, the sub-cellular localisation of PASD1, as determined by immunostaining with monoclonal antibodies, was variable [57]. The detection of nuclear staining was not unexpected and it likely reflected the presence of a nuclear localisation signal in the common region of the PASD1-1 and PASD1-2 proteins and the role of PASD1 as a transcription factor [58].

Immunogenic T-cell epitopes within PASD1a and PASD1b have proved to be more difficult to identify [59,60]. In AML, Hardwick et al. [60] modified HLA-A*02:01 binding PASD1-specific
peptides to generate effective T cell responses. One epitope, Pa14, caused limited expansion in CD8+ T cell numbers from two of three HLA-A*02:01 positive, PASD1-positive AML patient samples. This corresponds with the findings of Rezvani et al. [61], who also found AML T cells have limited capacity to respond to stimulation ex vivo. A 2–3 week limited expansion is the maximum that has been achieved prior to AML T cell death. Reasons for the limited responses may be due to the presence of myeloid suppressor cells in mixed lymphocyte assays [62], interleukin-6 (IL-6) secretion by myeloid leukaemia cells [63], and/or defects in T cell populations in myeloid leukaemia patients [61,64]. However, the stimulation of T cells from a colon cancer patient, by Hardwick et al, led to a substantial increase in the number of Pa14-specific T cells to 13.6% of the CD8+ cell population after four rounds of stimulation, with Pa14-specific IFN\(\gamma\) responses being evidenced [60].

PASD1 expression has not been described in solid tumours although the issues around publishing negative results [65] means that there is little record of which solid tumour have been investigated for PASD1 expression. However the absence of PASD1 expression in solid tumours, including basal cell cancer [66] and ovarian cancer [67], has been published suggesting low expression where it has been described.

6. The Role of Tumour Antigens as Biomarkers for Survival

Although tumour antigens were identified for their potential to act as targets for immunotherapy, using the patient immune response for their identification, a number of subsequent studies showed that some, but not all of these antigens could also act as biomarkers [68]. Indeed, despite their known role in cancer initiation and progression, some antigens with elevated expression correlated with improved survival.

Greiner and Guinn theorised that when leukaemia cells with elevated levels of LAAs are destroyed by chemotherapy the clean-up of the dead/dying cancer cells by the immune system leads to the presentation of antigens in an immunogenic and inflammatory context, leading to improved post-treatment immune responses. In acute promyelocytic leukaemia (APL) patients who harbour the t(15;17) translocation, had a decreased expression of Preferentially Expressed Antigen In Melanoma (PRAME) that correlated with a shorter overall survival [69], whereas the typically favourable t(8;21) translocation was associated with a higher level of PRAME in AML M2 patients [70]. Greiner et al. [71] had shown a significant correlation between high G250 mRNA expression levels and a longer overall survival \((p = 0.022)\) based on DNA microarray data from 116 AML patients. In addition, the SSX2 interacting protein (SSX2IP) has been found to be a marker of improved survival in AML patients who had no cytogenetic aberrations [72], while also being elevated in patients with t(15;17), associated with poor prognosis until the advent of (treatment) and decreased in patients harbouring the more favourable t(8;21) [73]. Guinn et al. found a positive correlation between the expression of SSX2IP and the poor prognostic indicator FLT-3-ITD \((p = 0.008, t\) test), but not between SSX2IP and other poor prognostic markers, such as cytogenetic abnormalities associated with poor survival, while cell count, age, sex, or survival [73].

However this has not been the case with all antigens. Liberante et al. [74] suggested a ‘Goldilocks’ effect of the relative levels of PRAME expression in terms of its role as a biomarker for survival. It was found that ‘very high’ and ‘very low’ levels of PRAME expression correlated with poor survival. Low levels of PRAME expression may reflect a situation where leukaemia cells are able to escape immune surveillance, while higher levels of PRAME could reflect a higher tumour load and/or the presence of more aberrant leukaemia cells [74]. In addition, elevated survivin expression has been shown to correlate with chemoresistance [42] and poor outcomes [75,76] in AML. This is more commonly the case in solid tumours, where the elevated expression of antigens tends to be associated with a worse clinical outcome, if there is an association. Examples include survivin in different solid tumours, including renal cell carcinoma [76] and HAGE in breast cancer [77]. In addition, differences between survival and antigen expression can vary with AML subtype, patient age, and cytogenetics perhaps reflecting the heterogeneity of AML. For example, RAGE-1 and MGEA6 were both found to have elevated expression in the less lineage restricted forms of AML [78], while microarray analysis showed elevated SSX2IP in patients with the t(15;17) and significantly decreased levels of SSX2IP in patients harbouring the t(8;21) [73].
Bergmann et al. showed that high levels of WT1 mRNA in AML were associated with poor long-term outcome [79], while others found no correlation [71,80,81]. However Bergmann’s findings reflected the situation in non-small cell lung cancer, where low WT1 mRNA expression has been associated with poor survival and lymph node metastases [82]. This may demonstrate the need to further sub-group patients based on age or other demographics. Indeed, the expression of BCL-2 and WT1 has been associated with a reduced rate of achieving complete remission and overall survival in patients that were younger than 60 years, and no effect on survival rates in patients older than 60 years [83].

7. Antigens that Have Been Shown to Play a Role in the Biological Basis of AML

A number of proteins were identified by virtue of an antibody response against them and were then shown to have an important role in the biological basis of AML. Greiner discussed the role of a number of LAAs in cell cycle proliferation (BAGE, BCL-2, OFA-iLRP, FLT3-ITD, G250, hTERT, PRAME, Hyaluronan-mediated motility receptor (HMMR, also known as RHAMM), proteinase 3, survivin, and WT1), meaning that immunotherapy strategies targeting them would also destroy leukaemic cells that are proliferating abnormally under the control of overexpressed or mutated antigens.

In AML patients with the t(15;17) translocation, SSX2IP levels were associated with gene expression of proteins involved in regulating cyclin dependent kinases (CDK) activity (p57Kip2, cdk7, cyclins D2, D3, E2, and B2), DNA replication (CDC6) and mitosis (survivin and CENP-J) [73]. We also found a very significant correlation between AML patients harbouring a t(8;21) and low cdc20 expression [73]. Boyapati et al. [84] had described a mouse model of AML M2 whose cells had a C-terminal truncated AML-ETO product and developed aneuploidy through the attenuation of the spindle checkpoint. Using microarray datasets for associations between SSX2IP and the genes involved in spindle checkpoints described by Boyapati et al., Guinn et al. [73] found a strong correlation between low-CDC20 expression, one of the substrate-targeting subunits of the anaphase-promoting complex and low-SSX2IP expression in patients harbouring a t(8;21) translocation when compared with AML patients without a t(8;21) translocation and normal donors.

In 2007, Denniss observed the variable expression of PASD1 in synchronised K562 cells over time [85], but could not demonstrate an association with the phases of the cell cycle. Others also noted that only a subset of K562 cells expressed PASD1 (around 17% of the cell population) [60,86] and they could be reproducibly killed by PASD1-specific T cells [60]. PASD1, a homologue to the mouse CLOCK gene, has now been shown to suppress circadian rhythms. The circadian clock regulates and responds to the physiological and environmental changes by regulating transcription in a roughly 24 h cycle. PASD1 through its interaction with CLOCK:BMAL1 reduces transcription regulation, leading to the transformation of cells. PASD1 C-terminal CC1 domain bears homology to the essential regulatory region encoded by CLOCK exon 19. Using molecular mimicry, PASD1 can restrict the activation of CLOCK exon 19 to disrupt the CLOCK:BMAL1 function, therefore supressing transcription [87].

Survivin, coded by the baculoviral IAP repeat-containing 5 (BIRC5) gene, has been shown to be involved in several central pathways that control cell proliferation and viability (reviewed recently by Garg et al. [88]). Of particular note, survivin is a key player of the survivin-Borealin-INCEPN core complex that regulates important proteins that are involved in cell division, like aurora B kinase or polo-like kinase 1 [89,90]. Several pathways, such as mTOR- and ran-GTP, are regulated by survivin [91,92], and survivin is involved in spindle formation and anti-apoptosis [91]. While in normal differentiated adult tissues little or no expression of survivin is found, high expression has been described in a number of different solid tumors and hematological malignancies [91]. Attempts to antagonize survivin using antisense molecules are ongoing, including immuno-targeting by vaccination and tyrosine kinase inhibition [93–95]. Notably, a repressor of survivin recently produced encouraging results in heavily pretreated cancer patients [96].

WT1 has emerged as one of the most promising targets for AML immunotherapy, because of its oncogenic role in leukaemogenesis, its high expression in the majority of AML cells, and its ability to function as a tumour rejection antigen [97]. Concomitantly, many other haematological [98–100] and
solid [99–101] tumours could benefit from WT1-directed therapy. Despite its ubiquitous expression during embryogenesis, WT1 expression in normal individuals is limited to renal podocytes, gonadal cells, and CD34+ bone marrow cells [102,103], where expression is significantly lower than in leukaemia cells (10–100 fold) [103], making it an excellent target for immunotherapy.

8. Clinical Trials–State-of-The-Art

As T cells are able to recognise and kill cancer cells [104], it was thought that T cell therapies would be the most effective form of immunotherapy. T cells are believed to have an exquisite specificity for epitopes within tumour antigens and they are able to effectively kill cancer cells in a controlled manner. Cytotoxic T-lymphocytes (CTLs) can be stimulated through the use of dendritic cells (DCs) [105], peptide vaccines [106], DNA vaccines [107], and natural killer (NK) cells [108].

DCs are antigen presenting cells that are able to cross present by ingesting and processing extracellular antigens and presenting them on Major Histocompatability Complex (MHC) class I molecules [109]. DC therapy involves extracting the patient’s own monocytes, maturing and activating them to DCs using antigens. The DCs are then injected back into the body to stimulate the immune system to eliminate the antigen expressing cancer cells [110].

AML cell lines were used to show that PRAME is involved in retinoic acid-regulated (RAR) cell proliferation and differentiation by inhibiting RAR signalling [111] and introducing all-trans-retinoic acid (ATRA) may be able to reverse this, especially in patients without the t(15:17) mutation. Combination treatment of targeting PRAME along with ATRA would potentially benefit patients expressing elevated levels of PRAME [111]. The presence of PRAME could be an indicator for relapse, as it was found to be increased, after decreasing during remission, even with multiple relapses [112]. PRAME has been shown to induce specific T-cell responses in both solid tumours and leukaemia [113]. However, in some patients expressing PRAME, the cytotoxic response is too weak but after treatment with a Histone deacetylase (HDAC) inhibitor chidamide enhanced PRAME levels are observed, with further improvement when chidamide is combined with the DNA demethylating agent decitabine resulting in immune cells recognizing the PRAME100–108 or PRAME300–309 peptide presented by HLA-A*02:01 [114].

Monoclonal antibodies are used to treat a number of cancers, including low-grade or follicular non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukaemia (CLL), through treatment with rituximab, which is a CD20 specific antibody. Rituximab targets CD20 that is present on the surface of the B cells, including the malignant NHL and CLL cells [115].

The best strategy for the effective treatment of cancer may include a combination of conventional and immunotherapy techniques [116], or even a combination of immunotherapy techniques, as demonstrated in increasing numbers of mouse models [117] and clinical trials [118–120]. Subsequently, adoptive T cell therapy has been shown to be very promising with the number of cells being returned to patients [121] and their status—activated but not matured [122], being the main considerations. Chimeric antigen receptors-T cells (CAR-T) are where a patients T cells are genetically engineered to express the CAR receptor on their surface against a specific antigen. Upon expansion, they are injected back into the body to recognise and kill the antigen expressing cancer cells. In a recent novel study, a T-cell receptor-mimic (TCRm) CAR, known as WT1-28z, responded to a peptide portion of the intracellular antigen WT1, as it is presented on the surface of the tumour cell in the context of HLA-A*02:01. T cells genetically modified to recognise WT1-28z specifically targeted and lysed HLA-A*02:01+ WT1+ tumours and improved the survival of mice engrafted with HLA-A*02:01+, WT1+ leukaemia cells [123].

There are a number of excellent reviews in this area of research that aim to identify and discuss effective immunotherapy strategies for the future (Table 1). These include cellular immunotherapy [124], whole cell vaccines [125], multidrug resistance [126], DCs [127], oncolytic viruses [128], and nanotechnology [129]. Targeted therapeutic strategies along with ever improving designs in clinical trials pave the way for further success [130].
Table 1. Some examples of current clinical trials involving antigenic targets in acute myeloid leukaemia (AML).

| Target Antigen(s) | Designated Name | Type of Immunotherapy | Phase | Findings                                                                                                                                                                                                 | Refs    |
|-------------------|-----------------|-----------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| CD33 and CLL1     | CD123b-CD33b cCAR | CAR-T/cellular immunotherapy | I     | 1 patient–44 year old female. Liu stated that the CD33 cCAR T cell therapy could be used as a conduit to transplant, in addition to conventional chemotherapy or alone.                                               | [131]   |
| MUC1-C plus decitabine | GO-203-2C       | Peptide inhibition of MUC1/targeted therapy | I/Ib  | Combination cohort, response was achieved in 57% compared to GO-203-2C alone who had resistant disease. Showed treatment is safe.                                                                         | [132]   |
| Proteinase 3      | PR1             | Peptide vaccine       | I/II  | PR1 vaccine induces specific immunity that correlates with clinical response, including molecular remission                                                                 | [133]   |
| Bcl-2             | Venetoclax      | Small molecule inhibitor | II    | Measurable reduction in bone marrow blast counts was observed in 53% of patients                                                                                                                        | [134]   |
| WT1               | galinpepimut-S  | Peptide vaccine       | II    | Median disease-free survival from CR1 was 16.9 months, whereas the overall survival from diagnosis is estimated to be ≥67.6 months 58% developed T-cell responses, 58% patients in CR were free of relapse after 52 months, 57% of patients aged ≥60 also were free of relapse after 54 months | [135]   |
| hTERT             | AST-VAC1        | hTERT expressing autologous DCs | II    |                                                                                                                                                                                                           | [136]   |
In addition, combinations of immunotherapy could further enhance survival, reducing residual disease where there are escape variants. Combining the antibodies anti-CTLA-4 and anti-4-1BB revealed CD8+ immune responses against advanced MC38 tumours as well as establishment of memory T cells. Combination treatments reduced autoimmunity in comparison to a single antibody therapy [137] and they often offer an opportunity to eliminate escape variants. Combination therapy could be the answer for drug resistant tumours as the resistance mechanisms of the tumour can be identified and targeted alongside standard treatments. Two cell lines (breast and gastric cancer), resistant to sacituzumab govitecan, became susceptible to therapy through the use of an ATP-binding cassette (ABC) transporter inhibitor that is used in combination with antibody treatment [138]. ABC transporters can cause drug resistance by efflux-removal of the drug from the cell [139]. Promising combination therapies utilising antibodies include Lapatinib with trastuzumab in Her2 positive breast cancer [140], Dabrafenib and Trametinib in relapsed ovarian cancer [141], carboplatin and pemetrexed in advanced non-small cell lung cancer [142], pidilizumab and rituximab in follicular lymphoma [143], albumin-bound paclitaxel and gemcitabine in pancreatic cancer [144], nivolumab and ipilimumab in untreated metastatic melanoma [145], cisplatin and topotecan or cisplatin and gemcitabine in advanced colon cancer [146], and bevacizumab plus oral capecitabine plus irinotecan in metastatic colon cancer [147].

9. Summary

We have described the multiplex of insights that novel antigens have provided into how AML develops and how it might be targeted by immunotherapy approaches during disease remission. We have not however discussed novel treatments that we felt were outside the scope of this review and dealt with in detail elsewhere. Obvious examples include CAR-T cells (recently reviewed in [148]), RNA interference (RNAi) targeting, for example, of Brd4 [149], and antibody therapies, including anti-CD33 (recently reviewed in [150]).

Poor T cells responses in AML patients [60,61] make gauging anti-tumour responses using ex vivo T cells from AML patients difficult, and expanding immune and leukaemia cells for therapy before patients relapse have struggled to succeed. However, the success of HSCT and DLIs has shown the capacity of the immune system to overcome leukaemia cells when advantaged to do so. For the monitoring of MRD and effective T cell responses, it is important that proteins specific to the disease are identified and for immunotherapy that cancer specific antigens are the targets of immune responses, including those enacted by B-cell responses (by definition) and their immune counterparts (CD4+ and CD8+ T-cells among others).

The issues remain when to give vaccines against leukaemia to best impact the disease and the effect of treatment on the immune system cannot be underestimated, especially in myeloid leukaemia. Clinical trials, for what is a relatively rare cancer, as compared to many solid tumours, include a limited number of immunotherapy treatments and perhaps a new list of prioritised tumour antigens for haematological malignancies/leukaemia/myeloid leukaemia are required.

Whatever the way forward for AML treatment, it will undoubtedly require the combination of SCT wherever possible, induction and consolidation therapies to achieve MRD, immune recovery, and a lot of trial and error for this heterogenous population.

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Abbreviations

AML: acute myeloid leukaemia; ATRA: all-trans-retinoic acid; BAGE: B melanoma antigen; CAR-T: Chimeric antigen receptors-T cells; CLL: chronic lymphocytic leukaemia; CTA: cancer-testis antigen; DC: dendritic cells; DLI: donor leukocyte infusion; GAGE: G antigen; GvHD: Graft-versus-Host disease; HAGE: helicase antigen;
HSCT: haematopoietic stem cell transplant; hTERT: human telomerase reverse transcriptase; LAA: leukaemia associated antigen; MAGE: Melanoma antigen; MHC: major histocompatibility complex; MRD: minimal residual disease; MUC1: Mucin1; NHL: Non-hodgkin’s lymphoma; PASD1: Per ARNT SIM domain containing 1; PB: peripheral blood; PRAME: Preferentially Expressed Antigen In Melanoma; PSA: prostate specific antigen; RAGE: Renal cell carcinoma antigen; RAR: retinoic acid-regulated SEREX: serological analysis of recombinant cDNA expression; SSX2IP: synovial sarcoma X breakpoint 2 interacting protein; WT1: Wilms’ Tumour protein.

References

1. Cancer Research UK: Acute Myeloid Leukaemia (AML) Incidence Statistics. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence (accessed on 21 January 2019).

2. NHS Overview: Acute Myeloid Leukaemia. Available online: www.nhs.uk/conditions.acute-myeloid-leukaemia (accessed on 21 January 2019).

3. Showel, M.M.; Levis, M. Advances in treating acute myeloid leukemia. F1000Prime Rep. 2014, 6, 96. [CrossRef] [PubMed]

4. Penn, I. Tumors of the immunocompromised patient. Annu. Rev. Med. 1988, 39, 63–73. [CrossRef] [PubMed]

5. Geiger, T.L.; Rubnitz, J.E. New approaches for the immunotherapy of acute myeloid leukemia. Discov. Med. 2015, 19, 275–284. [PubMed]

6. Döhner, H.; Estey, E.H.; Amadori, S.; Appelbaum, F.R.; Büchner, T.; Burnett, A.K.; Dombret, H.; Fenaux, P.; Grimwade, D.; Larson, R.A.; et al. Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 2010, 115, 453–474. [CrossRef] [PubMed]

7. Appelbaum, F.R. Haematopoietic cell transplantation as immunotherapy. Nature 2001, 411, 385–389. [CrossRef] [PubMed]

8. Cornelissen, J.J.; van Putten, W.L.; Verdonck, L.F.; Theobald, M.; Jacky, E.; Daenen, S.M.; van Marwijk Kooy, M.; Wijermans, P.; Schouten, H.; Huijgens, P.C.; et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: Benefits for whom? Blood 2007, 109, 3658–3666. [CrossRef] [PubMed]

9. McClune, B.L.; Weisdorf, D.J.; Pedersen, T.L.; Tunes da Silva, G.; Tallman, M.S.; Sierra, J.; Dipersio, J.; Keating, A.; Gale, R.P.; George, B.; et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J. Clin. Oncol. 2010, 28, 1878–1887. [CrossRef] [PubMed]

10. Marmont, A.M.; Horowitz, M.M.; Gale, R.P.; Sobocinski, K.; Ash, R.C.; van Bekkum, D.W.; Champlin, R.E.; Dicke, K.A.; Goldman, J.M.; Good, R.A.; et al. T-cell depletion of HLA-identical transplants in leukemia. Blood 1991, 78, 2120–2130. [PubMed]

11. Collins, R.H., Jr.; Shpilberg, O.; Drobyski, W.R.; Porter, D.L.; Giralt, S.; Champlin, R.; Goodman, S.A.; Wolff, S.N.; Hu, W.; Verfaillie, C.; et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J. Clin. Oncol. 1997, 15, 433–444. [CrossRef] [PubMed]

12. Estey, E.; de Lima, M.; Tibes, R.; Pierce, S.; Kantarjian, H.; Champlin, R.; Giralt, S. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Blood 2007, 109, 1395–1400. [CrossRef] [PubMed]

13. Dores, G.M.; Devesa, S.S.; Curtis, R.E.; Linet, M.S.; Morton, L.M. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. Blood 2012, 119, 34–43. [CrossRef] [PubMed]

14. Maynadié, M.; De Angelis, R.; Marcos-Gragera, R.; Visser, O.; Allemani, C.; Tereanu, C.; Capocaccia, R.; Giacomin, A.; Lutz, J.M.; Martos, C.; et al. Survival of European patients diagnosed with myeloid malignancies: A HAEMACARE study. Haematologica 2013, 98, 230–238. [CrossRef] [PubMed]

15. National Cancer Institute Cancer Stat Facts: Leukaemia–Acute Myeloid Leukaemia (AML). Available online: https://seer.cancer.gov/statfacts/html/amyl.html (accessed on 21 January 2019).

16. Master, S.; Mansour, R.; Devarakonda, S.S.; Shi, Z.; Mills, G.; Shi, R. Predictors of Survival in Acute Myeloid Leukemia by Treatment Modality. Anticancer Res. 2016, 36, 1719–1727.
17. Estey, E.; Döhner, H. Acute myeloid leukaemia. *Lancet* 2006, 368, 1894–1907. [CrossRef]
18. Ryan, J.F.; Hovde, R.; Glanville, J.; Lyu, S.C.; Ji, X.; Gupta, S.; Tibshirani, R.J.; Ray, D.C.; Boyd, S.D.; Chinthrajah, R.S.; et al. Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets. *Proc. Natl. Acad. Sci. USA* 2016, 113, E1286–E1295. [CrossRef] [PubMed]
19. Schadendorf, D.; Hodi, F.S.; Robert, C.; Weber, J.S.; Margolin, K.; Hamid, O.; Patt, D.; Chen, T.T.; Berman, D.M.; Wolchok, J.D. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J. Clin. Oncol.* 2015, 33, 1889–1984. [CrossRef] [PubMed]
20. Zhang, J.Y.; Looi, K.S.; Tan, E.M. Identification of tumor-associated antigens as diagnostic and predictive biomarkers in cancer. *Methods Mol. Biol.* 2009, 520, 1–10. [CrossRef] [PubMed]
21. Cheever, M.A.; Allison, J.P.; Ferris, A.S.; Finn, O.J.; Hastings, B.M.; Hecht, T.T.; Mellman, I.; Prindiville, S.A.; Viner, J.L.; Weiner, L.M.; et al. The prioritization of cancer antigens: A national cancer institute pilot project for the acceleration of translational research. *Clin. Cancer Res.* 2009, 15, 5323–5337. [CrossRef]
22. Soussi, T. p53 Antibodies in the sera of patients with various types of cancer: A review. *Cancer Res.* 2000, 60, 1777–1788.
23. Bykov, V.J.N.; Eriksson, S.E.; Bianchi, J.; Wiman, K.G. Targeting mutant p53 for efficient cancer therapy. *Nat. Rev. Cancer* 2018, 18, 89–102. [CrossRef]
24. Padua, R.A.; Guinn, B.A.; Al-Sabah, A.I.; Smith, M.; Taylor, C.; Pettersson, T.; Ridge, S.; Carter, G.; White, D.; Oscier, D.; et al. RAS, FMS and p53 mutations and poor clinical outcome in myelodysplasias: A 10-year follow-up. *Leukemia* 1998, 12, 887–892. [CrossRef] [PubMed]
25. Almstedt, M.; Blagitko-Dorfs, N.; Duque-Afonso, J.; Karbach, J.; Pfeifer, D.; Jager, E.; Lubbert, M. The DNA demethylating agent 5-aza-2’-deoxycytidine induces expression of NY-ESO-1 and other cancer/testis antigens in myeloid leukemia cells. *Leuk. Res.* 2010, 34, 899–905. [CrossRef] [PubMed]
26. Atanackovic, D.; Luetkens, T.; Kloth, B.; Fuchs, G.; Cao, Y.; Hildebrandt, Y.; Meyer, S.; Bartels, K.; Reinhard, H.; Lajmi, N.; et al. Cancer-testis antigen expression and its epigenetic modulation in acute myeloid leukemia. *Am. J. Hematol.* 2011, 86, 918–922. [CrossRef] [PubMed]
27. Burnett, A.K.; Goldstone, A.H.; Stevens, R.M.; Hann, I.M.; Rees, J.K.; Gray, R.G.; Wheatley, K. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: Results of MRC AML 10 trial. UK Medical Research Council Adult and Children’s Leukaemia Working Parties. *Lancet* 1998, 351, 700–708. [CrossRef]
28. Schlenk, R.F.; Döhner, H. Genomic applications in the clinic: Use in treatment paradigm of acute myeloid leukemia. *Hematol. Am. Soc. Hematol. Educ. Program.* 2013, 324–330. [CrossRef]
29. San Miguel, J.F.; Martínez, A.; Macedo, A.; Vidriales, M.B.; López-Berges, C.; González, M.; Caballero, D.; García-Marcos, M.A.; Ramos, F.; Fernández-Calvo, J.; et al. Immunophenotyping investigation of minimal residual disease is a useful approach for predicting relapse in acute myeloid leukaemia patients. *Blood* 1997, 90, 2465–2470. [PubMed]
30. Walter, R.B.; Buckley, S.A.; Pagel, J.M.; Wood, B.L.; Storer, B.E.; Sandmaier, B.M.; Fang, M.; Gyurkocza, B.; Delaney, C.; Radich, J.P.; et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. *Blood* 2013, 122, 1813–1821. [CrossRef]
31. Liu, H.; Kline, J. Novel Immunotherapy to Eliminate Minimal Residual Disease in AML Patients. *J. Hematol. Thromboemb. Dis.* 2013, 1. Available online: https://www.omicsonline.org/open-access/novel-immunotherapy-to-eliminate-minimal-residual-disease-in-aml-patients-2329-8790.1000112.php?aid=12874 (accessed on 21 January 2019). [CrossRef]
32. Coulie, P.G.; Van den Eynde, B.J.; van der Bruggen, P.; Boon, T. Tumour antigens recognized by T lymphocytes: At the core of cancer immunotherapy. *Nat. Rev. Cancer* 2014, 14, 135–146. [CrossRef]
33. Saulz, J.N.; Garzon, R. Acute Myeloid Leukemia: A Concise Review. *J. Clin. Med.* 2016, 5, 33. [CrossRef]
34. Adams, S.P.; Sahota, S.S.; Mijovic, A.; Czepulkowski, B.; Padua, R.A.; Mufti, G.J.; Guinn, B.A. Frequent expression of HAGE in presentation chronic myeloid leukaemias. *Leukemia* 2002, 16, 2238–2242. [CrossRef] [PubMed]
35. Guinn, B.A.; Bland, E.A.; Lodì, U.; Liggins, A.P.; Tobal, K.; Petters, S.; Wells, J.W.; Banham, A.H.; Mufti, G.J. Humoral detection of leukaemia-associated antigens in presentation acute myeloid leukaemia. *Biochem. Biophys. Res. Commun.* 2005, 335, 1293–1304. [CrossRef]
Buggins, A.G.; Patten, P.E.; Richards, J.; Thomas, N.S.; Mufti, G.J.; Devereux, S. Tumor-derived IL-6 may
Greiner, J.; Schmitt, M.; Li, L.; Giannopoulos, K.; Bosch, K.; Schmitt, A.; Dohner, K.; Schlenk, R.F.; Pollack, J.R.;
van Baren, N.; Chambost, H.; Ferrant, A.; Michaux, L.; Ikeda, H.; Millard, I.; Olive, D.; Boon, T.; Coulie, P.G.
Khan, G.; Brooks, S.E.; Mills, K.I.; Guinn, B.A. Infrequent Expression of the Cancer-Testis Antigen, PASD1, in
Ghafouri-Fard, S.; Abbasi, A.; Moslehi, H.; Faramarzi, N.; Taba Taba Vakili, S.; Mobasheri, M.B.;
Guinn, B. The future of publishing scientific data: Is it time to accept the wider publication of null data?
Mougiakakos, D.; Jitschin, R.; von Bahr, L.; Poschke, I.; Gary, R.; Sundberg, B.; Gerbitz, A.; Ljungman, P.;
Hardwick, N.; Buchan, S.; Ingram, W.; Khan, G.; Vittes, G.; Rice, J.; Pulford, K.; Mufti, G.; Stevenson, F.;
Rezvani, K.; Yong, A.S.; Tawab, A.; Jafarpour, B.; Eniafe, R.; Mielke, S.; Savani, B.N.; Keyvanfar, K.; Li, Y.;
Kurlander, R.; et al. Ex vivo characterization of polyclonal memory CD8+ T-cell responses to PRAME-specific
peptides in patients with acute lymphoblastic leukemia and acute and chronic myeloid leukemia. Blood 2009,
113, 2245–2255. [CrossRef]

55. Liggins, A.P.; Guinn, B.A.; Hatton, C.S.; Pulford, K.; Banham, A.H. Serologic detection of diffuse large B-cell lymphoma-associated antigens. Int. J. Cancer 2004, 110, 563–569. [CrossRef]
56. Sahin, U.; Tureci, O.; Schmitt, H.; Cocchioius, B.; Johannes, T.; Schmits, R.; Stenner, F.; Luo, G.; Schobert, I.; Pfreundschuh, M. Human neoplasms elicit multiple specific immune responses in the autologous host. Proc. Natl. Acad. Sci. USA 1995, 92, 11810–11813. [CrossRef]
57. Cooper, C.D.; Liggins, A.P.; Ait-Tahar, K.; Roncador, G.; Banham, A.H.; Pulford, K. PASD1, a DLBCL-associated cancer testis antigen and candidate for lymphoma immunotherapy. Leukemia 2006, 20, 2172–2174. [CrossRef] [PubMed]
58. Xu, Z.S.; Zhang, H.X.; Zhang, Y.L.; Liu, T.T.; Ran, Y.; Chen, L.T.; Wang, Y.Y.; Shu, H.B. PASD1 promotes
Cooper, C.D.; Liggins, A.P.; Ait-Tahar, K.; Roncador, G.; Banham, A.H.; Pulford, K. PASD1, a DLBCL-associated cancer testis antigen and candidate for lymphoma immunotherapy. Leukemia 2006, 20, 2172–2174. [CrossRef] [PubMed]
58. Xu, Z.S.; Zhang, H.X.; Zhang, Y.L.; Liu, T.T.; Ran, Y.; Chen, L.T.; Wang, Y.Y.; Shu, H.B. PASD1 promotes

59. Ait-Tahar, K.; Liggins, A.P.; Collins, G.P.; Campbell, A.; Barnardo, M.; Lawrie, C.; Moir, D.; Hatton, C.;
60. Hardwick, N.; Buchan, S.; Ingram, W.; Khan, G.; Vittes, G.; Rice, J.; Pulford, K.; Mufti, G.; Stevenson, F.;
61. Rezvani, K.; Yong, A.S.; Tawab, A.; Jafarpour, B.; Eniafe, R.; Mielke, S.; Savani, B.N.; Keyvanfar, K.; Li, Y.;
62. Mougiakakos, D.; Jitschin, R.; von Bahr, L.; Poschke, I.; Gary, R.; Sundberg, B.; Gerbitz, A.; Ljungman, P.;
63. Buggins, A.G.; Patten, P.E.; Richards, J.; Thomas, N.S.; Mufti, G.J.; Devereux, S. Tumor-derived IL-6 may
Greiner, J.; Schmitt, M.; Li, L.; Giannopoulos, K.; Bosch, K.; Schmitt, A.; Dohner, K.; Schlenk, R.F.; Pollack, J.R.;
van Baren, N.; Chambost, H.; Ferrant, A.; Michaux, L.; Ikeda, H.; Millard, I.; Olive, D.; Boon, T.; Coulie, P.G.
Khan, G.; Brooks, S.E.; Mills, K.I.; Guinn, B.A. Infrequent Expression of the Cancer-Testis Antigen, PASD1, in
Ghafouri-Fard, S.; Abbasi, A.; Moslehi, H.; Faramarzi, N.; Taba Taba Vakili, S.; Mobasheri, M.B.;
Guinn, B. The future of publishing scientific data: Is it time to accept the wider publication of null data?
EC Cancer 2014, 1, 1–2.
64. Wendelbo, Ø.; Nesthus, I.; Sjo, M.; Paulsen, K.; Ernst, P.; Bruserud, Ø. Functional characterization of T lymphocytes derived from patients with acute myelogenous leukemia and chemotherapy-induced leukopenia. Cancer Immunol. Immunother. 2004, 53, 740–747. [CrossRef] [PubMed]
65. Guinn, B. The future of publishing scientific data: Is it time to accept the wider publication of null data?
EC Cancer 2014, 1, 1–2.
66. Ghafouri-Fard, S.; Abbasi, A.; Moslehi, H.; Faramarzi, N.; Tabataba Vakili, S.; Mobasheri, M.B.;
67. Santamaria, C.; Chillön, M.C.; García-Sanz, R.; Balazsategui, A.; Sarasquete, M.E.; Alcoceba, M.; Ramos, F.;
Bernal, T.; Queizán, J.A.; Penarrubia, M.J.; et al. The relevance of preferentially expressed antigen of melanoma (PRAME) as a marker of disease activity and prognosis in acute promyelocytic leukemia. Haematologica 2008, 93, 1797–1805. [CrossRef]
68. Schumacher, T.N.; Schreiber, R.D. Neoantigens in cancer immunotherapy. Science 2015, 348, 69–74. [CrossRef]
69. Santamaria, C.; Chillön, M.C.; García-Sanz, R.; Balazsategui, A.; Sarasquete, M.E.; Alcoceba, M.; Ramos, F.;
Bernal, T.; Queizán, J.A.; Penarrubia, M.J.; et al. The relevance of preferentially expressed antigen of melanoma (PRAME) as a marker of disease activity and prognosis in acute promyelocytic leukemia. Haematologica 2008, 93, 1797–1805. [CrossRef]
70. van Baren, N.; Chambost, H.; Ferrant, A.; Michaux, L.; Ikeda, H.; Millard, I.; Olive, D.; Boon, T.; Coulie, P.G.
PRAME, a gene encoding an antigen recognized on a human melanoma by cytolytic T cells, is expressed in
acute leukaemia cells. Br. J. Haematol. 1998, 102, 1376–1379. [CrossRef] [PubMed]
71. Greiner, J.; Schmitt, M.; Li, L.; Giannopoulos, K.; Bosch, K.; Schmitt, A.; Dohner, K.; Schlenk, R.F.; Pollack, J.R.;
Dohner, H.; et al. Expression of tumor-associated antigens in acute myeloid leukemia: Implications for specific immunotherapeutic approaches. Blood 2006, 108, 4109–4117. [CrossRef]
72. Guinn, B.; Greiner, J.; Schmitt, M.; Mills, K.I. Elevated expression of the leukemia-associated antigen SSX2IP predicts survival in acute myeloid leukemia patients who lack detectable cytogenetic rearrangements. Blood 2009, 113, 1203–1204. [CrossRef] [PubMed]
73. Guinn, B.A.; Bullinger, L.; Thomas, N.S.; Mills, K.I.; Greiner, J. SSX2IP expression in acute myeloid leukemia: An association with mitotic spindle failure in t(8;21), and cell cycle in t(15;17) patients. *Br. J. Haematol.* 2008, 140, 250–251. [CrossRef] [PubMed]

74. Liberante, F.G.; Pellagatti, A.; Boncheva, V.; Bowen, D.T.; Mills, K.I.; Boultonwood, J.; Guinn, B.A. High and low, but not intermediate, PRAME expression levels are poor prognostic markers in myelodysplastic syndrome at disease presentation. *Br. J. Haematol.* 2013, 162, 282–285. [CrossRef] [PubMed]

75. Carter, B.Z.; Qiu, Y.; Huang, X.; Diao, L.; Zhang, N.; Coombes, K.R.; Mak, D.H.; Konopleva, M.; Cortes, J.; Kantarjian, H.M.; et al. Survivin is highly expressed in CD34+(+38(-)) leukemic stem/progenitor cells and predicts poor clinical outcomes in AML. *Blood* 2012, 120, 173–180. [CrossRef]

76. Tamm, I.; Richter, S.; Oltersdorff, D.; Creutzig, U.; Harbott, J.; Scholz, F.; Karawajew, L.; Ludwig, W.D.; Wucht, C. High expression levels of x-linked inhibitor of apoptosis protein and survivin correlate with poor overall survival in childhood de novo acute myeloid leukemia. *Clin. Cancer Res.* 2004, 10, 3737–3744. [CrossRef]

77. Abdel-Fatah, T.M.; McArdle, S.E.; Johnson, C.; Moseley, P.M.; Ball, G.R.; Pockley, A.G.; Ellis, I.O.; Rees, R.C.; Chan, S.Y. HAGE (DDX43) is a biomarker for poor prognosis and a predictor of chemotherapy response in breast cancer. *Br. J. Cancer* 2014, 110, 2450–2461. [CrossRef]

78. Guinn, B.A.; Gilkes, A.F.; Mufti, G.J.; Burnett, A.K.; Mills, K.I. The tumour antigens RAGE-1 and MGEA6 are expressed more frequently in the less lineage restricted subgroups of presentation acute myeloid leukemia. *Br. J. Haematol.* 2006, 134, 238–239. [CrossRef] [PubMed]

79. Bergmann, L.; Miething, C.; Maurer, U.; Brieger, J.; Karakas, T.; Weidmann, E.; Hoelzer, D. High levels of Wilms’ tumor gene (wt1) mRNA in acute myeloid leukemias are associated with a worse long-term outcome. *Blood* 1997, 90, 1217–1225. [PubMed]

80. Yanada, M.; Terakura, S.; Yamamoto, K.; Kiyoi, H.; Emi, N.; Kitamura, K.; Kohno, A.; Tanaka, M.; Tobita, T.; et al. Multiplex real-time RT-PCR for prospective evaluation of WT1 and fusion gene transcripts in newly diagnosed de novo acute myeloid leukemia. *Leuk. Lymphoma* 2004, 45, 1803–1808. [CrossRef]

81. Gaiger, A.; Schmid, D.; Heinze, G.; Linnerth, B.; Greinix, H.; Tisljar, K.; Priglinger, S.; Laczika, K.; Mitterbauer, M.; et al. Detection of the WT1 transcript by RT-PCR in complete remission has no prognostic relevance in de novo acute myeloid leukemia. *Leukemia* 1998, 12, 1886–1894. [CrossRef] [PubMed]

82. Hayashi, S.; Oji, Y.; Kanai, Y.; Teramoto, T.; Kitaichi, M.; Kawaguchi, T.; Okada, M.; Sugiyama, H.; Matsumura, A. Low Wilms’ tumor gene expression in tumor tissues predicts poor prognosis in patients with non-small-cell lung cancer. *Cancer Investig.* 2012, 30, 165–171. [CrossRef]

83. Karakas, T.; Miething, C.C.; Maurer, U.; Weidmann, E.; Ackermann, H.; Hoelzer, D.; Bergmann, L. The coexpression of the apoptosis-related genes bcl-2 and wt1 in predicting survival in adult acute myeloid leukemia. *Leukemia* 2002, 16, 846–854. [CrossRef]

84. Boyapati, A.; Yan, M.; Peterson, L.F.; Biggs, J.R.; Le Beau, M.M.; Zhang, D.E. A leukemia fusion protein attenuates the spindle checkpoint and promotes aneuploidy. *Blood* 2007, 109, 3963–3971. [CrossRef] [PubMed]

85. Denniss, F. The Protein Expression of Two Leukaemia Associated Antigens in AML: PASD1 and SSX2IP and Their Potential as Targets for Immunotherapy. MSc Thesis, King’s College London, London, UK, 2006.

86. Denniss, F.A.; Breslin, A.; Ingram, W.; Hardwick, N.R.; Mufti, G.J.; Guinn, B.A. The leukemia-associated antigen, SSX2IP, is expressed during mitosis on the surface of myeloid leukemia cells. *Br. J. Haematol.* 2007, 138, 668–669. [CrossRef] [PubMed]

87. Michael, A.K.; Harvey, S.L.; Sammons, P.J.; Anderson, A.P.; Kopalle, H.M.; Banham, A.H.; Partch, C.L. Cancer/Testis Antigen PASD1 Silences the Circadian Clock. *Mol. Cell* 2015, 58, 743–754. [CrossRef]

88. Garg, H.; Suri, P.; Gupta, J.C.; Talwar, G.P.; Dubey, S. Survivin: A unique target for tumor therapy. *Cancer Cell Int.* 2016, 16, 49. [CrossRef] [PubMed]

89. Jeyaprakash, A.A.; Klein, U.R.; Lindner, D.; Ebert, J.; Nigg, E.A.; Conti, E. Structure of a Survivin-Borealin-INCENP core complex reveals how chromosomal passengers travel together. *Cell* 2007, 131, 271–285. [CrossRef] [PubMed]

90. Ruchaud, S.; Carmena, M.; Earnshaw, W.C. The chromosomal passenger complex: One for all and all for one. *Cell* 2007, 131, 230–231. [CrossRef]

91. Altieri, D.C. Survivin, cancer networks and pathway-directed drug discovery. *Nat. Rev. Cancer* 2008, 8, 61–70. [CrossRef] [PubMed]
92. Xia, F.; Canovas, P.M.; Guadagno, T.M.; Altieri, D.C. A survivin-ran complex regulates spindle formation in tumor cells. *Mol. Cell. Biol.* 2008, 28, 5299–5311. [CrossRef] [PubMed]

93. Chang, M.L.; Chen, J.C.; Alonso, C.R.; Kornblihtt, A.R.; Bissell, D.M. Regulation of fibronectin splicing in sinusoidal endothelial cells from normal or injured liver. *Proc. Natl. Acad. Sci. USA* 2004, 101, 18093–18098. [CrossRef] [PubMed]

94. Pennati, M.; Folini, M.; Zaffaroni, N. Targeting survivin in cancer therapy. *Expert Opin. Ther. Targets* 2008, 12, 463–476. [CrossRef] [PubMed]

95. Sung, B.; Pandey, M.K.; Ahn, K.S.; Yi, T.; Chaturvedi, M.M.; Liu, M.; Aggarwal, B.B. Anacardic acid (6-nonadecyl salicylic acid), an inhibitor of histone acetyltransferase, suppresses expression of nuclear factor-kappaB-regulated gene products involved in cell survival, proliferation, invasion, and inflammation through inhibition of the inhibitory subunit of nuclear factor-kappaBalpha kinase, leading to potentiation of apoptosis. *Blood* 2008, 111, 4880–4891. [PubMed]

96. Nakahara, T.; Takeuchi, M.; Kinoyama, I.; Minematsu, T.; Shirasuna, K.; Matsuhisa, A.; Kita, A.; Tominaga, F.; Yamanaka, K.; Kudoh, M.; et al. YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts. *Cancer Res.* 2007, 67, 8014–8021. [CrossRef] [PubMed]

97. Sugiyama, H. WT1 (Wilms’ tumor gene 1): Biology and cancer immunotherapy. *Jpn. J. Clin. Oncol.* 2010, 40, 377–387. [CrossRef] [PubMed]

98. Oka, Y.; Tsuboi, A.; Murakami, M.; Hirai, M.; Tominaga, N.; Nakajima, H.; Elisseeva, O.A.; Masuda, T.; Nakano, A.; Kawakami, I.; et al. Wilms tumor gene peptide-based immunotherapy for patients with overt leukemia from myelodysplastic syndrome (MDS) or MDS with myelofibrosis. *Int. J. Hematol.* 2003, 78, 56–61. [CrossRef] [PubMed]

99. Tsuboi, A.; Oka, Y.; Udaka, K.; Murakami, M.; Masuda, T.; Nakano, A.; Nakajima, H.; Yasukawa, M.; Hiraki, A.; Oji, Y.; et al. Enhanced induction of human WT1-specific cytotoxic T lymphocytes with a 9-mer WT1 peptide modified at HLA-A*2402-binding residues. *Cancer Immunol. Immunother.* 2002, 51, 614–620. [CrossRef] [PubMed]

100. Oka, Y.; Tsuboi, A.; Oji, Y.; Kawase, I.; Sugiyama, H. WT1 peptide vaccine for the treatment of cancer. *Curr. Opin. Immunol.* 2008, 20, 211–220. [CrossRef]

101. Inoue, K.; Ogawa, H.; Sonoda, Y.; Kimura, T.; Sakabe, H.; Oka, Y.; Miyake, S.; Tamaki, H.; Oji, Y.; Yamagami, T.; et al. Aberrant overexpression of the Wilms tumor gene (WT1) in human leukemia. *Blood* 1997, 89, 1405–1412. [PubMed]

102. Hosen, N.; Sonoda, Y.; Oji, Y.; Kimura, T.; Minamiguchi, H.; Tamaki, H.; Kawakami, M.; Hasegawa, K.; et al. Induction of a Wilms tumor gene (WT1)-specific cytotoxic T lymphocytes by WT1 peptide vaccine and the resultant cancer regression. *Proc. Natl. Acad. Sci. USA* 2004, 101, 13885–13890. [CrossRef] [PubMed]

103. Hosen, N.; Sonoda, Y.; Oji, Y.; Kimura, T.; Minamiguchi, H.; Tamaki, H.; Kawakami, M.; Hasegawa, K.; et al. Very low frequencies of human normal CD34+ haematopoietic progenitor cells express the Wilms’ tumour gene WT1 at levels similar to those in leukaemia cells. *Br. J. Haematol.* 2002, 116, 409–420. [CrossRef] [PubMed]

104. Bae, J.; Smith, R.; Daley, J.; Mikkola, N.; Tai, Y.T.; Anderson, K.C.; Munshi, N.C. Myeloma-specific multiple peptides able to generate cytotoxic T lymphocytes: A potential therapeutic application in multiple myeloma and other plasma cell disorders. *Clin. Cancer Res.* 2012, 18, 4850–4860. [CrossRef] [PubMed]

105. Nguyen-Hoai, T.; Baldehofer, G.; Ahmed, M.S.; Pham-Duc, M.; Gries, M.; Lipp, M.; Dörken, B.; Pezzutto, A.; Westermann, J. CCL19 (ELC) improves TH1-polarized immune responses and protective immunity in a murine Her2/neu DNA vaccination model. *J. Gene Med.* 2012, 14, 128–137. [CrossRef] [PubMed]
108. Anderson, M.W.; Zhao, S.; Freud, A.G.; Czerwinski, D.K.; Kohrt, H.; Alizadeh, A.A.; Houot, R.; Azambuja, D.; Biasoli, I.; Morais, J.C.; et al. CD137 is expressed in follicular dendritic cell tumors and in classical Hodgkin and T-cell lymphomas: Diagnostic and therapeutic implications. Am. J. Pathol. 2012, 181, 795–803. [CrossRef] [PubMed]

109. Nierkens, S.; Tel, J.; Janssen, E.; Adema, G.J. Antigen cross-presentation by dendritic cell subsets: One general or all sergeants? Trends Immunol. 2013, 34, 361–370. [CrossRef] [PubMed]

110. Sabado, R.L.; Bhardwaj, N. Dendritic cell immunotherapy. Ann. N. Y. Acad. Sci. 2013, 1284, 31–45. [CrossRef] [PubMed]

111. Bullinger, L.; Schlenk, R.F.; Götz, M.; Botzenhardt, U.; Hofmann, S.; Russ, A.C.; Babiak, A.; Zhang, L.; Schneider, V.; Döhner, H.; et al. PRAME-induced inhibition of retinoic acid receptor signaling-mediated differentiation—A possible target for ATRA response in AML without t(15;17). Clin. Cancer Res. 2013, 19, 2562–2571. [CrossRef]

112. Paydas, S.; Tanriverdi, K.; Yavuz, S.; Disel, U.; Baslamisli, F.; Burgut, R. PRAME mRNA levels in cases with acute leukemia: Clinical importance and future prospects. Am. J. Hematol. 2005, 79, 257–261. [CrossRef]

113. Greiner, J.; Bullinger, L.; Guinn, B.A.; Dohner, H.; Schmitt, M. Leukemia-associated antigens are critical for the proliferation of acute myeloid leukemia cells. Clin. Cancer Res. 2008, 14, 7161–7166. [CrossRef]

114. Yao, Y.; Zhou, J.; Wang, L.; Gao, X.; Ning, Q.; Jiang, M.; Wang, J.; Yu, L. Increased PRAME-specific CTL killing of acute myeloid leukemia cells by either a novel histone deacetylase inhibitor chidamide alone or combined treatment with decitabine. PLoS ONE 2013, 8, e70522. [CrossRef]

115. Yang, H.; Rosove, M.H.; Figlin, R.A. Tumor lysis syndrome occurring after the administration of rituximab in lymphoproliferative disorders: High-grade non-Hodgkin’s lymphoma and chronic lymphocytic leukemia. Am. J. Hematol. 1999, 62, 247–250. [CrossRef]

116. Peng, Z. Current status of gendicine in China: Recombinant human Ad-p53 agent for treatment of cancers. Expert Rev. Anticancer Ther. 2012, 12, 236–243. [CrossRef] [PubMed]

117. Bose, A.; Lowe, D.B.; Rao, A.; Storkus, W.J. Combined vaccine+axitinib therapy yields superior antitumor efficacy in a murine melanoma model. Melanoma Res. 2012, 22, 236–243. [CrossRef] [PubMed]

118. Karan, D.; Van Veldhuizen, P. Combination immunotherapy with prostate GVAX and ipilimumab: Safety and toxicity. Immunotherapy 2012, 4, 577–580. [CrossRef] [PubMed]

119. Ciccarese, C.; Nobili, E.; Grilli, D.; Casolari, L.; Rihawi, K.; Gelsomino, F.; Tortora, G.; Massari, F. The safety and efficacy of enzalutamide in the treatment of advanced prostate cancer. Expert Rev. Anticancer Ther. 2016, 16, 681–696. [CrossRef] [PubMed]

120. Daniels, G.A.; McKinney, M.; Ongkoko, W.; Wang-Rodriguez, J.; Sakamoto, K.; Elliott, R.L.; Head, J.F. A phase 1 clinical trial of a PSA/IL-2/GM-CSF containing prostate cancer vaccine in PSA defined biochemical recurrent prostate cancer patients. J. Clin. Oncol. 2016, 34, e14584. [CrossRef]

121. Gattinoni, L.; Finkelstein, S.E.; Klebanoff, C.A.; Antony, P.A.; Palmer, D.C.; Spiess, P.J.; Hwang, L.N.; Yu, Z.; Wrezinska, C.; Heimann, D.M.; et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. J. Exp. Med. 2005, 202, 907–912. [CrossRef] [PubMed]

122. Klebanoff, C.A.; Gattinoni, L.; Palmer, D.C.; Muranski, P.; Ji, Y.; Hinrichs, C.S.; Borman, Z.A.; Kerkar, S.P.; Scott, C.D.; Finkelstein, S.E.; et al. Determinants of successful CD8+ T-cell adoptive immunotherapy for large established tumors in mice. Clin. Cancer Res. 2011, 17, 5343–5352. [CrossRef]

123. Rafiq, S.; Purdon, T.J.; Daniyan, A.F.; Koneru, M.; Ao, T.; Liu, C.; Scheinberg, D.A.; Brentjens, R.J. Optimized T-cell receptor-mimic chimeric antigen receptor T cells directed toward the intracellular Wilms Tumor 1 antigen. Leukemia 2017, 31, 1788–1797. [CrossRef]

124. Smiths, E.L.; Lee, C.; Hardwick, N.; Brooks, S.; Van Tendeloo, V.F.; Orchard, K.; Guin, B.A. Clinical evaluation of cellular immunotherapy in acute myeloid leukaemia. Cancer Immunol. Immunother. 2011, 60, 757–769. [CrossRef]

125. Keenan, B.P.; Jaffee, E.M. Whole cell vaccines—past progress and future strategies. Semin. Oncol. 2012, 39, 267–286. [CrossRef]

126. Curiel, T.J. Immunotherapy: A useful strategy to help combat multidrug resistance. Drug Resist. Updat. 2012, 15, 106–113. [CrossRef] [PubMed]

127. Palucka, K.; Banchereau, J. Cancer immunotherapy via dendritic cells. Nat. Rev. Cancer 2012, 12, 265–277. [CrossRef] [PubMed]
128. Guo, Z.S.; Liu, Z.; Bartlett, D.L. Oncolytic Immunotherapy: Dying the Right Way is a Key to Eliciting Potent Antitumor Immunity. *Front. Oncol.* 2014, 4, 74. [CrossRef] [PubMed]

129. Goldberg, M.S. Immunoengineering: How nanotechnology can enhance cancer immunotherapy. *Cell* 2015, 161, 201–204. [CrossRef]

130. Mellman, I.; Coukos, G.; Dranoff, G. Cancer immunotherapy comes of age. *Nature* 2011, 480, 480–489. [CrossRef]

131. Liu, F.; Pinz, K.; Ma, Y.; Wada, M.; Chen, K.; Ma, G.; Su, Y.; Zhang, S.; He, G.; Ma, Y. First-in-human CLL1-CD33 compound CAR Tcells as a two-pronged approach for the treatment of refractory acute myeloid leukemia. In Proceedings of the 23rd Congress of the European Hematology Association, Stockholm, Sweden, 14–17 June 2018.

132. Liegel, J.; Rosenblatt, J.; Stone, R.M.; McMasters, M.; Levine, J.D.; Nahas, M.; Joyce, R.M.; Jain, S.; DeAngelo, D.J.; Garcia, J.S.; et al. Phase I/Ib Trial of the MUC1 Inhibitor GO-203-2C Alone and in Combination with Decitabine for Acute Myeloid Leukemia. *Blood* 2017, 130, 2659.

133. Kocak, E.; Lute, K.; Chang, X.; May, K.F.; Exten, K.R.; Zhang, H.; Abdessalam, S.F.; Lehman, A.M.; Jarjoura, D.; Sen, D.; Wirth, E.D.; 3rd; et al. Immune responses and long-term disease recurrence status after telomerase-based dendritic cell immunotherapy in patients with acute myeloid leukemia. *Cancer* 2017, 123, 3061–3072. [CrossRef]

134. Kocak, E.; Lute, K.; Chang, X.; May, K.F.; Exten, K.R.; Zhang, H.; Abdessalam, S.F.; Lehman, A.M.; Jarjoura, D.; Zheng, P.; et al. Combination therapy with anti-CTL antigen-4 and anti-4-1BB antibodies enhances cancer immunity and reduces autoimmunity. *Cancer Res.* 2006, 66, 7276–7284. [CrossRef]

135. Chang, C.H.; Wang, Y.; Zalath, M.; Liu, D.; Cardillo, T.M.; Goldenberg, D.M. Combining ABCG2 Inhibitors with IMMU-132, an Anti-Trop-2 Antibody Conjugate of SN-38, Overcomes Resistance to SN-38 in Breast and Gastric Cancers. *Mol. Cancer Ther.* 2016, 15, 1910–1919. [CrossRef]

136. Fanale, M.; Samaniego, F.; et al. Safety and activity of PD1 blockade by pidilizumab in combination with pembrolizumab for patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J. Clin. Oncol.* 2013, 31, 2849–2853. [CrossRef]

137. Roberts, C.; Kaszewska, B.; Schachter, J.; Rutkowska, P.; Mackiewicz, A.; Stojakowski, D.; Lichtenstein, M.; Dummer, R.; Grange, F.; Mortier, L.; et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N. Engl. J. Med.* 2015, 372, 30–39. [CrossRef]

138. Zukin, M.; Barrios, C.H.; Pereira, J.R.; Ribeiro, R.E.A.; Beato, C.A.; do Nascimento, Y.N.; Murad, A.; Franke, F.A.; Precivale, M.; Araujo, L.H.; et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J. Clin. Oncol.* 2013, 31, 2849–2853. [CrossRef]

139. Westin, J.R.; Chu, F.; Zhang, M.; Fayad, L.E.; Kwak, L.W.; Fowler, N.; Romaguera, J.; Hagemeister, F.; Fanale, M.; Samaniego, F.; et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: A single group, open-label, phase 2 trial. *Lancet Oncol.* 2014, 15, 69–77. [CrossRef]

140. Von Hoff, D.D.; Ervin, T.; Arena, F.P.; Chiorean, E.G.; Infante, J.; Moore, M.; Seay, T.; Tjulandin, S.A.; Ma, W.W.; Saleh, M.N.; et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl. J. Med.* 2013, 369, 1691–1703. [CrossRef]

141. Larkin, J.; Hodi, F.S.; Wolchok, J.D. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N. Engl. J. Med.* 2015, 373, 1270–1271. [CrossRef]
146. Leath, C.A.; Straughn, J.M. Chemotherapy for advanced and recurrent cervical carcinoma: Results from cooperative group trials. *Gynecol. Oncol.* 2013, 129, 251–257. [CrossRef]

147. Ducreux, M.; Adenis, A.; Pignon, J.P.; François, E.; Chauffert, B.; Ichanté, J.L.; Boucher, E.; Ychou, M.; Pierga, J.Y.; Montoto-Grillot, C.; et al. Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: Final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). *Eur. J. Cancer* 2013, 49, 1236–1245. [CrossRef]

148. Jurcic, J.G. Novel Immunotherapy Approaches in AML: Focus on Monoclonal Antibodies. *Clin. Lymphoma Myeloma Leuk.* 2017, 17, S115–S119. [CrossRef]

149. Zuber, J.; Shi, J.; Wang, E.; Rappaport, A.R.; Herrmann, H.; Sison, E.A.; Magoon, D.; Qi, J.; Blatt, K.; Wunderlich, M.; et al. RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. *Nature* 2011, 478, 524–528. [CrossRef]

150. Laing, A.A.; Harrison, C.J.; Gibson, B.E.S.; Keeshan, K. Unlocking the potential of anti-CD33 therapy in adult and childhood acute myeloid leukemia. *Exp. Hematol.* 2017, 54, 40–50. [CrossRef]