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Review Article

Protein Arginine Methyltransferase 5 (PRMT5) Inhibitors in Oncology Clinical Trials: A review

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ABSTRACT

Protein arginine methyltransferase 5 (PRMT5) inhibitors are a new class of antineoplastic agents showing promising preliminary clinical efficacy. Targeting an enzyme involved in a wide array of cellular and transcriptional pro-oncogenic processes, this class offers multifaceted tumor-suppressive effects. Partial response has been seen in adenoid cystic carcinoma from both GSK3326595 and JNJ-64619178, with four cases of stable disease seen with PRT543. Highly significant is a durable complete response in isocitrate dehydrogenase 1-mutated glioblastoma multiforme with PRT811. Both alone and in combination with existing chemotherapies and immunotherapies, this class shows promising preliminary data, particularly in cancers with splicing mutations and DNA damage repair deficiencies. Further studies are warranted, and there are clinical trials to come whose data will be telling of the efficacy of PRMT5 inhibitors in both hematologic and solid malignancies. The aim of this study is to compile available results of PRMT5 inhibitors in oncology clinical trials.

Keywords: protein arginine methyltransferase, splicing, histone, cancer, clinical trial, review, PRMT5

INTRODUCTION

The protein arginine methyltransferase (PRMT) family of proteins function as posttranslational modifiers by methylating arginine residues. PRMT5 is a type II PRMT that catalyzes the formation of ω-N^G, N^G–symmetric dimethylarginine (sDMA).[1] PRMT5 is the most active of only two PRMT enzymes that catalyze formation of sDMA, the other being PRMT9, making sDMA an attractive molecule for measuring targeted pharmaceutical effects on the catalytic activity of PRMT5.[2] PRMT5 forms a homotetramer that joins with methylosome protein 50/*WD repeat domain 77* (MEP50/*WDR77*) in a highly active hetero-octameric complex, PRMT5/MEP50, which exhibits high affinity for arginine residues flanked by glycines.[3] PRMT5 functions as a transcriptional corepressor via histone methylation and has proved vital for RNA splicing in its role to methylate Sm proteins for appropriate assembly into small nuclear ribonucleoproteins (SnRNPs).[4]

PRMT5 methylates histones H4R3me2s and H3R8me2s to repress gene expression. It also methylates H3R2me2s to prevent recruitment of repressor complexes and enhances binding of the WDR5 transcriptional coactivator. PRMT5 substrates and downstream protein effects range from oncogenic to tumor suppressive by regulation of the expression of numerous proteins known to drive or interfere with oncogenesis, including TP53, FOXP1, FOXP3, SLC7A11, c-Myc, BCL6, BAX, EGFR, and TDP1, as shown in Figures 1 and 2.[5] PRMT5 is essential in its role to maintain embryonic stem cell pluripotency via H2R3me2s methylation to repress differentiation genes. Not surprisingly, PRMT5 knockdown mice die early in embryogenesis.[6] Furthermore, hematopoietic stem cells require PRMT5 for maintenance during quiescence and progenitor proliferation.[7] Along with histone regulation, PRMT5 has many regulatory targets ranging from transcription (Fig. 2) to cell signaling and assembly of snRNPs and other splicing machinery.[5]

PRMT5 expression is upregulated epigenetically, and its increased expression is directly linked to poor prognosis in many malignancies.[8,9] Expression levels have been linked to large tumor size and advanced tumor grade in lung and breast cancers, hepatocellular carcinoma (HCC), and glioblastoma multiforme (GBM).[10–13] PRMT5 association with lymph node metastasis has been shown in lung, breast, gastric, head and neck, colorectal, and epithelial ovarian cancers as well as urothelial carcinoma of the bladder.[14–20] In addition to oncogenesis, PRMT5 expression has been shown to promote drug resistance. For example, in breast

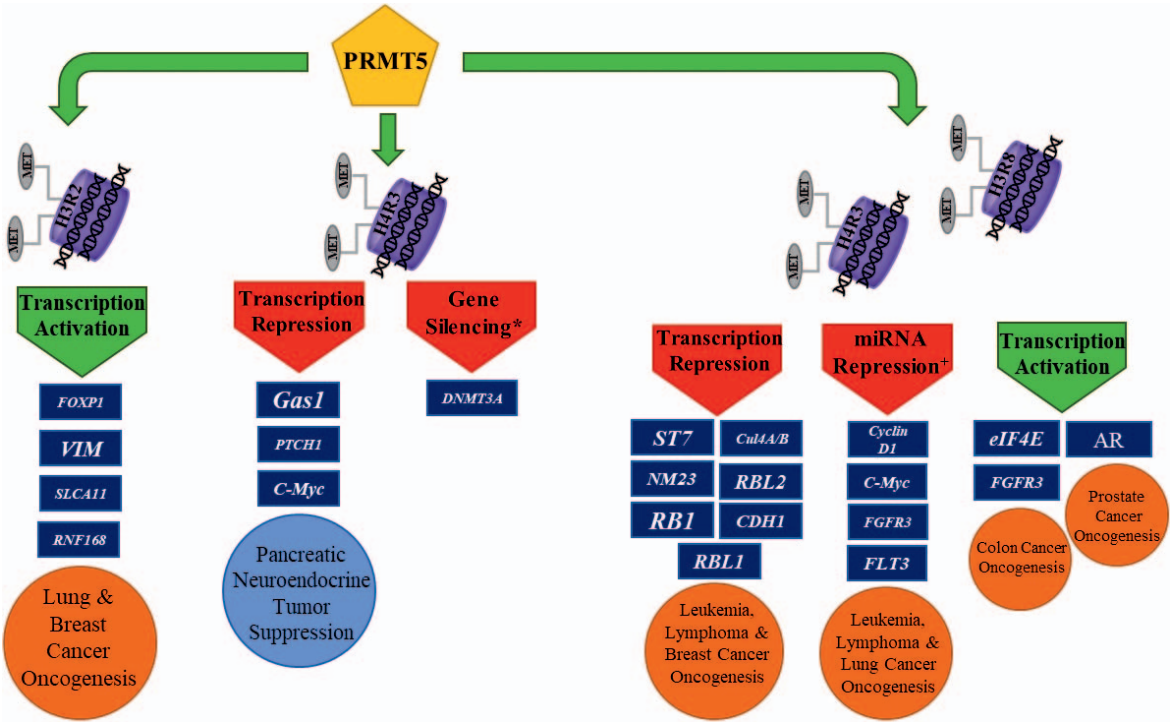

Figure 1. Downstream effects of PRMT5 histone methylation. *: PRMT5 recruits DNMT3A for adjacent CpG dinucleotide methylation on H4R3 to induce gene silencing. +: tumor suppressor miRNAs. AR: androgen receptor; MET: methyltransferase; miRNA: mitochondrial RNA.

cancer, PRMT5 promotes doxorubicin resistance via regulation of OCT4/A, c-MYC, and KLF4.[21]

In leukemia and lymphoma, PRMT5 propels tumor progression via MYC splicing regulation, cooperation with the cyclin D1 oncogenic mutant D1T286A, and miR-29b repression via Sp1 interaction leading to increased expression of mutant FLT3. [22–24] Neuroblastomas can be propagated by MYCN expression, driven by PRMT5 activity.[25] Both lung adenocarcinoma and squamous cell carcinoma (SCC) express increased PRMT5/MEP50, which is directly related to their phenotypic invasiveness, possibly also related to TGFβ activity.[26] In prostate cancer, PRMT5 promotes androgen receptor expression and function by acting as a cofactor for the transcription factors Sp1 and Brg1, as well as a cofactor for the androgen receptor itself.[27] PRMT5 further promotes prostate cancer formation via interaction with ERG in TMPRSS2:ERG translocated cells, an ETS transcription factor.[28]

Preclinical studies of oral PRMT5 inhibitors have shown significant antitumor activity across a wide variety of tumor types in mouse xenograft models. In mantle cell lymphoma xenograft mouse models treated with YQ36286, 95% tumor growth inhibition was observed at 21 days of dosing. Ibrutinib-resistant mantle cell lymphoma patient-derived xenograft mouse models treated with PRT382 exhibited significantly decreased disease burden and increased survival as compared with xenograft mice treated with ibrutinib therapy. Ex vivo analysis showed increased BCL2, MYC, and pAKT/pERK in the xenograft mice MCL cells treated with PRT382.[29] AMI-1 was designed as a PRMT1 inhibitor found to have more significant PRMT5 inhibition. AMI-1 was studied in cervical cancer xenograft mouse models, which showed 52% tumor volume and 53% tumor weight reductions as compared with controls.[30] LLY-283, an orthogonal-acting PRMT5 inhibitor, was tested in a mouse model of GBM and showed brain/cerebrospinal fluid favoring distribution, with double concentrations found in brain samples versus plasma.[31] Mice treated with LLY-283 lived for an average 7 days longer than their vehicle-treated counterparts whose average life span postimplantation was 30 days. Further tumor tissue showed undetectable sDMA via western blot analysis versus high-intensity signal in the control group.[31] EPZ015666, an oral PRMT5 inhibitor, was studied in triple negative breast cancer xenograft murine models, showing 39% tumor growth inhibition as compared with untreated controls.[32]

At least six oral PRMT5 inhibitors have been investigated, with few adverse effects in preclinical studies of murine xenograft models. YQ36286 is a PRMT5 inhibitor with broad activity against other histone methyltransferases that shows no reported adverse effects in a mouse model of mantle cell lymphoma.[33] Similarly, in a study with PRT382, no adverse effects on study animals were reported.[29] In a trial of AMI-1 in a cervical cancer murine model, no difference in mouse body weight between the two study groups was observed.[30] LLY-238 was studied in a mouse model of GBM, and toxicity of significant weight loss, >20% body weight, was noted when administered every other day, and less (<10% body weight) when administered consecutively for 3

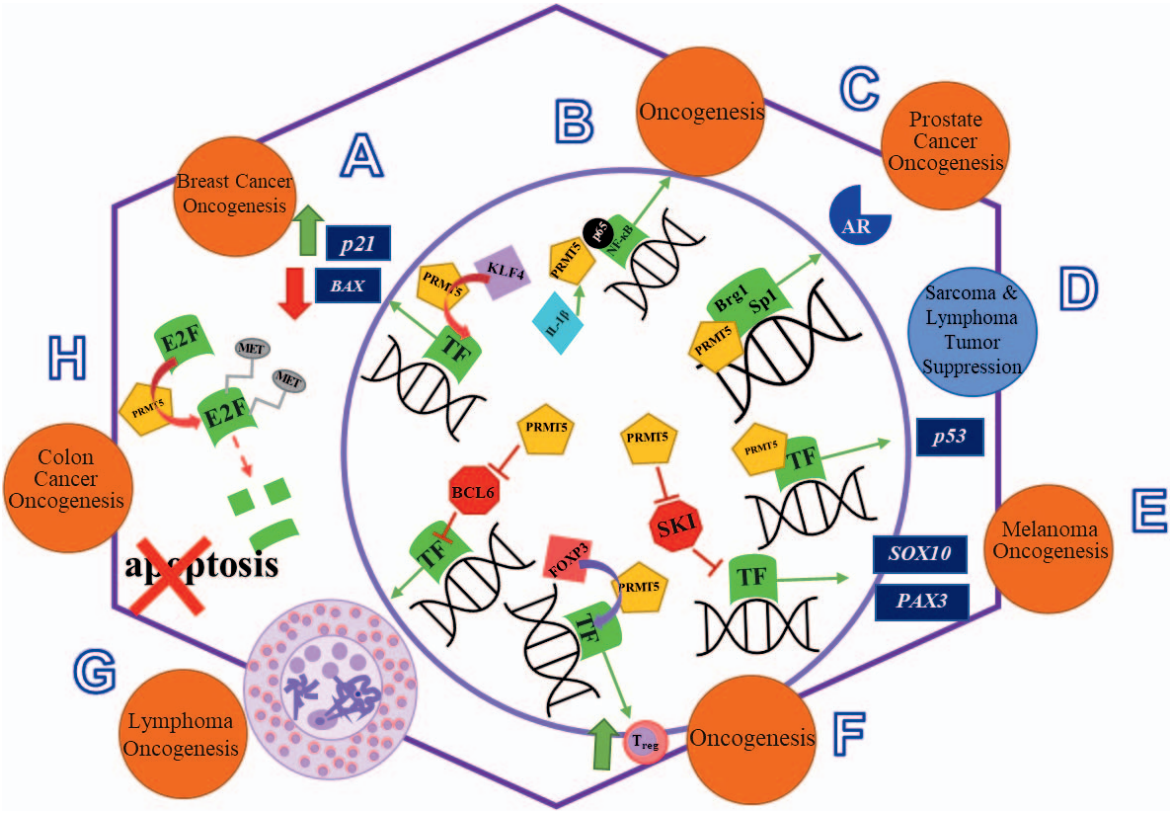

Figure 2. Examples of PRMT5's role in transcription and oncogenesis. Content based on Kim and Ronai.[5]

Large hexagon: cell wall; large circle: cell nucleus.

(A) Methylation of KLF4 by PRMT5 prolongs the protein half-life leading to p21 and Cip1 and repression of BAX, thus promoting breast cancer oncogenesis. (B) PRMT5 methylates the p65 subunit of NF-κB in an IL-1β–dependent manner, driving tumorigenesis. (C) Sp1, the primary transcription factor responsible for androgen receptor (AR) transcription, recruits PRMT5 to the AR promoter to form a complex with Brg1 to promote AR transcription. (D) PRMT5 promotes transcription of p52, which in studies has been determined to cause cell cycle arrest and apoptosis in sarcoma and lymphoma. (E) PRMT5 inhibits SKI repression of recruitment to target promoter, activating SKI target genes *SOX10* and *PAX3*, which have been shown to be oncogenic in melanoma. (F) PRMT5 enhances FOXP3 activity, further enhancing regulatory T cell (T_{reg}) function. (G) PRMT5 enhances BCL6 repressor activity and target genes, leading to germinal center formation (purple circle) and proliferation of malignant lymphoma cells. (H) PRMT5 decreases E2F1 protein half-life, promoting cell growth and inhibiting apoptosis as studied in colon cancer.

BCL6: B-cell lymphoma 6 protein; BRG1: SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; E2F: E2F transcription factor; FOXP3: forkhead box P3; IL-1β: interleukin 1 beta; MET: methyltransferase; NF-κB: nuclear factor kappa B; SKI: avian sarcoma viral oncogene homolog; SP1: specificity protein 1; TF: transcription factor.

days followed by no dosing for 4 days.[31] HLCL-61, a small molecule inhibitor of PRMT5, was tested in an acute myeloid leukemia (AML) murine model, and no adverse effects were reported.[34] EPZ015666 was studied in triple negative breast cancer xenograft murine models, showing 39% tumor growth inhibition without observed toxicities, specifically, no mouse weight loss or death.[32]

This clinical review aims to provide a concise compilation of the currently available results of clinical trials of PRMT5 inhibitors (see Table 1).

PRMT5 INHIBITOR CLINICAL TRIALS IN SOLID TUMORS AND HEMATOLOGIC MALIGNANCIES

AMG 193

AMG 193 (Amgen, Thousand Oaks, CA, USA) is an oral MTA cooperative PRMT5 inhibitor. A phase I monotherapy dose-escalation trial began recruiting February, 2022. The trial design includes a part 2b in which AMG 193 will be administered in combination with intravenous docetaxel to patients with methylthioadenosine phosphorylase-null (MTAP-null) non–small cell lung cancer (NSCLC).[35]

GSK3326595

GSK3326595 (previously EPZ015666; GlaxoSmithKline, Brentford, London, UK) is a selective small molecule inhibitor of PRMT5 with potential antiproliferative and antineoplastic activity.[36] One of its mechanisms is inhibiting cellular mRNA splicing to suppress tumor suppressor function. Two clinical trials are evaluating GSK3326595.[37–39] In I first trial, for patients with solid tumor cancers, the phase I portion enrolled 54 patients, primarily adenoid cystic carcinoma (ACC; n = 14), colorectal (n=9), and breast (n=3) cancers. The doses

Table 1. Protein arginine methyltransferase 5 inhibitor trials

Drug Name	Trial Phase	Tumor Type	MTD/RP2D	Dose-Limiting Toxicities	Terminal Half-Life	Number of Patients	Antitumor Activity	Biomarkers Examined
AMG 193+/− Docetaxel[35]	I	Advanced MTAP-null solid tumors	NA	NA	NA	Not yet recruiting	NA	NA
GSK3326595+/− Pembrolizumab[36–38]	I	Advanced or recurrent solid tumors and non-Hodgkin's lymphoma	400 mg QD	Thrombocytopenia, anemia, neutropenia, fatigue	NA	54	PR: 1 patient with HPV+ cervical cancer and 3 patients with ACC SD: bladder cancer, other malignancies not further defined	Plasma and tumor SDMA
GSK3326595+/− 5-azacitidine[39,40]	I/II	Refractory MDS, CMML, AML	NA	NA	NA	Not yet recruiting	NA	NA
GSK3326595[41]	II	Early stage HR+ breast cancer	NA	NA	NA	Not yet recruiting	NA	NA
JNJ-64619178[42–44]	Ia	Advanced solid tumors and non-Hodgkin's lymphoma	1.5 mg 14 days on/7 days off and 1 mg QD	Thrombocytopenia, anemia, neutropenia	NA	54	PR: one patient with ACC SD: 13% of patients enrolled including ACC, prostate cancer, and salivary cancer	Plasma SDMA
PF-06939999[45,46]	I	Advanced or metastatic NSCLC, HNSCC, esophageal cancer, endometrial cancer, cervical cancer, and bladder cancer	6 mg QD	Thrombocytopenia, anemia, neutropenia	NA	28	PR: 1 patient with HNSCC, 1 patient with NSCLC	Plasma SDMA
PRT543[47,48]	I	Advanced solid tumors and hematologic malignancies	45 mg /5× per week	Thrombocytopenia, anemia	NA	49	Durable CR: 1 patient with HRD+ ovarian cancer SD: 4 patients with ACC and 1 patient with uveal melanoma	Plasma SDMA
PRT811[49,50]	I	Advanced cancers and high-grade gliomas that have exhausted available treatment options	600 mg QD	Thrombocytopenia	5.8 h	45	Durable CR: 1 patient with IDH1 mutated GBM PR: 1 patient with SF3B1 mutant uveal melanoma, 47% decreased tumor burden, and 1 patient with triple negative breast cancer, 27% decreased tumor burden SD: one patient with SF3B1 mutant uveal melanoma, 25% decrease of tumor burden	Plasma SDMA

ACC: adenoid cystic carcinoma; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR: complete response; DLTs: dose-limiting toxicities; GBM: glioblastoma multiforme; HNSCC: head and neck squamous cell carcinoma; HPV: human papillomavirus; HRD: homologous recombination deficiency; IDH1: isocitrate dehydrogenase 1; MDS: myelodysplastic syndrome; MTAP: methylthioadenosine phosphorylase; MTD: maximum tolerated dose; NA: not available; NSCLC: non-small cell lung cancer; PR: partial response; QD: daily; RP2D: recommended phase II dose; SD: stable disease; SDMA: symmetric dimethylarginine; SF3B1: splicing factor 3b subunit 1.

investigated ranged from 12.5 to 600 mg once daily (QD) and 50 to 200 mg twice daily (BID), and the RP2D was determined to be 400 mg QD. Eighty-nine percent ($n=48$) of patients experienced treatment-related adverse events (AEs), the most common of which included fatigue ($n=21$), anemia ($n=17$), nausea ($n=17$), alopecia ($n=15$), and dysgeusia ($n=14$). Treatment-related gr 3/4 AEs were observed, including anemia ($n=8$), thrombocytopenia ($n=4$), neutropenia ($n=4$), and fatigue ($n=4$). Forty-one percent ($n=22$) of patients required at least one dose reduction. sMDA evaluation demonstrated target engagement. Peak concentration and area under the curve (AUC) were dose dependent. Partial response (PR) was achieved in human papillomavirus (HPV)+ cervical cancer (1/1 subject) and ACC (3/14 subjects). Stable disease was demonstrated in bladder cancer and other tumors but was not further described in the published abstract.[38] The phase II portion of the trial is ongoing and has not yet been presented or published. A second study, a phase I/II safety and clinical activity trial for relapsed and/or refractory myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and hypoproliferative AML from MDS is ongoing.[39,40] The phase I/II has a part 2: part 2a will be a randomized control against standard of care, and 2b will investigate safety and efficacy of 5-azacitidine in combination with GSK3326595. Phase 2c will enroll patients with refractory or relapsed AML with mutant pre-mRNA splicing machinery to be treated with GSK3326595 alone. The rationale for this trial includes the observation that up to 40% of patients with MDS and up to 60% of patients with CMML harbor mutations in mRNA splicing.[40] A third trial, which is not yet recruiting, is a phase II, window of opportunity trial for early stage breast cancer.[41]

JNJ-64619178

JNJ-64619178 (Janssen Research & Development, Raritan, NJ, USA) is an irreversible PRMT5 inhibitor that binds to the S-adenosylmethionine and guanidino-binding pockets of the PRMT5/MEP50, which inhibits arginine residue methylation of histones H2A, H3, and H4 to decrease cellular proliferation.[42] A phase I, first-in-human, open-label, dose-escalation study was initiated in July 2018 and is currently ongoing.[43] In a preliminary analysis presented at ESMO 2020, 54 participants had enrolled, with various advanced solid tumors, including ACC, prostate cancer, and uveal melanoma, along with non-Hodgkin lymphoma. Patients received the oral capsule in 21-day cycles, either QD or 14 days on/7 days off (14/7). The range of doses administered included 1–2 mg for the QD and 0.5–4 mg for the 14/7 regimen. The only dose-limiting toxicity (DLT) was thrombocytopenia, observed at 2 mg QD and at 3–4 mg 14/7. Other grade 3/4 treatment-related adverse events (TRAEs) in addition to thrombocytopenia (20%) were anemia (17%) and neutropenia (6%). Grade 1/2 TRAEs also included nausea (39%), fatigue (32%), dysgeusia (30%), asthenia (24%), and diarrhea (20%). Thirty patients (i.e., >50%) experienced dose interruptions or reductions due to AEs. Plasma sDMA was measured and demonstrated target engagement. Pharmacokinetics was linear. Stable disease for >6 months was noted in 13% of participants, including those with ACC, prostate, and salivary cancers. One participant with ACC achieved PR. Two different recommended phase II doses were determined, including 1 mg QD and 1.5 mg 14 days on / 7 days off [44]

PF-06939999

PF-06939999 (Pfizer, New York, NY, USA) is another oral PRMT5 inhibitor whose complete mechanism has not been fully elucidated. Data from the phase I dose-escalation study in 28 participants show promising results.[45,46] Enrollees had malignancies with potential frequent splicing factor mutations, such as endometrial, urothelial, cervical, and esophageal cancers, as well as NSCLC and head and neck squamous cell carcinoma (HNSCC). The 28-day cycles of continuous QD or BID dosing ranged from 0.5 to 12 mg total per day. The maximum cycles completed were 13, with the fewest being 1. Seventeen percent ($n=4$) experienced DLTs of thrombocytopenia ($n=2$; 6 mg BID), anemia ($n=1$; 8 mg QD), and neutropenia ($n=1$; 6 mg QD). Other non-dose-limiting AEs, experienced by 24 of 28 patients, included anemia ($n=12$), thrombocytopenia ($n=9$), dysgeusia ($n=8$), fatigue ($n=8$), and nausea ($n=8$). Plasma sDMA was measured as a marker of target engagement.[45] Two patients experienced confirmed PR in NSCLC and HNSCC. Pfizer is currently enrolling patients for part 2, dose expansion, at 6 mg QD with NSCLC, HNSCC, and urothelial cancer.[45]

PRT543

PRT543 (Prelude Therapeutics, Wilmington, DE, USA) selectively binds PRMT5, inhibiting its methyltransferase activity.[47] An ongoing phase I dose-escalation open-label study in August 2021 preliminarily provided promising results from 49 participants who had a variety of 18 solid tumors and lymphoma.[48] Target engagement was confirmed by serum sDMA. Dosing was 45 mg orally five times weekly. The highest response achieved was durable complete response (CR) for over 18 months in homologous recombination deficiency ovarian cancer; the patient remains on treatment. Stable disease was noted in five patients, four of whom have ACC and one uveal melanoma. TRAEs were thrombocytopenia ($n=13$) and anemia ($n=6$), necessitating dose interruptions in 27% ($n=13$), dose reductions in 22% ($n=11$), but discontinuation in only 4% ($n=2$) of participants.[49] The phase I dose escalation and expansion study remains ongoing and continues to enroll patients with biomarker-selected solid tumors.[49]

PRT811

PRT811 (Prelude Therapeutics, Wilmington, DE, USA) is a selective PRMT5 inhibitor that crosses the

blood–brain barrier.[49] Forty-five participants with high-grade gliomas ($n = 18$), either glioblastoma multiforme ($n = 17$) or anaplastic astrocytoma ($n = 1$), as well as 27 patients with advance solid tumors, including ACC ($n = 4$), uveal melanoma ($n = 4$), acinar cell pancreatic cancer ($n = 1$), and large cell neuroendocrine lung cancer ($n = 1$), have been enrolled in the ongoing phase I, dose-escalation study. Preliminary results were reported at the AACR-NCI-EORTC conference in 2021.[50] Dosing ranged from 15 to 800 mg PO in 21-day cycles in either as 2 weeks on/1 week off or continuous daily dosing. Patients with GBM rarely experienced AEs, with only one showing grade 3 thrombocytopenia. Of the whole cohort, 69% ($n = 31$) experienced AEs such as nausea ($n = 17$), vomiting ($n = 12$), fatigue ($n = 9$), thrombocytopenia ($n = 8$), anemia ($n = 7$), anorexia ($n = 6$), diarrhea ($n = 5$), hypophosphatemia ($n = 4$), pruritis ($n = 3$), and weight loss ($n = 3$). No deaths were reported. Only 13% experienced treatment interruptions, 4% dose reductions, and 3% discontinuations due to AEs. T_{max} was 1 to 3 h and $T_{1/2}$ was 5.8 h, showing linear pharmacokinetics. PRT811 shows dose-dependent inhibition of serum sDMA and intron retention in PRMT5-regulated transcripts. Durable CR was seen in GBM ($n = 1$) with isocitrate dehydrogenase 1 (IDH1) mutation. PRT811 signals particular effectiveness in uveal melanoma with splicing mutation in SF3B1: one patient achieved SD with 25% tumor regression and another achieved PR with 47% decrease in primary target lesion size. At the 800 mg QD dosing, 27% target lesion decrease of triple negative breast cancer ($n = 1$) was observed.[50]

PRECLINICAL COMBINATION STRATEGIES UNDER INVESTIGATION

Combination strategies with PRMT5 inhibitors appear promising. The upcoming trial of AMG 193 includes a part 2b arm for patients with MTAP-null NSCLC in combination with docetaxel. GSK3326595 has opened two trials in separate combinations with pembrolizumab and 5-azacitidine.

Multiple combinations have been investigated in the preclinical setting. A mouse model of ibrutinib-resistant mantle cell lymphoma proved sensitive to venetoclax, a BCL-2 inhibitor, in combination with PRT543 and venetoclax/PRT382 without evidence of toxicities in either combination.[51] In a cellular study of A549 and DMS 53 lung cancer cells, a PRMT5 inhibitor, arginine methyltransferase inhibitor 1 (AMI-1), in combination with cisplatin, induced significantly higher G1 cell cycle arrest than did either therapy alone.[52] GSK3326595 combined with an AKT inhibitor, tricribrine, showed synergistic antineoplastic activity in diffuse large B-cell lymphoma with ABC, GCB, and MYC-BCL-2 double-hit cell lines as compared with either therapy alone.[53] EPZ015666 in combination with erlotinib, an EGFR inhibitor, showed additive effects against MDA-MB-468, BT20, and HCC70 breast cancer cells as compared with either therapy alone.[32] In GBM, mTOR inhibition linearly increases PRMT5 activity, but not mRNA or protein levels. In vitro studies of EPZ015666 with mTORc1/2 inhibition showed synergistic apoptosis and increased cyclin D1 and c-MYC expression. In vivo mouse LN229 xenograft studies again showed significantly increased antitumor activity with 75% growth inhibition as compared with EPZ015666 (30%) and mTORc1/2 inhibition (29%) alone.[54]

In a mouse model of erbB2/neu breast cancer, EPZ004777 in combination with an anti-erbB2-targeted antibody significantly limited regulatory T cell (Treg) tumor infiltration, greater than either therapy alone. It is interesting that EPZ015666 was also explored in this study, and mouse models treated with EPZ015666 showed increased Treg infiltration. The authors suspect this is due to EPZ004777 competitively binding to the S-adenosylmethionine active side of PRMT5, whereas EPZ015666 does not.[55]

In a cellular study of mixed-lineage leukemia with t(9;11) and t(4;11) translocations, combination therapy of PRMT5 with DOT1L inhibitors showed dose-dependent decrease in cell proliferation and impairment of cell cycles, as well as increased cell differentiation and apoptosis.[56] Cytarabine, standard therapy, was studied in combination with DOT1L inhibition, with PRMT5 inhibition, and in concert with both. Cytarabine with both inhibitors showed significantly decreased cell proliferation in one cell line as compared with either therapy in combination with cytarabine. In the second cell line studied, cytarabine plus both inhibitors was comparable to DOT1L inhibition plus cytarabine. It is promising that there are ongoing clinical trials of pinometostat, an intravenous DOT1L inhibitor.[57]

Emerging data suggest a role for PD-1 inhibitor combination with PRMT5 inhibitors. PD-L1 expression is PRMT5 dependent in cervical cancer, as shown in a mouse model. PRMT5 blockade resulted in increased expression of PD-L1 with subsequent increase in CD4+ and CD8+ T cell activity as characterized by IFN-γ, TNF-α, and granzyme B.[58] GSK3326595 was studied in a mouse melanoma (B16 and YUMM1.7 cell tumor allograft) model alone and in combination with anti-PD1 therapy. Combination therapy showed significant decrease in tumor size as compared with PRMT5 inhibitor or anti-PD-1 therapies alone and, similarly, significant increase in survival. This study showed an important role of PRMT5 in melanoma oncogenesis is to reduce surface MHC-I expression, limiting immune recognition. PRMT5 inhibition led to increased expression of MHC-I and tumor cell recognition, making previously PD-1 inhibitor-resistant tumors susceptible to PD-1 inhibition.[59] Their study suggests a promising role for PRMT5 inhibitors in promoting antigen presentation in cold tumors to allow for CD8+ T cell-dependent tumor lysis.

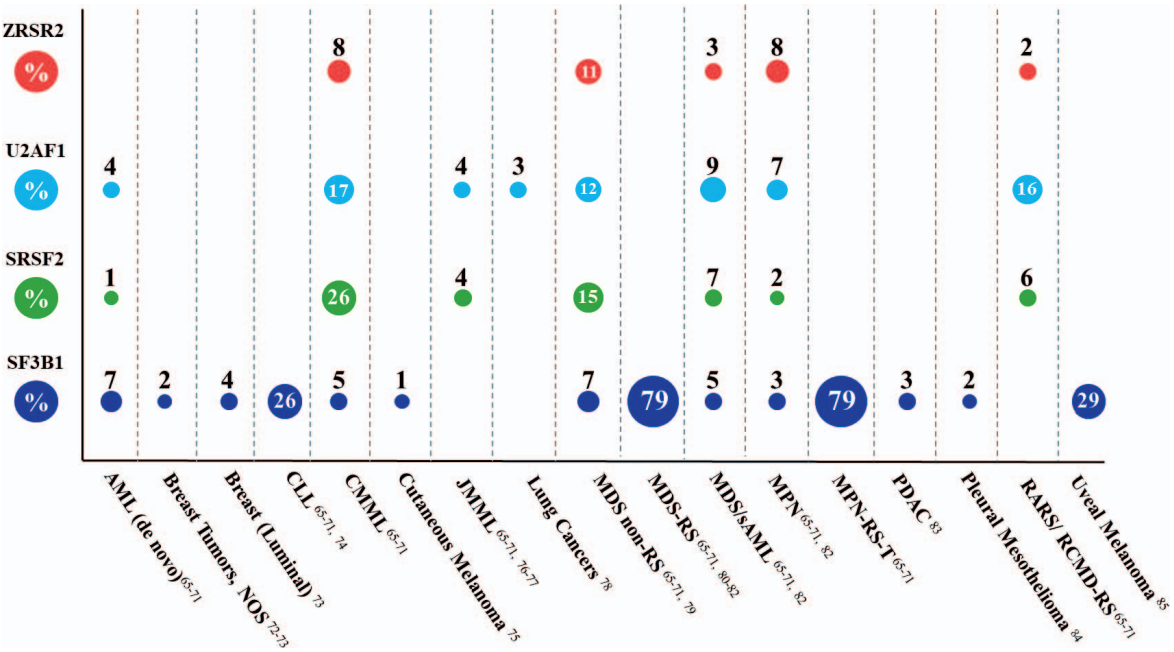

Figure 3. Prevalence of splicing mutations in malignancies. Content based on Anczuków and Krainer.[64]

Bubbles show highest percent prevalence studied of each splicing mutant (y-axis) for each malignancy (x-axis).

ALL: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CMML: chronic myelomonocytic leukemia; JMML: juvenile myelomonocytic leukemia; MDS/sAML: myelodysplastic syndrome with secondary AML; MDS non-RS: myelodysplastic syndrome without ring sideroblasts; MPN: myeloproliferative neoplasm; NOS: not otherwise specified; PDAC: pancreatic ductal adenocarcinoma; RARS: refractory anemia with ring sideroblasts; RCMD-RS: refractory cytopenia with multilineage dysplasia and ring sideroblasts; SF3B1: splicing factor 3b subunit 1; SRSF2: serine- and arginine-rich splicing factor 2; U2AF1: U2 small nuclear RNA auxiliary factor 1; ZRSR2: zinc finger CCCH-type RNA binding motif and serine- and arginine-rich 2.

DISCUSSION

A wide variety of malignancies have been treated with PRMT5 inhibitors in clinical trials to date. PRMT5 inhibitors have demonstrated preliminary evidence of efficacy against treatment-resistant malignancies, including ACC, GBM, and uveal melanoma. Among patients with ACC, objective responses have been observed in 7/11 patients treated with JNJ-64619178. Stable disease was observed in 4 patients treated with PRT543 and 2/4 patients treated with PRT811. PRMT5 inhibitors appear especially promising for patients with uveal melanoma. One patient achieved prolonged stable disease with PRT543, and PRT811 therapy has shown objective response in 1/4 patients and stable disease in 1/4. A durable CR lasting 2 years was observed in a patient with HRD+ ovarian cancer treated with PRT543.

PRMT5 inhibitors appear promising for additional tumor types as well. PRMT5 is overexpressed in the KRAS mutant colorectal cancer (CRC).[60] Currently a directed KRAS therapy is not formulated for cases of KRAS mutant CRC, making PRMT5 inhibition a plausible target.

Due to the physiological role of PRMT5, it is logical to assume inhibitors of this enzyme may be best targeted at tumors with splicing variants. Taken together with the small pool of preliminary data, there is a signal supporting such efficacy. MDS is notorious for splicing machinery somatic missense mutations, especially in SF3B1, U2AF1, and SRSF2 (Fig. 3).[61] The most common genetic mutation in MDS, CLL, and uveal melanoma is SF3B1, which further supports the early clinical data supporting PRMT5 inhibitors as a promising new treatment option for the latter, treatment-resistant disease. SF3B1 mutations are also found in gastric and prostate cancers, U2AF1 mutation was found in a mucinous ovarian tumor, and SRSF2 mutations were discovered in childhood ALL.[62] SF3B1 mutations have been shown to promote tumorigenesis via downstream c-MYC and BCL2 stabilization. PRMT5 inhibitors have been shown to inhibit c-MYC via two mechanisms, which may prove to be therapeutic in both solid and hematologic malignancies, especially lymphomas.[63] The prevalence of ZRSR2, U2AF1, SRSF2, and SF3B1 splicing mutations in malignancies are summarized in Figure 3.[64–85]

One patient with HRD+ ovarian cancer showed durable CR. This finding warrants further investigation of cancers with compromised DNA damage repair. Although in basic laboratory studies, PRMT5 has not been shown to be involved with DNA damage repair, there may be an unelucidated mechanism by which these novel therapies interact with this type of aberrancy. Similarly, PRMT5 does not appear to play a crucial

role in metabolism but clinically has shown great efficacy in IDH1-mutated GBM, producing durable CR in the only patient investigated thus far.

Like other antineoplastics, PRMT5 inhibitors commonly cause gastrointestinal upset with diarrhea, nausea, and vomiting being most common, although these adverse effects have not been reported as DLTs in preliminary studies. Dysgeusia was also reported by few. Pancytopenia is another common adverse effect, with all current trials reporting grade 3/4 thrombocytopenia as a DLT and most reporting a similar outcome with neutropenia. Further common AEs were fatigue and asthenia. Less frequently, pruritis, hypophosphatemia, and alopecia also occurred in preliminary trial subjects.

CONCLUSION

PRMT5 inhibitors have shown early clinical promise as effective cancer therapies in both solid and hematologic malignancies. They may be most effective in cancers with splicing mutations such as SF3B1, U2AF1, and SRSF2. Ongoing studies will further investigate the efficacy and safety of PRMT5 inhibitors in various cancer types, in combination with other agents, and in various molecular subsets.

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